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Summary Report for the Screening-Level Review of Toxicity Information Contained in the Integrated Risk Information System (IRIS) Database – Phase II

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Summary Report for the Screening-level Review of Toxicity Information Contained in the Integrated Risk Information System (IRIS) Database Phase II

National Center for Environmental Assessment
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1.0 INTRODUCTION AND PURPOSE

The Integrated Risk Information System (IRIS) is a U.S. Environmental Protection Agency (EPA) database containing EPA consensus positions on potential adverse health effects that may result from chronic (or lifetime) exposure to chemical substances found in the environment. This database is maintained by EPA's National Center for Environmental Assessment (NCEA). The consensus positions for individual chemicals are documented in the form of IRIS summaries,[1] which contain qualitative and quantitative health information, including reference doses (RfDs) for non-cancer health effects resulting from oral exposure, reference concentrations (RfCs) for non-cancer health effects resulting from inhalation exposure, cancer weight-of-evidence (WOE) designations, and cancer slope factors (CSFs) and inhalation unit risks (IURs) for the carcinogenic effects of chemicals via ingestion and inhalation, respectively.

IRIS was originally developed in the mid-1980s to ensure consistency among health assessments completed and utilized by various EPA regions and program offices. Since IRIS was created, summaries for over 500 chemicals have been added to IRIS. For a number of chemicals summarized in IRIS, additional health effects research has since been published in the literature, but is not reflected in the current IRIS summaries. Consideration of these more recent research findings could potentially result in revised toxicity values (i.e., RfDs, RfCs, CSFs, or IURs) or cancer WOE designations for some chemicals.

In order to address questions about how well IRIS toxicity values reflect the current scientific literature, EPA initiated a screening-level review of the available literature for chemicals in the IRIS database. The purpose of the review was to reach preliminary determinations regarding the likelihood that a toxicological reassessment based on an evaluation of new health effects literature could potentially result in significant changes in the existing toxicity values or WOE designations. In addition, the results of the screening-level review will provide information for the annual IRIS Program priority-setting process for identifying chemicals for reassessment.

A screening-level methodology was adopted because an in-depth evaluation of recent health effects literature is a time- and resource-intensive process that represents the majority of the effort required in assessing a chemical. The screening-level methodology was designed to preliminarily identify and characterize new health effects literature for chemicals listed in the IRIS database. This methodology is not intended to provide a comprehensive or critical evaluation of this literature.

The size of the IRIS database precluded screening-level reviews of all of the chemicals included in this database at one time. Under the Phase I screening-level review, completed in November 2001, screening-level reviews were conducted for 100 chemicals randomly selected from the

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[1] IRIS summaries prepared since 1996 include supporting Toxicological Review documents.

IRIS database of more than 500 chemicals. Under Phase II, screening-level reviews were conducted for 200 chemicals randomly selected from the more than 400 remaining chemicals in the IRIS database. This report summarizes the results of the Phase II screening-level review. The remaining chemicals from the IRIS database will undergo screening-level reviews in the future.

2.0 METHODS

The screening-level review of the toxicity values contained in the IRIS summaries was conducted in five steps: 1) randomly selecting the 200 chemicals for review, 2) identifying recent toxicology literature compilations prepared by EPA and other authoritative organizations, 3) conducting literature searches to identify relevant health effects literature published since the IRIS summaries were completed, 4) sorting the literature (based primarily on a review of titles and abstracts) identified during the literature searches, and 5) evaluating the new health effects information and determining if this information could potentially produce a significant change in the current IRIS toxicity values.

2.1 Task 1: Selecting 200 IRIS Chemicals

EPA prepared a list of all chemicals currently in the IRIS database, excluding chemicals being reassessed under the IRIS program or those chemicals evaluated under the Phase I screening-level review. The list of remaining chemicals was imported into Microsoft Excel to randomly select 200 chemicals for the Phase II screening-level reviews. Using the RAND() function, each chemical was assigned a random number greater than or equal to 0 and less than 1. The list of these chemicals was then reorganized using the Sort tool and the chemicals were arranged in ascending order by the randomly assigned number. The first 200 chemicals identified in this random sort were selected for the Phase II literature-screening reviews and are listed in Appendix A.

2.2 Task 2: Identifying Existing Authoritative Scientific Literature Compilations

A chemical-specific strategy for identifying toxicity literature was developed for each chemical. These strategies were based on the date that the current toxicity values or WOE designation were posted on IRIS and the availability of toxicity literature compilations produced by authoritative scientific organizations. This section describes the process used to gather and evaluate this information, as well as the protocol applied to develop chemical-specific literature search strategies.

For each chemical, information regarding the toxicity value or WOE designation, the principal study or studies on which a value was based, and the consensus date was extracted from the IRIS database, as listed in Table 1. For many chemicals, one or more toxicity values or the WOE designation was unavailable, either because EPA has not yet undertaken an assessment of the given value or because EPA conducted an assessment and concluded that insufficient information was available to derive a toxicity value. The reason why a toxicity value or WOE designation was unavailable was also extracted from the IRIS database.

EPA programs such as the Office of Pesticide Programs (OPP) and other authoritative scientific organizations such as the International Agency for Research on Cancer (IARC) and the Agency

for Toxic Substances and Disease Registry (ATSDR) periodically review and summarize the toxicology literature for chemicals that are included in the IRIS database. Literature compilations, like these, for individual chemicals were identified by searching Web-based databases or EPA files, as listed in Table 1. Key toxicity information extracted from each of these documents is also listed in Table 1.

Table 1: Literature Compilations and Toxicity Information Considered in the Phase II Screening-Level Review

Source	Information Extracted	Location of Source[1]
IRIS	Toxicity values and WOE designation Principal study descriptions Consensus date	http://www.epa.gov/iris/subst/index.html
IRIS Submission Desk	Publication date Relevant information	Available through EPA
ATSDR Toxicological Profiles[2]	Publication date Minimal risk levels Principal study descriptions	TERA's on-line ITER database http://iter.ctcnet.net/publicurl/pub_search_list.cfm http://www.atsdr.cdc.gov/toxpro2.html
Health Canada[3]	Publication date Toxicity values and cancer classification Principal study descriptions	TERA's on-line ITER database http://iter.ctcnet.net/publicurl/pub_search_list.cfm
IARC Monographs	Publication date IARC classification	http://193.51.164.11/monoeval/grlist.html
WHO/IPCS	Publication date	http://www.who.int/dsa/cat98/zehc.htm
NTP Cancer Bioassay	Publication date Results	http://ntp-server.niehs.nih gov/main_pages/ NTP_ALL_STDY_PG.html
NTP Report on Carcinogens	Publication date Cancer classification	http://ntp-server.niehs.nih.gov/NewHomeRoc/AboutRoC.html
OPP RED documents	Publication date Toxicity values Principal study descriptions	http://www.epa.gov/REDs/

Table 1: Literature Compilations and Toxicity Information Considered in the Phase II Screening-Level Review

Source	Information Extracted	Location of Source[1]
NCEA Provisional Assessments[4]	Date of assessment Toxicity values and cancer classification Principal study descriptions	Available through EPA

Notes:

[1] Several of the Web site addresses changed between Phase I and Phase II; however, the content contained on these Web sites remained the same. The Web sites listed were accessed during the Phase II screening-level reviews and are only as accurate as the date of the latest revision of this document.

[2] ATSDR Supplemental Documents were considered during the Phase I screening-level review. These documents, however, did not add to the information contained in the ATSDR Toxicological Profiles. As such, the ATSDR Supplemental Documents were not included as a source of toxicity information in the Phase II screening-level review.

[3] Health Canada toxicity values were compiled from several sources including: Environmental Carcinogenesis and Ecotoxicology Review, Part C of Journal of Environmental Science and Health; and the Health Canada priority substances list assessment reports.

[4] Provisional toxicity values are developed by NCEA for the Superfund Health Risk Assessment Technical Support Center and the Hazardous Waste Identification Rule. These toxicity values undergo internal and external peer review, but do not undergo EPA consensus review and do not appear in the IRIS database.

ATSDR	Agency for Toxic Substances and Disease Registry	IRIS	Integrated Risk Information System
EPA	U.S. Environmental Protection Agency	NCEA	National Center for Environmental Assessment
IARC	International Agency for Research on Cancer	NTP	National Toxicology Program
IPCS	International Programme on Chemical Safety	OPP	Office of Pesticide Programs
		RED	Reregistration Eligibility Decision
		WHO	World Health Organization

A Lotus Notes database was developed to organize the information for each chemical extracted from both the IRIS database and literature compilations. Procedures were incorporated to ensure the accuracy of the information entered into the Lotus Notes database. For example, data entry fields in the Lotus Notes database were formatted to accept only specific formats (e.g., text or number). For fields with a limited number of possible entries (e.g., cancer classification), entry options were limited. Some fields also included limits on the number of characters that could be entered. In addition, hard copies of the IRIS summaries and literature compilations were obtained and a manual quality assurance/quality control review was conducted for information entered in the Lotus Notes database.

The Lotus Notes database was formatted to present toxicity information available for each chemical in a standard report. These reports not only presented toxicity values from various sources, but also indicated where toxicity values or literature compilations were unavailable. Appendix B contains a sample of the standard report generated for one of the chemicals included in the Lotus Notes database. Appendix C contains copies of the electronic files, including the Lotus Notes database, created for the screening-level review.

Information contained in the Lotus Notes database was then used to develop a literature search strategy for each individual chemical. The literature search strategy was based on the consensus date for the toxicity values or WOE designations in the existing IRIS summaries and the availability of literature compilations from authoritative scientific organizations. The literature search strategies fell into one of the following general categories:

1. No literature compilations from authoritative scientific sources were published after the consensus date for the IRIS toxicity values and/or WOE designation. A determination was made to conduct a literature search beginning with the year before the consensus date to the present.

   Example: The consensus date was June 4, 1990. No literature compilations were identified. A determination was made to conduct a literature search from 1989 to the present.

2. A literature compilation from an authoritative scientific source was published after the consensus date for the IRIS toxicity values and/or WOE designation. A determination was made to conduct a literature search beginning with the year before that compilation was published to the present.

   Example: The consensus date was June 4, 1990. ATSDR published a toxicological profile in 1997, which included a toxicity value (Minimal Risk Level) based on data considered in the existing IRIS summary. A determination was made to conduct a literature search from 1996 to the present.

3. A literature compilation from an authoritative scientific source was published after the consensus date for the IRIS toxicity values and/or WOE designation. The literature compilation contained a toxicity value based on study information made available after the IRIS consensus date, suggesting that significant new health effects literature exists that may result in a revised IRIS toxicity value. A literature search was considered unnecessary to establish that potentially significant new health effects information exists.

   Example: The consensus date was June 4, 1990. ATSDR published a toxicity value in 1997 that was different from the value presented in the existing IRIS summary and was based on a 1995 study. The 1995 study was identified as health effects information that

could potentially produce a change in the IRIS summary. An additional literature search was considered unnecessary.

For each chemical, literature search strategies were developed for each of the toxicity values assessed in the IRIS summary, including the RfD, RfC, and cancer endpoints (CSF, IUR, and WOE designation). These literature search strategies were documented in the Lotus Notes database for each chemical, as shown in the sample report provided in Appendix B.

When no assessment of the health effects literature for a toxicity value or WOE designation has been conducted for an individual chemical, a screening-level review to determine whether the value reflected the current health effects literature could not be performed. Nonetheless, if information that might support the derivation of a toxicity value was identified when screening the selected literature compilations, this information was noted in the Lotus Notes database.

2.3 Task 3: Conducting Literature Searches

Based on the literature search strategies developed in Task 2, chemical-specific literature searches were conducted to identify toxicologic and epidemiologic studies relevant to the development of IRIS toxicity values or WOE designations. For the purposes of this screening-level review, the following Web-based databases[2] were searched:

- *TOXLINE Special (http://toxnet.nlm.nih.gov/):* This database contains bibliographic information covering the biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals. References from an assortment of specialized journals and other sources are included.

- *MEDLINE (available through PUBMED at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi):* This databases contains bibliographic citations and author abstracts from more than 4,000 biomedical journals.

- *CANCERLIT (http://www.cancer.gov/search/cancer_literature/):* This database contains bibliographic citations and abstracts about chemical carcinogenicity from biomedical journals, proceedings, books, reports, and doctoral theses.

- *CCRIS (http://toxnet.nlm.nih.gov/):* This database summarizes data regarding carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition test results. The reported data are derived from studies cited in primary journals, current awareness tools, NCI reports, and other special sources.

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[2] Several of the Web sites addressees changed between Phase I and Phase II; however, the content contained on these Web sites remained the same. The Web sites listed were accessed during the Phase II screening-level reviews and are only as accurate as the date of the latest revision of this document.

- *TSCATS (http://esc.syrres.com/efdb/TSCATS.htm):* The Toxic Substance Control Act Test Submission (TSCATS) database was developed as a central location of information regarding unpublished technical reports submitted by industry to EPA under the Toxic Substances Control Act (TSCA). The database categorizes studies on over 8,000 chemicals by health effects, environmental effects, and environmental fate.

- *EPA Office of Pesticide Programs (OPP) (http://www.epa.gov/pesticides/search.htm):* OPP maintains a search page that allows users to search the Consumer Fact Sheets, Chemical Fact Sheets *(technical information)*, OPP Publications *(by title or publication number)*, Pesticide Registration (PR) Notices, Reregistration Eligibility Decisions (REDs), or the entire Web site for information regarding pesticides.

Additional information about each of the databases searched is provided on the listed Web sites.

For chemicals with IRIS summaries containing toxicity values and WOE designations, the first five databases were searched. For chemicals with IRIS summaries containing only a RfD and/or a RfC, only TOXLINE, MEDLINE, and TSCATS were searched because CANCERLIT and CCRIS contain information specific to cancer endpoints only. For pesticides, the OPP Web site was also searched.

A consistent set of search terms was applied in searching TOXLINE, MEDLINE, and CANCERLIT. Searches were initially performed using the chemical abstracts registry service (CAS) number and synonyms. If less than 50 references were found, the search was refined to identify studies containing the CAS number, synonyms, and any of the toxicology terms listed in Table 2. Results from the refined search were saved. All the terms listed in Table 2 were used when refining searches of TOXLINE and MEDLINE; however, only those search terms related to cancer endpoints were used to refine searches of CANCERLIT.

Table 2: Literature Search Terms

toxic	mutat *	neurotox
adverse effect	genotox *	immunotox
cancer *	fetotox	pharmacokinetic
carcinog *	embryotox	metabolism
tumor *	teratolog	epidemiol
oncogen *	teratogen	human stud
neoplasm *	reproduct, toxic	
mutag *	development, toxic	

* terms that apply to cancer endpoints and used to search CANCERLIT

CCRIS summarizes cancer-related study results by chemical name or CAS number. As such, searching by CAS number alone identified all relevant entries. If the CAS number was listed in

CCRIS, the search results were saved. If the CAS number was not listed in CCRIS, then no cancer-related data were available.

TSCATS also provides study results by chemical name or CAS number, but also allows the user to specify the category of study types sought. For each chemical, TSCATS was searched by CAS number first to identify the chemical and then by "health effects" to identify only those studies related to chemical toxicity.

In addition to REDs, which were included in the Lotus Notes database where available, the OPP Web site may contain other documents relevant to the toxicity of individual pesticides. Thus, a search of the OPP Web site (by CAS number) was conducted for pesticides included in the Phase II screening-level review. Additional information, if available, was most often identified in the OPP "Index of Cleared Science Reviews."

The literature search protocol described above was followed for each of the 200 chemicals included in the Phase II screening-level review with one exception. This protocol was slightly modified for inorganic arsenic. The modified literature search protocol is described in detail in the chemical summary for inorganic arsenic (Appendix F).

EndNote, a reference managing software program, was used to manage and organize results obtained from the literature search. For each chemical, results from searching TOXLINE, MEDLINE, and CANCERLIT were automatically imported into an EndNote file and sorted by publication date. The Find Duplicates tool was used to identify and delete references that appeared in multiple search results. Results from the CCRIS, TSCATS, and OPP Web site cannot be automatically entered into EndNote. References found when searching these sources were manually entered into the EndNote file for a chemical if the reference had not been captured when searching TOXLINE, MEDLINE, or CANCERLIT and the reference presented data relevant to the toxicity of the chemical under review (as described under Task 4). In many instances, results from the TSCATS search provided additional information, such as study completion date and author, for studies identified in TOXLINE. (TOXLINE captured the date that unpublished studies were submitted to EPA for review under TSCA rather than the date that these studies were completed.) This additional information was manually entered into EndNote. The resulting EndNote file then served as the collection of references used to conduct the literature screening under Task 4. The EndNote files for each chemical are provided electronically in Appendix C.

2.4 Task 4: Sorting Literature Search Results

Individual references obtained in the literature search were sorted by their relevance to the development of a given IRIS toxicity value. For the purpose of this screening-level review, this sorting process was limited only to the information contained in the literature search records (e.g., study titles and abstracts). Reviewing full-text articles and conducting in-depth data

reviews were outside the scope of the screening-level review. Individual references were sorted into the following nine categories:

1. Potential to produce a significant change in an existing noncancer toxicity value
2. Potential to produce a significant change in an existing cancer toxicity value
3. Potential to produce a significant change in an existing cancer WOE designation
4. Physiologically-based pharmacokinetic (PBPK) modeling studies
5. Other toxicity studies not directly useful for establishing IRIS toxicity values
6. Studies with information on health effects in young populations
7. Compilations of health effects studies
8. Not useful
9. Unknown relevance

Each of these categories and the criteria used to assign categories are described in more detail in Appendix D.

An individual reference may contain information relevant to more than one category. For example, a multigeneration reproductive toxicity study would fall in category 1 (potential to produce a change in an existing noncancer toxicity value) and category 6 (studies with information on health effects in young populations). In sorting references, references were coded with all appropriate categories.

For the majority of the 200 randomly selected chemicals, all references identified during the literature search were screened and coded. When the literature search retrieved a large number of references (i.e., greater than 300), EndNote functions were used to identify those reference most likely relevant to the development of IRIS toxicity values. For some chemicals, the literature searches identified a large number of references unrelated to the chemical of interest because chemical synonyms are also common words. For example, the literature search for the pesticide with the trade name "Assure" identified over 1,100 references. References not relevant to an IRIS assessment for Assure were identified through a search of EndNote and were coded N/A in the EndNote file. Other chemicals, such as Dicamba, have been the subject of extensive toxicity testing in both plants and animals. In these instances, references containing common laboratory species and toxicological terms (Table 3) were identified and coded. Remaining references were retained in EndNote and coded N/A. Literature searches for some chemicals identified large numbers of references because of chemical-specific characteristics. Strychnine, for example, has been studied for its use as an anticonvulsant. Therefore, studies related to strychnine as a treatment for seizures were found using a search of EndNote and coded N/A. The use of the additional search terms, such as those listed in Table 3, to refine literature searches with large numbers of records was documented in the chemical-specific summaries prepared under Task 5. The EndNote files for each chemical are provided electronically in Appendix C.

Table 3: Laboratory Species and Toxicological Terms

rat(s)	human(s)	epidemiol
mouse/mice	rabbit(s)	genotox
gerbil(s)	pig(s)	mutat
hamster(s)	monkey(s)	mutag
beagle(s)	primate(s)	
dog(s)	worker(s)	

2.5 Task 5: Evaluating Health Effects Information

In the final phase of the screening-level review, summary information contained in available literature compilations and in the sorted literature searches was evaluated to determine if recent health effects information could potentially produce a significant change in existing IRIS toxicity values or WOE designations. Judgements about the potential impact of the more recent literature on existing IRIS toxicity values were guided by a set of decision rules developed by the EPA. These judgements considered both the basis for current toxicity values or WOE designations and the nature of more recent toxicity literature. These decision rules are described in a set of decision trees for noncancer RfDs and RfCs, CSFs and IURs, and WOE designations. Decision trees are provided in Appendix E. Each IRIS toxicity value (i.e., RfD, RfC, CSF, or IUR) and WOE designation currently contained in IRIS was evaluated separately. Such evaluations were not performed if an assessment in support of an individual toxicity value or WOE designation was absent from the existing IRIS assessment for a given chemical.

The literature screening conducted in Task 4 served to focus evaluations during Task 5. References coded as category 1 (potential to produce a change in an existing noncancer toxicity value) were evaluated against current RfDs and RfCs and principal studies used to derive these values. References coded as category 2 (potential to produce a change in an existing cancer toxicity value) were evaluated against current CSFs and IURs and principal studies used to derive these values. References coded as category 2 and category 3 (potential to produce a change in an existing cancer toxicity value or WOE designation) were evaluated in light of the evidence used to derive the WOE designations. References coded as category 4 (PBPK modeling studies) were evaluated for their potential to influence uncertainty factors for interspecies extrapolation. References assigned a code of 5, 6, or 7 were those that would not typically be used as the basis for a toxicity value, but might be considered more generally in developing an IRIS summary. References coded as category 9 (unknown relevance) contained insufficient information to evaluate their relevance to the development of toxicity values or WOE designations. Further examination of these studies may be warranted in the future.

The findings of the screening-level review for each of the 200 chemicals were summarized in brief narratives (1 or 2 pages). These narratives are provided in Appendix F. Narratives briefly characterized the basis of toxicity values and WOE designations in existing IRIS summaries and the nature of new health effects information. Narratives also included conclusions regarding the

likelihood that new health effects information identified in authoritative literature compilations or the literature search could produce a significant change in existing IRIS toxicity values. Conclusions were drawn for each toxicity value and WOE designation. When no assessment of the health effects literature for a given toxicity value or WOE designation has been conducted, similar conclusions could not be drawn. Nonetheless, relevant information identified during the screening-level review was noted in the narratives. A brief statement summarizing the number of references coded as category 9 (unknown relevance) was also included in each narrative.

3.0 RESULTS AND CONCLUSIONS

A screening-level review of 200 chemicals randomly selected from the IRIS database was conducted to address questions about whether or not current health effects literature could potentially produce a change in the existing IRIS toxicity values or WOE designation. The results of this review are summarized in the following text and Table 4. Results for individual chemicals are provided in Appendix G.

For 121 (60%) of the 200 chemicals reviewed, no significant new health effects information that would likely produce a significant change in existing IRIS toxicity values or the WOE designation was identified. For 79 chemicals (40%) new health effects information was identified that, if evaluated in detail, could possibly result in a change to an existing IRIS toxicity value or WOE designation.

Results relevant to the specific toxicity values and WOE designations are as follows:

- RfDs were available for 141 of the chemicals reviewed. New health effects information that could potentially result in a significant change in the RfD was identified for 61 of the 141 chemicals.
- RfCs were available for 40 of the chemicals reviewed. New health effects information that could potentially result in a significant change in the RfC was identified for 9 of the 40 chemicals.
- CSFs were available for 30 of the chemicals reviewed. New health effects information that could potentially result in a significant change in the CSF was identified for 6 of the 30 chemicals.
- IURs were available for 21 of the chemicals reviewed. New health effects information that could potentially result in a significant change in the IUR was identified for 6 of the 21 chemicals.
- WOE designations were available for 80 of the chemicals reviewed. New health effects information that could potentially result in a significant change in the WOE designations was identified for 11 of the 80 chemicals.

For most chemicals in IRIS, one or more toxicity values are not available in the IRIS database (e.g., for dibutyl phthalate, an RfD, RfC and WOE are available in IRIS, but not a CSF or IUR). In some instances, the lack of a toxicity value or WOE designation reflects the fact that EPA has not yet undertaken a determination of a toxicity value or WOE designation. In other cases, a chemical-specific toxicity value or WOE designation is not present in IRIS because its derivation is inappropriate. For example, 1,1-methylphenol and trichloroacetic acid have been assigned a

WOE classification of Group C—possible human carcinogen. Deriving a CSF or IUR for these chemicals was not supported by the available data. As previously noted, screening-level reviews were not specifically conducted when no assessment of the health effects literature for a toxicity value or WOE designation had been conducted; however, relevant studies identified in the literature screen were noted in the chemical-specific narratives. Of the 200 chemicals evaluated, information relevant to a toxicity value not assessed in the current IRIS summary was identified for 107 chemicals (54%). Because the literature search for these toxicity values was not intended to be comprehensive and because a detailed review of new study literature was outside the scope of this review, it cannot be determined whether the available toxicity information would support the derivation of a toxicity value not currently available in IRIS.

Table 4: Results of Screening-Level Review of IRIS

Summary of Assessments	RfD	RfC	CSF	IUR	WOE
Available in the existing IRIS summary	141	40	30	21	80
Not available in the existing IRIS summary	59	160	170	179	120
No literature likely to produce a significant change in the IRIS summary was identified	80	31	24	15	69
New literature was identified that could potentially produce a significant change in the IRIS summary	61	9	6	6	11
Not available in the IRIS summary, but potentially relevant information was identified	23	20	18	9	75

Notes:

CSF	oral cancer slope factor	RfD	oral reference dose
IRIS	Integrated Risk Information System	RfC	inhalation reference concentration
IUR	inhalation unit risk	WOE	cancer weight-of-evidence

Given the application of a screening-level methodology to evaluate current IRIS assessments, certain limitations and uncertainties are inherent in the results of the assessment. These limitations and uncertainties are as follows:

- The screening-level review involved screening, coding, and evaluating studies identified (1) in the literature compilations based on available study summaries and (2) in the literature searches based only on study titles and abstracts. The literature was not subjected to an in-depth assessment or independent critical evaluation. As such, no conclusions regarding the validity of new toxicity information or appropriateness for its use in developing toxicity values could be drawn. In general, it was conservatively

assumed that the more recent toxicity literature that passed the initial Task 4 screen had the potential to produce a change in an existing IRIS value. It is expected that toxicity values for some chemicals for which new toxicity information was identified would not be subject to change upon a more detailed, critical examination of the study data.

- No literature search can be assured of capturing all relevant literature. The screening-level review sought to capture the majority of potential new health effects studies; however, some information, such as unpublished toxicology studies, may have been overlooked. This is a specific concern when identifying new health effects literature for pesticides, which comprise approximately 40% of the IRIS chemicals evaluated in the current screening-level review. Many studies of pesticides are directly submitted to EPA OPP and are considered confidential business information. Although OPP REDs, which include reviews of all toxicity studies submitted to EPA, were one of the literature compilations relied on, these documents were not available for all the pesticides undergoing the screening-level review. For the pesticides, a search of the OPP Web site was conducted to identify additional information possibly available through OPP.

- The literature search records for some studies contained insufficient information to permit a determination of the relevance of the reference to a health assessment for a given chemical (e.g., the record did not provide a complete citation or sufficient information on the chemical(s) under study, endpoints measured, or date that the study was conducted). The numbers of studies categorized as being of unknown relevance are provided in the individual chemical narratives (Appendix F) and are summarized in Appendix G. Full text review of these references, which was beyond the scope of this screening-level review, would be required to determine their relevance to an updated health assessment for a given chemical.

- Since the mid-1980s when the first IRIS summaries were developed, EPA has modified some risk assessment methods for deriving toxicity values and WOE designations (e.g., benchmark dose approach, inter-species scaling factor, guidelines for carcinogen risk assessment). Consideration of how the application of new methodologies might affect existing IRIS values was beyond the scope of this screening-level review.

- The TSCATS database contains unpublished technical reports submitted by industry to EPA under TSCA. The TOXLINE database includes records from TSCATS and was the preferred source of TSCATS records because TOXLINE search results could be automatically downloaded into EndNote. The TSCATS information provided in TOXLINE records, however, is incomplete. Therefore, some manual editing of the TSCATS information was required. Two dates, one representing the date the study was completed and one representing the date the study was submitted to EPA Office of Toxic Substances (OTS), are reported in the TSCATS database. The TOXLINE database, however, lists only the date that the study was submitted to EPA. Periodically, the date of

study completion predates the date of submission to EPA by 10 years or more. For example, a study completed in 1970 may have a submission date to EPA of 1987. TOXLINE would list the publication date for this study as 1987. In TSCATS, the designation "00/00/00" is used if no submission date is available. TOXLINE incorrectly converts this entry to a publication date of 2000.

To the extent possible, errors in TOXLINE were corrected by manually entering into the EndNote databases for individual chemicals information regarding the actual study completion date and study authors taken directly from TSCATS. However, not all submissions to OTS that were contained in TOXLINE were also listed in TSCATS. As such, information in these records could not be confirmed and the publication dates may be erroneous. Therefore, unpublished technical reports submitted to OTS that were lacking abstracts were generally coded as being of "unknown relevance." There exists the possibility that unpublished OTS submissions that contained new study data may have been dropped using this procedure.

APPENDICES

Appendix A: 200 Randomly Selected IRIS Chemicals

Appendix A: 200 Randomly Selected IRIS Chemicals

Number	Chemical	CAS Number
1	Acetonitrile	75-05-8
2	Acrylonitrile	107-13-1
3	Adiponitrile	111-69-3
4	Aldicarb	116-06-3
5	Aldrin	309-00-2
6	Ally	74223-64-6
7	Allyl alcohol	107-18-6
8	Ametryn	834-12-8
9	4-Aminopyridine	504-24-5
10	Amitraz	33089-61-1
11	Ammonium acetate	631-61-8
12	Ammonium sulfamate	7773-06-0
13	Aniline	62-53-3
14	Antimony	7440-36-0
15	Antimony trioxide	1309-64-4
16	Apollo	74115-24-5
17	Arsenic (inorganic)	7440-38-2
18	Arsine	7784-42-1
19	Assure	76578-14-8
20	Azobenzene	103-33-3
21	Barium cyanide	542-62-1
22	Baythroid	68359-37-5
23	Benefin	1861-40-1
24	Benomyl	17804-35-2
25	Bidrin	141-66-2
26	Biphenthrin	82657-04-3
27	1,1-Biphenyl	92-52-4
28	Bis(2-chloroethoxy)methane	111-91-1
29	Bis(2-chloroisopropyl) ether	39638-32-9
30	Bisphenol A	80-05-7
31	Bromodichloromethane	75-27-4
32	p-Bromodiphenyl ether	101-55-3
33	Bromoform	75-25-2
34	Bromoxynil octanoate	1689-99-2
35	Cacodylic acid	75-60-5
36	Captafol	2425-06-1

Number	Chemical	CAS Number
37	Carbaryl	63-25-2
38	Carbofuran	1563-66-2
39	Carbon disulfide	75-15-0
40	Carbonyl sulfide	463-58-1
41	Carbosulfan	55285-14-8
42	Carboxin	5234-68-4
43	Chlorimuron-ethyl	90982-32-4
44	Chlorine	7782-50-5
45	1-Chlorobutane	109-69-3
46	2-Chlorobutane	78-86-4
47	2-Chlorophenol	95-57-8
48	p-Chlorophenyl methyl sulfide	123-09-1
49	Coke oven emissions	8007-45-2
50	Cumene	98-82-8
51	Cyanazine	21725-46-2
52	Cyanogen	460-19-5
53	Cyclohexanone	108-94-1
54	Cyclohexylamine	108-91-8
55	Dalapon (sodium salt)	75-99-0
56	Danitol	39515-41-8
57	2,4-Diaminotoluene	95-80-7
58	Dibenzofuran	132-64-9
59	Dibromochloromethane	124-48-1
60	Dibromodichloromethane	594-18-3
61	p,p'-Dibromodiphenyl ether	2050-47-7
62	Dicamba	1918-00-9
63	p,p'-Dichlorodiphenyltrichloroethane	50-29-3
64	1,1-Dichloroethane	75-34-3
65	cis-1,2-Dichloroethylene	156-59-2
66	trans-1,2-Dichloroethylene	156-60-5
67	Dichloromethane	75-09-2
68	4-(2,4-Dichlorophenoxy)butyric acid	94-82-6
69	1,2-Dichloropropane	78-87-5
70	2,3-Dichloropropanol	616-23-9
71	Dicofol	115-32-2
72	Diethyl phthalate	84-66-2
73	Diethyl-p-nitrophenyl phosphate	311-45-5
74	Dimethipin	55290-64-7

Number	Chemical	CAS Number
75	N,N-Dimethylformamide	68-12-2
76	2,4-Dimethylphenol	105-67-9
77	3,4-Dimethylphenol	95-65-8
78	2,4-Dinitrotoluene	121-14-2
79	Diphenamid	957-51-7
80	1,2-Diphenylhydrazine	122-66-7
81	Disulfoton	298-04-4
82	Endosulfan	115-29-7
83	Endothall	145-73-3
84	Epichlorohydrin	106-89-8
85	1,2-Epoxybutane	106-88-7
86	Ethephon	16672-87-0
87	S-Ethyl dipropylthiocarbamate	759-94-4
88	Ethyl p-nitrophenyl phenylphosphorothioate	2104-64-5
89	Ethylene glycol monobutyl ether (EGBE)	111-76-2
90	Ethylphthalyl ethylglycolate	84-72-0
91	Fluridone	59756-60-4
92	Flurprimidol	56425-91-3
93	Fluvalinate	69409-94-5
94	Fomesafen	72178-02-0
95	Formic acid	64-18-6
96	Furmecyclox	60568-05-0
97	Glycidaldehyde	765-34-4
98	n-Heptane	142-82-5
99	alpha-Hexachlorocyclohexane	319-84-6
100	beta-Hexachlorocyclohexane	319-85-7
101	Hexachlorophene	70-30-4
102	1,6-Hexamethylene diisocyanate	822-06-0
103	Hexazinone	51235-04-2
104	Hydrazine/Hydrazine sulfate	302-01-2
105	Hydroquinone	123-31-9
106	Isobutyl alcohol	78-83-1
107	Lead and compounds (inorganic)	7439-92-1
108	d-Limonene	5989-27-5
109	Malathion	121-75-5
110	Maleic anhydride	108-31-6
111	Maleic hydrazide	123-33-1
112	Manganese	7439-96-5

Number	Chemical	CAS Number
113	Mepiquat chloride	24307-26-4
114	Mercuric chloride	7487-94-7
115	Mercury, elemental	7439-97-6
116	Merphos oxide	78-48-8
117	Methamidophos	10265-92-6
118	Methyl isocyanate	624-83-9
119	Methyl methacrylate	80-62-6
120	2-Methyl-4-chlorophenoxyacetic acid	94-74-6
121	2-(2-Methyl-4-chlorophenoxy) propionic acid	93-65-2
122	Methylmercury	22967-92-6
123	3-Methylphenol	108-39-4
124	4-Methylphenol	106-44-5
125	Metribuzin	21087-64-9
126	Nitrate	14797-55-8
127	Nitrite	14797-65-0
128	N-Nitrosodimethylamine	62-75-9
129	N-Nitrosodi-N-propylamine	621-64-7
130	N-Nitrosodiphenylamine	86-30-6
131	Oxyfluorfen	42874-03-3
132	Pentabromodiphenyl ether	32534-81-9
133	Pentachlorocyclopentadiene	25329-35-5
134	Pentafluoroethane	354-33-6
135	m-Phenylenediamine	108-45-2
136	Phenylmercuric acetate	62-38-4
137	Phosmet	732-11-6
138	Phthalic anhydride	85-44-9
139	Picloram	1918-02-1
140	Pirimiphos-methyl	29232-93-7
141	Potassium silver cyanide	506-61-6
142	Prometon	1610-18-0
143	Pronamide	23950-58-5
144	Propanil	709-98-8
145	Propargyl alcohol	107-19-7
146	Propham	122-42-9
147	Propylene glycol monomethyl ether	107-98-2
148	Propylene glycol	57-55-6
149	Propyleneimine	75-55-8
150	Pyridine	110-86-1

Number	Chemical	CAS Number
151	Quinalphos	13593-03-8
152	Quinoline	91-22-5
153	Quinone	106-51-4
154	Radium 226,228	7440-14-4
155	Radon 222	14859-67-7
156	Resmethrin	10453-86-8
157	Savey	78587-05-0
158	Selenious acid	7783-00-8
159	Selenium sulfide	7446-34-6
160	Selenium and Compounds	7782-49-2
161	Selenourea	630-10-4
162	Silver cyanide	506-64-9
163	Simazine	122-34-9
164	Sodium diethyldithiocarbamate	148-18-5
165	Strychnine	57-24-9
166	Systhane	88671-89-0
167	Tebuthiuron	34014-18-1
168	Terbutryn	886-50-0
169	Tetrabromodiphenyl ether	40088-47-9
170	1,2,4,5-Tetrachlorobenzene	95-94-3
171	Tetrachlorocyclopentadiene	695-77-2
172	1,1,1,2-Tetrachloroethane	630-20-6
173	1,1,2,2-Tetrachloroethane	79-34-5
174	2,3,4,6-Tetrachlorophenol	58-90-2
175	Tetraethyl lead	78-00-2
176	Thallic oxide	1314-32-5
177	Thallium carbonate	6533-73-9
178	Thallium nitrate	10102-45-1
179	Thallium(I) sulfate	7446-18-6
180	Thiobencarb	28249-77-6
181	Thiophanate-methyl	23564-05-8
182	Toxaphene	8001-35-2
183	1,2,4-Tribromobenzene	615-54-3
184	Tributyltin oxide	56-35-9
185	Trichloroacetic acid	76-03-9
186	Trichlorocyclopentadiene	77323-84-3
187	Trichlorofluoromethane	75-69-4
188	2,4,5-Trichlorophenol	95-95-4

Number	Chemical	CAS Number
189	2,4,6-Trichlorophenol	88-06-2
190	2 (2,4,5-Trichlorophenoxy) propionic acid	93-72-1
191	1,2,3-Trichloropropane	96-18-4
192	1,1,2-Trichloropropane	598-77-6
193	1,1,2-Trichloro-1,2,2-trifluoroethane	76-13-1
194	Tridiphane	58138-08-2
195	Triethylene glycol monobutyl ether	143-22-6
196	Triethylene glycol monoethyl ether	112-50-5
197	Trifluralin	1582-09-8
198	Uranium, soluble salts	N.A.
199	Vanadium pentoxide	1314-62-1
200	Vinclozolin	50471-44-8

Notes:

CAS Number chemical abstracts registry service number

Appendix B: Sample Lotus Notes Report

Appendix B: Sample Lotus Notes Report

Summary of Toxicity Information for Chemicals Listed in IRIS

Chemical Name: Acetonitrile **CASRN:** 75-05-8 **Number:** 1

IRIS

RfD (mg/kg/day):
Date of Last Significant Revision: 01/26/99
Availability: Withdrawn
Critical Effect:
UF:
MF:
Was an UF assigned based on lack of supporting data?
What was the data gap?
Study Animal/Species:
Principal Study Description:
Principal Study Reference:

RfC (mg/m3): 0.06
Date of Last Significant Revision: 01/26/99
Availability:
Critical Effect: Mortality
UF: 100
MF: 10
Was an UF assigned based on lack of supporting data? Yes
What was the data gap? Limited data on reproductive endpoints involving exposure of laboratory animals before and during mating through parturition; and the absence of hematological measurements in either mouse study
Study Animal/Species: Mouse
Principal Study Description: Subchronic/chronic inhalation sutides
Principal Study Reference: NTP, 1996

CSF (mg/kg/day)-1:
Date of Last Significant Revision:
Availability: Not available
Tumor Type:
Study Animal/Species:
Principal Study Reference:

IUR (ug/m3)-1:
Date of Last Significant Revision:
Availability: Not available
Tumor Type:
Study Animal/Species:
Principal Study Reference:

WOE Classification: D
Date of Last Significant Revision: 01/26/99

Information Available through the IRIS Submission Desk

Comments: Not Available

ATSDR

Toxicological Profile (date of most recent update): Not available

Oral MRL (mg/kg/day):
Duration:
Critical Organ/Effect:
Study Animal/Species:
Principal Study Reference:

Inhalation MRL (mg/m3):
Duration:
Critical Organ/Effect:
Study Animal/Species:
Principal Study Reference:

ATSDR Supplemental Document:

Health Canada

Health Canada Assessment (date of assessment): Not available

TDI (mg/kg/day):
Critical Organ/Effect:
Study Animal/Species:
Principal Study Reference:

TC (mg/m3):
Critical Organ/Effect:
Study Animal/Species:
Principal Study Reference:

TD05 (mg/kg/day):
Tumor Type:
Study Animal/Species:
Principal Study Reference:

TC05 (mg/m3):
Tumor Type:
Study Animal/Species:
Principal Study Reference:

Cancer classification:

IARC

Date of Most Recent Monograph: Not available
Classification:

WHO

Publication Date: 1993
Publishing Organization: IPCS

NTP Cancer Bioassay (published since 1986)

Publication Date: 4/96
Route of exposure: Inhalation
Result: EE - Equivocal evidence of carcinogenicity

NTP Report on Carcinogens

Date Listed: Not available
Classification:

Reregistration Eligibility Decisions (RED)

Publication Date: Not available

RfD (mg/kg/day):
Critical Effect:
UF:
MF:
Study Animal/Species:
Principal Study Description:
Principal Study Reference:

RfC (mg/m3):
Critical Effect:
UF:
MF:
Study Animal/Species:
Principal Study Description:
Principal Study Reference:

CSF (mg/kg/day)-1:
Tumor Type:
Study Animal/Species:
Principal Study Reference:

IUR (ug/m3)-1:
Tumor Type:
Study Animal/Species:
Principal Study Reference:

NCEA Provisional Assessments

Publication Date: Not available

RfD (mg/kg/day):
- **Critical Effect:**
- **UF:**
- **MF:**
- **Study Animal/Species:**
- **Principal Study Description:**
- **Principal Study Reference:**

RfC (mg/m3):
- **Critical Effect:**
- **UF:**
- **MF:**
- **Study Animal/Species:**
- **Principal Study Description:**
- **Principal Study Reference:**

CSF (mg/kg/day)-1:
- **Tumor Type:**
- **Study Animal/Species:**
- **Principal Study Reference:**

IUR (ug/m3)-1:
- **Tumor Type:**
- **Study Animal/Species:**
- **Principal Study Reference:**

WOE Classification:

Comments: RfD: Conduct literature search from 1998 to present.
RfC: Conduct literature search from 1998 to present
Carcinogenicity: Conduct literature search from 1998 to present.

Note: A 14-day inhalation teratology study on rats, 13-week inhalation toxicity study on rats and mice, and a 90-day inhalation toxicity study on rats and mice were found while searching the NTP Management Status Document.
Note (2): In the NTP Cancer Bioassay study, although equivocal evidence of carcinogenic activity was found in male F334/N rats, there was no evidence found in female F344/N rats nor in male or female B6C3F1 mice.

Appendix C: Electronic Files

Appendix C: Electronic Files

The following electronic files are provided on the enclosed CD-ROM

1. Lotus Notes database
2. EndNote files for each of the 100 chemicals
3. WordPerfect narratives for each of the 200 chemicals

Appendix D: Reference Sorting Criteria

Appendix D: Reference Sorting Criteria

Code	Category	Criteria for Including in the Category
1	Potential to produce a change in an existing noncancer toxicity value	Animal studies • subchronic toxicity study (usually minimum of 90-day exposure duration) • chronic toxicity study • reproductive and developmental toxicity studies • only studies involving oral and inhalation exposure routes (i.e., studies involving dermal or injection administration would be considered "Other") Epidemiologic studies • only studies that could potentially demonstrate a causal relationship, i.e., case-control and cohort studies only (e.g., no case reports) • studies examining effects associated with a single chemical exposure only
2	Potential to produce a change in an existing cancer toxicity value	Animal studies • cancer bioassay (involving lifetime or near lifetime exposures) • only studies involving oral and inhalation exposure routes (i.e., studies involving dermal or injection administration would be considered "Other") Epidemiologic studies • only studies that could potentially demonstrate a causal relationship, i.e., case-control and cohort studies only (e.g., no case reports) • studies examining effects associated with single chemical exposure only
3	Potential to produce a change in an existing cancer WOE designation	Studies that could be used in the determination of a cancer weight-of-evidence (WOE) designation – other than those studies that fall into Category 2 (in vivo cancer bioassays and epidemiological studies). Studies in this category would include: • genotoxicity studies • DNA adduct studies • other short-term in vivo assays, including tests for non-genotoxic agents Studies in this category may include those that report results for a series of chemicals, as long as the study includes the chemical of interest and the results appear to be previously unreported in the peer-reviewed literature.
4	PBPK modeling studies	Primarily complete physiologically-based pharmacokinetic (PBPK) models, studies that compare the relationship between exposure and target tissue dose in an animal species and humans, or other study that compares the pharmacokinetics in an animal species and humans.

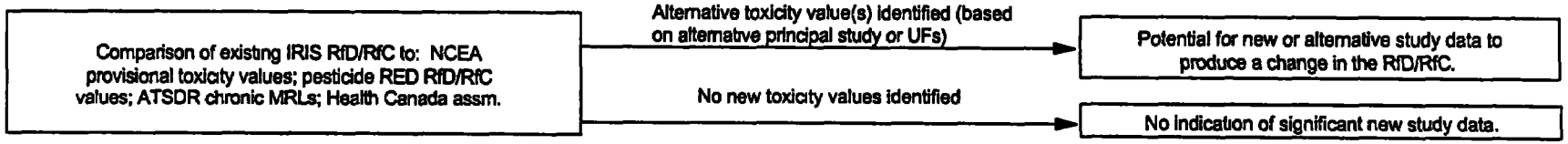
Code	Category	Criteria for Including in the Category
5	Other toxicity studies not directly useful for establishing IRIS toxicity values	Studies containing health effects information for the given chemical that might appropriately be considered in a comprehensive review of the toxicity of that chemical, but would not likely be considered in establishing a toxicity value (RfD, RfC, or cancer slope factor/unit risk) or WOE designation. The following would be included in this category: (1) Laboratory studies other than subchronic and chronic toxicity studies, including studies of acute toxicity, dermal toxicity/sensitization, and various short-term assays (2) Studies involving exposure routes other than oral and inhalation (e.g., dermal, injection) (3) Human studies not useful for demonstrating a causal association (e.g., case study, cluster investigation) or meta analysis of previously published studies (4) Studies of the absorption, distribution, metabolism or excretion of the chemical that do not fall into Category 4 (PBPK models or studies that examine pharmacokinetic difference/similarities across species) (5) Studies that address mechanism (mode) of action that do not fall into other categories
6	Studies with information on health effects in young populations	Health effect studies in human or animal populations that specifically examine the effects of a given chemical on early life stages. Studies in humans: • Epidemiological studies that look at effects associated with in utero or childhood exposures • Epidemiological studies that include children as cohorts Experimental studies. *Examples of such studies would include:* • Cancer bioassays that include in utero exposure • Developmental toxicity studies • Reproductive toxicity studies, especially multigeneration studies • Special studies that include examination of effects on the developing organism (e.g., developmental neurotoxicity studies or developmental immunotoxicity studies) • Studies that examine transplacental transfer • Studies that characterize the pharmacokinetic handling of a chemical at different life stages
7	Compilations of health effects studies	Reviews of the toxicity of the given chemical such as ATSDR, WHO, IARC, NTP, and other review papers published in the peer-reviewed literature [In limited instances, a decision may be made to retrieve a review paper for use in assessing the currency of a given IRIS assessment]

Code	Category	Criteria for Including in the Category
8	Not useful	Including the following: • Studies that do not appear to address the chemical of interest • Studies that address mixtures, such that an association between an effect and the chemical of interest cannot be discerned • Studies that do not address chemical toxicity • Studies not directly relevant to an assessment of mammalian toxicity (e.g., ecological toxicity studies) • Studies already cited in an IRIS assessment • Reviews, book chapters, symposia and conference proceedings, etc. that address a large number of chemicals, an endpoint of toxicity (e.g., neurotoxicity of solvents), or an analysis based on previously reported findings (e.g., correlations between carcinogenic potency and mutagenicity for a series of chemicals)
9	Uncertain relevance	For a limited number of records, it may be essentially impossible to discern from the literature search record whether or not a particular reference contains relevant information on the toxicity of a given chemical. In some cases it may be appropriate to identify such studies and to consider, based on the literature search as a whole, retrieving and reviewing the full text copy of the paper.

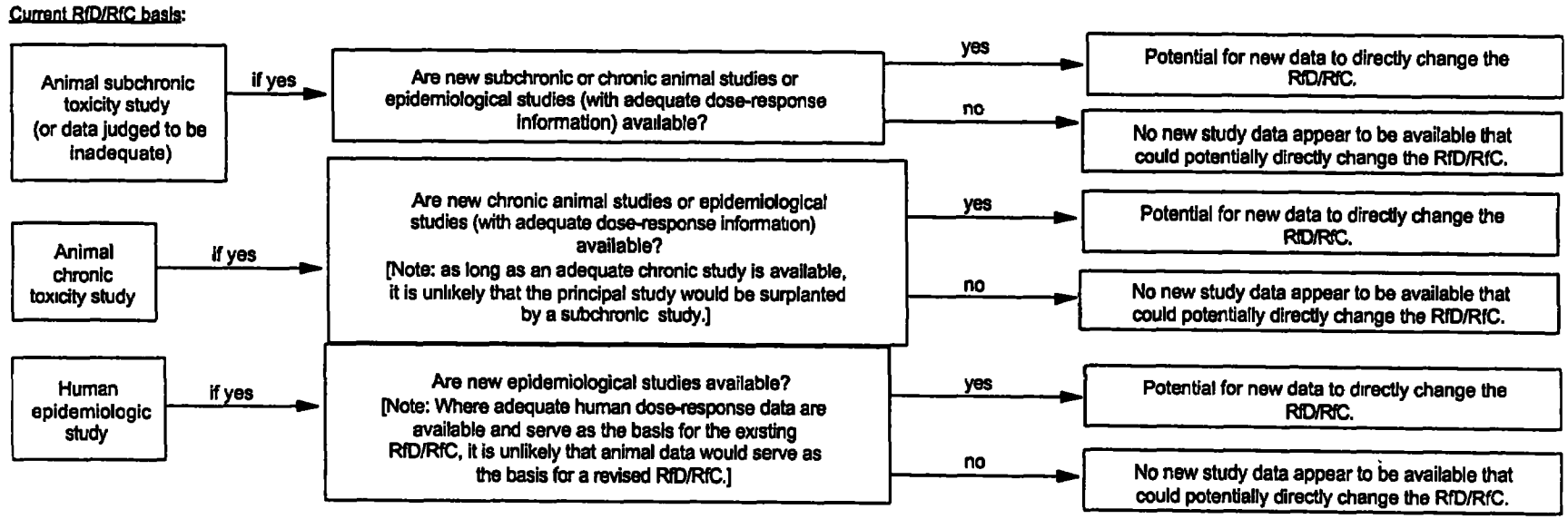
Appendix E: Decision Trees

IRIS Oral Reference Dose (RfD) or Inhalation Reference Concentration (RfC)

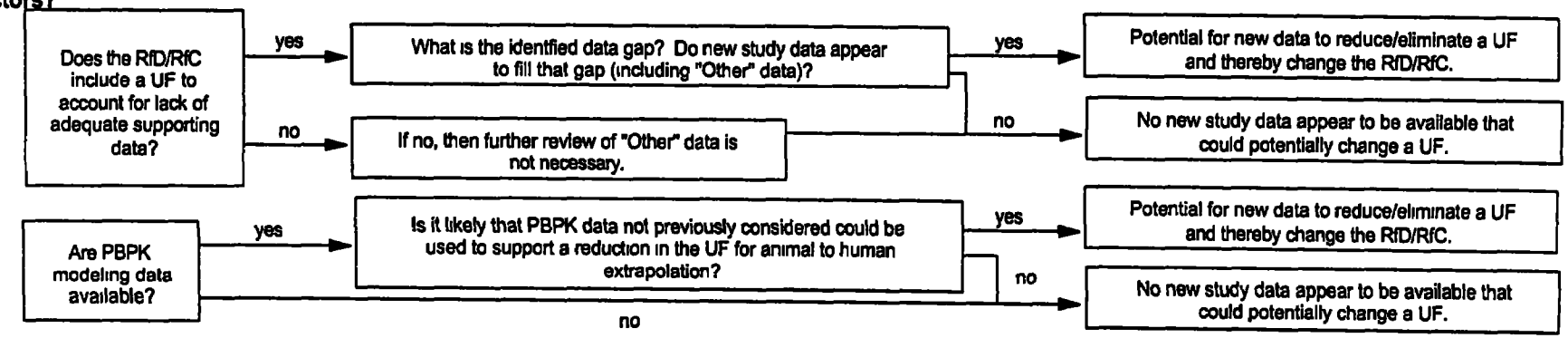
(1) Does a more recent health assessment suggest an alternative basis for the IRIS RfD/RfC?



(2) Does a screen of the more recent literature reveal studies that could potentially support revision of the IRIS RfD/RfC?

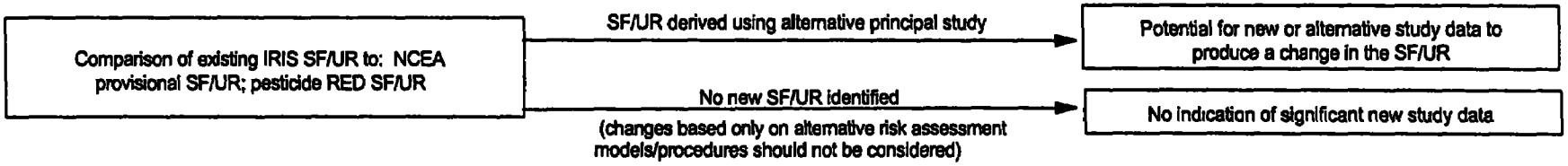


(3) Does a screen of the more recent literature reveal studies that could potentially support modification of uncertainty factors?

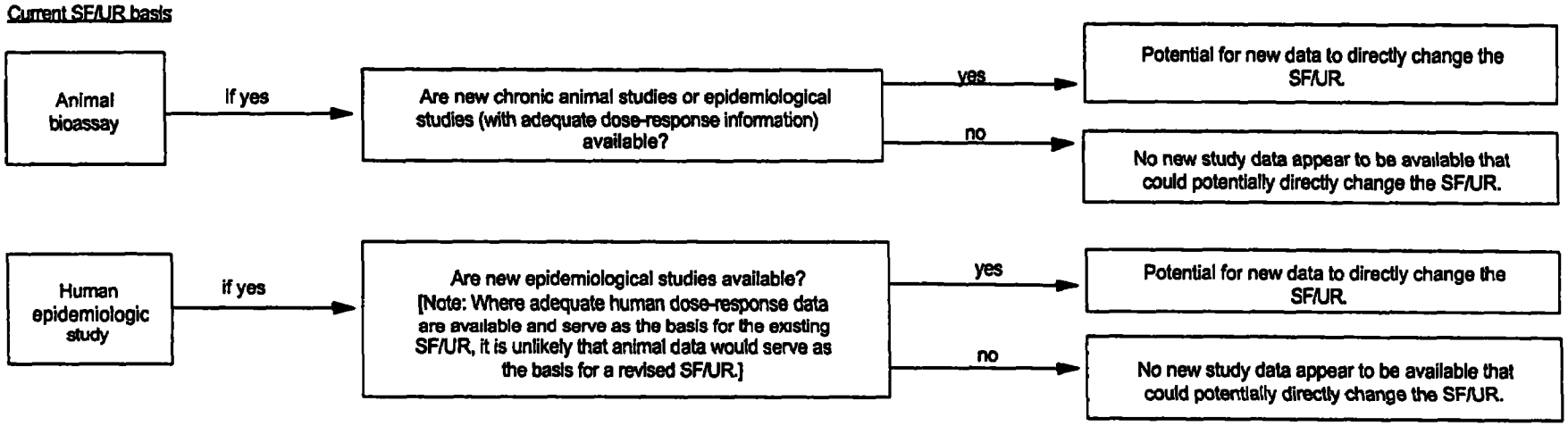


IRIS Oral Cancer Slope Factor (SF) or Inhalation Cancer Unit Risk (UR)

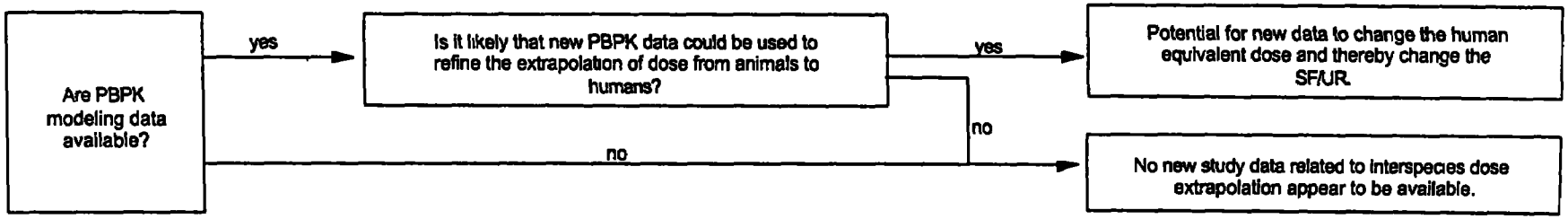
(1) Does a more recent health assessment suggest support for an alternative SF/UR?



(2) Does a screen of the more recent literature reveal studies that could potentially support revision of the IRIS SF/UR?



(3) Does a screen of the more recent toxicokinetic data support a revision of interspecies extrapolation?



IRIS Weight-of-Evidence (WOE) Classification as to Human Carcinogenicity

(1) Does a more recent health assessment suggest support for a different WOE classification?

Comparison of existing IRIS WOE classification to: NCEA provisional assessment; pesticide RED; IARC monographs; NTP Report on Carcinogens

- Alternative WOE designation identified → Potential for new study data to produce a change in the WOE classification
- No WOE designation identified that significantly differed from IRIS → No indication of significant new study data that would change the WOE classification

(2) Does a screen of the more recent literature reveal studies that could potentially support revision of the WOE classification?

A
Human Carcinogen
(sufficient evidence of carcinogenicity in humans)

- if yes → Because sufficent positive evidence of human carcinogenicity is required to classify a chemcial as an "A" carcinogen, new carcinogenicity studies are unlikely to change EPA's cancer assessment.

B1 or B2
Probable Human Carcinogen
(B1: limited evidence of carcinogenicity in humans;
B2: Sufficient evidence of carcinogenicity in animals with inadequate or lack of evidence in humans)

- if yes → Are new epidemiological studies or extensive new mechanistic data available?
  [Note: The existing animal bioassay data for "B" carcinogens is generally sufficient to demonstrate carcinogenic potential in animals. Only adequate human evidence or extensive mechanistic data would likely change the WOE classification (e g., demonstration of carcinogenicity in humans, or determination that carcinogenic action in experimental models is not relevant to humans.]
  - yes → New study data are available that could potentially change the WOE classification.
  - no → No new study data appear to be available that could potentially change the WOE classification.

C
Possible Human Carcinogen
(Limited evidence of carcinogenicity in animals and inadequate or lack of human data)

- if yes → Are new positive animal or epidemiological data or extensive mechanistic data available?
  [Note: The evidence for carcinogenicity for "C" carcinogens is generally equivocal. Additional negative evidence is unlikely to change the WOE classification to "D". Only positive evidence of carcinogenicity from animal bioassays or epidemiological studies could potentially change the designation from "C" to "B" or "A." Extensive mechanistic data could "drop" the WOE designation to "D" or "E."]
  - yes → New study data are available that could potentially change the WOE classification
  - no → No new study data appear to be available that could potentially change the WOE classification.

D
Not Classifiable as to Human Carcinogenicity
(inadequate or no evidence)

- if yes → Are new animal or epidemiological data available?
  [Note: Positive evidence could potentially change the WOE classification to "C," "B," or even "A." Sufficient negative evidence could potentially change the designation to "E."]
  - yes → New study data are available that could potentially change the WOE classification.
  - no → No new study data appear to be available that could potentially change the WOE classification.

E
Evidence for Noncarcinogenicity for Humans

- if yes → Because substantial negative evidence of human carcinogenicity is required to classify a chemical as an "E" carcinogen, it is unlikely that new positive studies will be available to change EPA's existing cancer assessment.

Appendix F: Chemical Summaries

Evaluation of the Recent Literature and Determination of Currency for:
Acetonitrile (CAS No. 75-05-8)

Oral Reference Dose (RfD)
An oral RfD for acetonitrile is not available because EPA determined that the data were insufficient to support development of an RfD (latest assessment 1999). The oral RfD and supporting information previously on IRIS were withdrawn. A literature search conducted for the years 1998 to 2002 does not appear to contain study data that could be used to develop an RfD.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for acetonitrile was derived (1999) does not appear to contain study data that could potentially produce a change in the RfC. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for acetonitrile.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1999) does not appear to contain study data that could potentially produce a change in the WOE. One micronucleus study (2001) found that acetonitrile did not increase the incidence of micronucleated polychromatic erythrocytes in either mouse bone marrow or peripheral blood.

Unknown Relevance
Three documents were categorized as being of unknown relevance, including a study titled "Auto-immune Diseases and Chronic Acetonitrile Exposure" (1998).

Evaluation of the Recent Literature and Determination of Currency for:
Acrylonitrile (CAS No. 107-13-1)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A literature search conducted for the years 1997 to 2002 identified a 1998 update to a retrospective cohort study of workers exposed to acrylonitrile and a 2001 National Toxicity Program (NTP) study in which male and female B6C3F1 mice received acrylonitrile in water by gavage for 14 weeks or 2 years. A 90-day gavage toxicity study was identified while searching the NTP Management Status Report.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for acrylonitrile was derived (1991) does not appear to contain study data that could potentially produce a change in the RfC. A review of the Health Canada Assessment (1998) and a literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for acrylonitrile.

Oral Slope Factor (CSF)
The literature published since the CSF for acrylonitrile was derived (1987) contains study data that could potentially produce a change in the CSF.

The IRIS CSF is based on a 2-year study and two 18-month studies in which rats were exposed to acrylonitrile in drinking water (1980). A 1998 Health Canada Assessment identified no new studies that would be directly useful in the derivation of a CSF for acrylonitrile. A literature search conducted for the years 1997 to 2002 identified a 2001 NTP study in which male and female B6C3F1 mice received acrylonitrile in water by gavage for 2 years.

Inhalation Unit Risk (IUR)
The literature published since the IUR for acrylonitrile was derived (1987) appears to contain study data that could potentially produce a change in the IUR.

The IRIS IUR is based on a study of respiratory cancer incidences in textile workers (1980). A review of the Health Canada Assessment (1998) and a literature search conducted for the years 1997 to 2002 identified a 1998 study assessing cancer mortality and incidence among employees exposed to acrylonitrile in a nitrogen fixation plant, a 1998 update to a retrospective cohort study of workers exposed to acrylonitrile during fiber production, a 1998 epidemiology study of acrylonitrile workers, a 1999 historical cohort study of workers exposed to acrylonitrile in a chemical plant, and a 2001 reevaluation of the 1999 historical cohort study. A 1997 review paper noted that a follow-up to the 1980 study that served as the basis for the IUR has been published.

Evaluation of the Recent Literature and Determination of Currency for:
Acrylonitrile (CAS No. 107-13-1)
(continued)

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B1—probable human carcinogen) was derived (1987) contains study data that could potentially produce a change in the WOE.

An NTP Cancer Bioassay (2001) concluded from a gavage study in B6C3F1 mice that there was clear evidence of carcinogenicity. A literature search conducted for the years 1997 to 2002 identified two 1998 studies assessing cancer mortality and incidence among employees exposed to acrylonitrile, a 1998 review and meta-analysis of 25 epidemiologic studies of workers exposed to acrylonitrile, a 1998 study of possible epigenetic mechanisms in the brain of rats exposed to acrylonitrile, a 1998 genotoxicological monitoring study of workers exposed to acrylonitrile and/or dimethylformamide, a 1999 summary and evaluation of 12 epidemiology studies that evaluate central nervous system cancer in workers exposed to acrylonitrile, a 1999 genotoxicity study in male mice, a 1999 historical cohort study of cancer mortality in workers exposed to acrylonitrile and other substances, a 2000 study of the ability of acrylonitrile to induce morphological transformation and oxidative damage in Syrian hamster cells, and a 2001 reevaluation of lung cancer risk in a cohort study of workers exposed to acrylonitrile.

Unknown Relevance
Eight documents were categorized as being of unknown relevance, including a study titled "Addendum to Twenty Four Month Oral Toxicity Carcinogenicity Study of Acrylonitrile Administered in the Drinking Water Fischer to 344 Rats" (2000).

Evaluation of the Recent Literature and Determination of Currency for:
Adiponitrile (CAS No. 111-69-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified a 13-week inhalation toxicity study and fertility assessment in rats exposed to atmospheres containing adiponitrile (1990).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Twenty-four documents, many of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Thirteen-Week Inhalation Toxicity of Adiponitrile Vapor-Aerosol to Sprague Dawley Rats" (2000). The majority of the OTS submissions were studies conducted in the 1970s and early 1980s.

Evaluation of the Recent Literature and Determination of Currency for:
Aldicarb (CAS No. 116-06-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for aldicarb was derived (1992) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for aldicarb was derived based on four acute oral exposure studies in humans (1971, 1987, 1990, 1992). A literature search conducted for the years 1991 to 2002 identified a 1991 subchronic neurotoxicity study in male rats given aldicarb by oral gavage, a 1992 immunotoxicity study of aldicarb in mice exposed for 28 or 90 days, and a 1993 study in which male rats were exposed to aldicarb for up to 16 weeks.

Note: 14-day and 13-week oral toxicity studies were identified while searching the NTP Management Status Report; study dates were not provided.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1987) does not appear to contain study data that could potentially produce a change in the WOE. An International Agency for Research on Cancer (IARC) Monograph (1991) characterized aldicarb as Group 3—not classifiable as to carcinogenicity in humans. A review of the World Health Organization (WHO) Environmental Health Criteria (1991) and a literature search conducted for the years 1990 to 2002 identified two genotoxicity studies in animal and human cells (1996 and 1997).

Unknown Relevance
Seven documents were categorized as being of unknown relevance.

Note: The EPA Office of Pesticide Programs (OPP) Web site provides the "Index of Cleared Science Reviews" for aldicarb, including a 1996 developmental neurotoxicity study in rats.

Note: Because of the large number of references found in the literature search (approximately 840), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Aldrin (CAS No. 309-00-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for aldrin was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for aldrin.

Note: 14-day and 13-week oral toxicity studies were identified while searching the NTP Management Status Report; study dates were not provided.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for aldrin was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF. A review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for aldrin.

Inhalation Unit Risk (IUR)
The literature published since the IUR for aldrin was derived (1987) contains study data that could potentially produce a change in the IUR.

The IRIS IUR is based on a 2-year and an 80-month dietary study in mice (1965, 1978). A review of the ATSDR Toxicological Profile (2000) identified two series of retrospective cancer mortality studies with follow-ups, including studies published in 1991, 1992, 1995, 1997. A literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of a IUR for aldrin.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1987) contains study data that could potentially produce a change in the WOE. A review of the ATSDR Toxicological Profile (2000) identified two series of retrospective cancer mortality studies with follow-ups, including studies published in 1991, 1992, 1995, 1997. A literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Note: The International Agency for Research on Cancer (IARC) Monograph (1987) classified aldrin as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
One document was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Ally (CAS No. 74223-64-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ally was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for ally.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Five documents were categorized as being of unknown relevance. Among these studies is an initial submission to EPA Office of Toxic Substances (OTS) entitled "Embryo-Fetal Toxicity & Teratogenicity Study of Metsulfuron-Methyl in Rats with Cover Letter Dated 08/20/92."

Note: Because of the large number of references found in the literature search (more than 1,100), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Allyl alcohol (CAS No. 107-18-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for allyl alcohol was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for allyl alcohol was derived based on a subchronic oral study in rats (1978). A literature search conducted for the years 1985 to 2002 found one reproductive toxicity study in rats (1990) and one chronic carcinogenicity study in rats (1987).

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Eleven studies were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 400), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

IEvaluation of the Recent Literature and Determination of Currency for:
Ametryn (CAS No. 834-12-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ametryn was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an oral RfD for ametryn.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: A literature search conducted for the years 1986 to 2002 identified a mammary tumorigenesis study of ametryn in rats (1994).

Unknown Relevance
Five studies were categorized as being of unknown relevance, including one titled "Two Generation Study on the Effect of the Triazine Herbicide Ametryne in Rats."

Evaluation of the Recent Literature and Determination of Currency for:
4-Aminopyridine (CAS No. 504-24-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Four documents were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 550), search results were limited with a secondary search in EndNote to identify references containing both the CAS number or common name of the chemical and common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Note: Much of the literature identified is centered around the effects of 4-aminopyridine in the pharmacological dose range—looking at effects in central nervous and neuromuscular systems and mechanism of action associated with those systems.

Evaluation of the Recent Literature and Determination of Currency for:
Amitraz (CAS No. 33089-61-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for amitraz was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for amitraz was derived based on a 2-year oral dietary study in dogs (1972). The EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) (1995) provides an RfD derived from an unpublished 2-year oral toxicity study in dogs (study date not provided). Comparison of the summaries of the dog studies in IRIS and the RED suggest that they are the same study. A literature search conducted for the years 1994 to 2002 identified no new studies that would be directly useful in the derivation of an oral RfD for amitraz.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: The OPP RED reported that EPA's Cancer Assessment Group and Health Effects Division Cancer Peer Review Committee classified amitraz as Group C—possible human carcinogen (1986, 1990).

Unknown Relevance
Four studies were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Ammonium acetate (CAS No. 631-61-8)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain information that could potentially produce a change in the WOE classification. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Four studies were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Ammonium sulfamate (CAS No. 7773-06-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ammonium sulfamate was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for ammonium sulfamate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Aniline (CAS No. 62-53-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: Health Canada developed a tolerable daily intake (TDI) (0.007 mg/kg/day) in 1993 based on CIIT, 1982.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for aniline was derived (1990) does not appear to contain study data that could potentially produce a change in the RfC. Review of Health Canada's 1993 assessment and a literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for aniline.

Oral Slope Factor (CSF)
The literature published since the CSF for aniline was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF. Review of Health Canada's 1993 assessment and a literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for aniline.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1990) does not appear to contain study data that could potentially produce a change in the WOE classification. Review of Health Canada's 1993 assessment, which classified aniline as a Group III—possibly carcinogenic to humans—and a literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Four documents were categorized as being of unknown relevance. Among these studies are an initial submission to EPA Office of Toxic Substances (OTS) titled "Final Report & Addendum, Aniline - Dominant Lethal Study in the Rat" and a study titled "Profound methemoglobinemia induced by dermal and inhalation exposure to aniline dye."

Note: Because of the large number of references found in the literature search (more than 1,000), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. References addressing aniline hydrochloride or other chemicals with aniline in their name were coded 8.

Evaluation of the Recent Literature and Determination of Currency for:
Antimony (CAS No. 7440-36-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for antimony was derived (1985) appears to contain study data that could potentially produce a change in the RfD. Review of the ATSDR Toxicological Profile (1992), a literature search conducted for the years 1991 to 2002, and submissions to the IRIS Submissions Desk identified new studies that would be potentially useful in the derivation of an RfD for antimony.

The IRIS RfD for antimony was derived based on a chronic oral bioassay in rats (1970). The ATSDR Toxicological Profile (1992), literature search conducted for the years 1991 to 2002, and submissions to the IRIS Submissions Desk included a 90-day drinking water study of potassium antimony tartrate in rats (1998), a 90-day dietary study of antimony trioxide in rats (1999), a 13-week intraperitoneal study of potassium antimony tartrate in rats and mice conducted by the National Toxicology Program (NTP) (1992), and a 90-day feeding study of antimony trioxide in rats (1997; unpublished).

Note: ATSDR, in its 1992 Toxicological Profile, evaluated the noncancer oral toxicity data for antimony, but did not derive a chronic oral minimal risk level (MRL) because, at the lowest dose tested in animals, decreased lifespan was observed. ATSDR does not consider this an appropriate basis for a chronic-duration MRL. The National Center for Environmental Assessment (NCEA) (1999) developed a provisional subchronic RfD for antimony (2×10^{-4} milligrams per kilogram body weight per day [mg/kg/day]) based on a 90-day drinking water study of antimony potassium tartrate in the rat.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: Review of the ATSDR Toxicological Profile (1992), a literature search conducted for the years 1991 to 2002, and submissions to the IRIS Submission Desk identified a 90-day and 12-month inhalation study of antimony trioxide in the rat (1994) and a mortality study of antimony smelter workers (1995). ATSDR, in its 1992 Toxicological Profile, evaluated the noncancer inhalation toxicity data for antimony, but did not derive a chronic inhalation MRL because, at the lowest dose tested in animals and humans, the effects were considered to be serious and ATSDR does not consider this an appropriate basis for a chronic MRL. NCEA (1999) developed a provisional subchronic inhalation RfC for antimony (4×10^{-4} milligrams per cubic meter [mg/m^3]) based on a 13-week inhalation study of antimony trioxide in the rat.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A literature search conducted for the years 1991 to 2002 identified two mortality studies of antimony smelter workers (1994, 1995).

Evaluation of the Recent Literature and Determination of Currency for:
Antimony (CAS No. 7440-36-0)
(continued)

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In a 1999 Provisional Assessment prepared by NCEA, the evidence for carcinogenicity of antimony was was characterized as inconsistent and insufficient. A literature search conducted for the years 1991 to 2002 identified a comparison of the clastogenic effects of antimony trioxide in mice *in vivo* following acute and chronic exposure (1992).

Unknown Relevance
Five documents were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 1,100), search results were limited with a secondary search in EndNote to identify references containing common laboratory species or toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as NA. References *containing* laboratory species or toxicological terms were coded "labanimal". Because a large number of references remained, references coded "labanimal" were searched to identify those references containing the CAS number for antimony. References identified in this search were coded. The current IRIS RfD for antimony is based on a study of potassium antimony tartrate. As such, the search in EndNote for antimony's CAS number may have excluded studies of antimony compounds. As such, a third search in EndNote identified the references coded "labanimal" that also contained "chronic," "subchronic," or "subacute," and "antimony". References identified in this search were coded.

Evaluation of the Recent Literature and Determination of Currency for:
Antimony trioxide (CAS No. 1309-64-4)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A literature search conducted for the years 1993 to 2002 identified a 90-day feeding study of antimony trioxide in rats (1999).

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for antimony trioxide was derived (1995) does not appear to contain study data that could potentially produce a change in the RfC. A literature search conducted for the years 1993 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for antimony trioxide.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1989) classified antimony trioxide as group B2—possibly carcinogenic to humans. A literature search conducted for the years 1993 to 2002, identified three studies which could potentially influence the derivation of a WOE classification. A 1994 study of antimony trioxide administered to mice by gavage monitored for chromosomal aberrations in bone marrow and sperm head abnormalities in germ cells. A 1997 study measured RNA activity following exposure to antimony trioxide in human hepatoma cells. A 1998 study assessed genetic toxicity of antimony trioxide in mice and rats after exposure by gavage.

Unknown Relevance
Two documents were categorized as being of unknown relevance, including a study titled "Carcinogenicity and Toxicity of Inhaled Antimony Trioxide and Antimony Ore Concentrate in Rats" (2000).

Evaluation of the Recent Literature and Determination of Currency for:
Apollo (CAS No. 74115-24-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for apollo was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for apollo.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
One document was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Arsenic, inorganic (CAS No. 7440-38-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for arsenic was derived (1990) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for arsenic was derived based on chronic oral exposure studies in humans (1968, 1977). EPA published in the Federal Register (January 22, 2001) a summary of health effects studies considered in revising the National Primary Drinking Water Regulations for arsenic. Of these, ten studies published between 1990 and 2000 considered noncancer effects of drinking water exposure in humans and two studies discussed noncancer effects of occupational exposures to arsenic (1995, 1998).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the oral slope factor was derived (1994) contains study data that could potentially produce a change in the WOE.

The IRIS CSF for arsenic was derived based on studies of the development of skin cancers after exposure to arsenic in drinking water (1968, 1977). EPA published in the Federal Register (January 22, 2001) a summary of health effects studies considered in revising the National Primary Drinking Water Regulations for arsenic. Of these, six studies published between 1996 and 1998 considered the carcinogenicity in humans of drinking water exposure to arsenic. As noted in the Federal Register, EPA chose to develop quantitative risk estimates based on the Taiwan studies published between 1989 and 1992.

Inhalation Unit Risk (IUR)
The literature published since the IUR was derived (1994) contains study data that could potentially produce a change in the IUR.

The IRIS IUR for arsenic was derived based on studies of the development of lung cancers in humans after exposure to arsenic (1982, 1983). Review of the ATSDR Toxicological Profile (2000) identified a number of epidemiology studies examining inhalation exposures to arsenic and increases in the risk of lung cancer, including six studies completed between 1995 and 1997. A literature search conducted for the years 1999 to 2002 identified a quantitative risk assessment of health risks (including cancer) associated with occupational exposure to arsenic (1997) and a study of the exposure-response curve for respiratory cancer in copper smelter workers exposed to arsenic (2000).

Evaluation of the Recent Literature and Determination of Currency for:
Arsenic, inorganic (CAS No. 7440-38-2)
(continued)

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (A—human carcinogen) was derived (1994) does not appear to contain study data that would likely support a change in the WOE.

EPA published in the Federal Register (January 22, 2001) a summary of the evidence for human carcinogenicity of arsenic in support of revisions to the National Primary Drinking Water Regulations for arsenic. EPA concluded that "inorganic arsenic is a multi-site human carcinogen by the drinking water route," and that "the weight of evidence for ingested arsenic as a causal factor of carcinogenicity is much greater now than a decade ago."

Unknown Relevance
No documents were categorized as being of unknown relevance.

Note: The IRIS summary for inorganic arsenic included an RfD, CSF, IUR, and WOE designation. A Federal Register notice, published by EPA, provided a summary of health effects studies considered in revising the National Primary Drinking Water Standards. This summary included new study data relevant to the derivation of the RfD, CSF, and WOE designation, but not the IUR. Therefore, the literature search targeted studies of inhalation exposures that might be relevant to the derivation of a revised IUR. As such, TOXLINE, PUBMED, and CANCERLIT were searched using the CAS number for arsenic, "inhalation," and terms that apply to cancer endpoints, including cancer, carcinog*, tumor*, oncogen*, neoplasm*, mutag*, mutat*, and genotox*. CCRIS and TSCATS were searched by CAS number alone, however, only studies of inhalation exposures and cancer endpoints were entered into the EndNote database for inorganic arsenic.

Evaluation of the Recent Literature and Determination of Currency for:
Arsine (CAS No. 7784-42-1)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for arsine was derived (1993) contains study data that could potentially produce a change in the RfC.

The IRIS RfC for arsine was derived based on a 13-week and 28-day inhalation study in rats, mice, and hamsters (1989) and a 12-week inhalation study in mice (1990). A literature search conducted for the years 1992 to 2002 identified a 1992 study of arsine gas toxicity in hamsters, mice, and rats after inhalation exposures ranging from 0.5 hr to 90-days.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized arsine as Group 1—carcinogenic to humans.

Unknown Relevance
Three documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Assure (CAS No. 76578-14-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for assure was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for chemical.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1988) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Seven documents were categorized as being of unknown relevance. Among these, one study was titled "Letter from Dupont Chem to USEPA Regarding Subchronic Dietary Toxicity of Propanoic Acid* in Mice with Cover Letter and Attachments."

Note: Because of the large number of references found in the literature search (approximately 5,000), search results were limited with a secondary search in EndNote to identify references containing both the CAS number and common name of the chemical (reducing references to approximately 435). A tertiary search, conducted in EndNote, to identify common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag* yielded approximately 240 references. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Azobenzene (CAS No. 103-33-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A 90-day dosed-feed toxicity study was identified during a search of the NTP Management Status Report.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for azobenzene was derived (1988) does not appear to contain study data that could potentially produce a change in the CSF. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for azobenzene.

Inhalation Unit Risk (IUR)
The literature published since the IUR for azobenzene was derived (1988) does not appear to contain study data that could potentially produce a change in the IUR. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for azobenzene.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1988) does not appear to contain study data that could potentially produce a change in the WOE.

The IRIS WOE for azobenzene was based on evidence of carcinogenicity in a rat bioassay, genotoxicity, and potential for conversion in the stomach to the carcinogen benzidine. A literature search conducted for the years 1989 to 2002 identified additional studies of the mutagenic potential of azobenzene, including the findings in micronucleus assays (1990) and in the Ames assay (1994). An International Agency for Research on Cancer (IARC) Monograph (1987) characterized azobenzene as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
A 1991 study titled "Evaluation of Teratogenicity of Certain Azo and Azoxy Compounds through Dominant Lethal Studies" was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Barium cyanide (CAS No. 542-62-1)

Oral Reference Dose (RfD)
The RfD for barium cyanide was withdrawn in 1993. The literature published since 1993 does not appear to contain study data that would support the derivation of an RfD. A literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for barium cyanide.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Baythroid (CAS No. 68359-37-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for baythroid was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for baythroid.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Eleven documents were categorized as being of unknown relevance. Among these studies is "Four Toxicity Studies with Cyfluthrin in Rats" (1992).

Evaluation of the Recent Literature and Determination of Currency for:
Benefin (CAS No. 1861-40-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for benefin was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for benefin.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Benomyl (CAS No. 17804-35-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for benomyl was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for benomyl was derived based on a three-generation reproduction study in rats (1968). The World Health Organization (WHO) Environmental Health Criteria (1993) for benomyl identified a 1990 two-generation reproduction study in rats fed diets containing benomyl. The WHO document also identified studies published in 1988 and 1991 that evaluated the reproductive effects of benomyl administered to male rats by gavage.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In Table 1 of the Ninth Report on Carcinogens (2001), the National Toxicology Program (NTP) classified benomyl as a probable carcinogen based on a 1995 study of Benlate DF with Flusilazole and Chlorothalonil.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Bidrin (CAS No. 141-66-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for bidrin was derived (1986) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for bidrin (0.001 milligrams per kilogram body weight per day [mg/kg/day]) was derived based on a three-generation rat reproduction study published in 1965. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for bidrin. However, the EPA Office of Pesticide Programs (OPP) risk assessment (1999) produced for the Reregistration Eligibility Decision (RED) presented an oral RfD of 0.00002 mg/kg/day based on a combined chronic toxicity and carcinogenicity study in rats. The citation for the chronic toxicity study that served as the basis for the RED RfD was not provided; however, a comparison of the principal studies used to develop the IRIS and RED RfDs revealed differences in the lowest-observed-adverse-effects-levels (LOAELs) (0.05 mg/kg/day and 0.02 mg/kg/day, respectively) and in the critical effects (inhibition of plasma cholinesterase and inhibition of plasma, brain, and RBC cholinesterases, respectively). This suggests that new study data were available to OPP for their assessment of bidrin.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Biphenthrin (CAS No. 82657-04-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for biphenthrin was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for biphenthrin.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: One study (1997) observed tumors of the urinary bladder (initially reported as leiomyosarcomas) in Swiss Webster mice when fed biphenthrin in the diet for 604 to 644 days.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Three documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
1,1-Biphenyl (CAS No. 92-52-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,1-biphenyl was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 1,1-biphenyl.

Inhalation Reference Concentration (RfC)
An IRIS RfC is not available because EPA determined that data were inadequate for derivation of an RfC (latest assessment 1990). The literature published since 1990 does not appear to contain study data that could be used to develop an RfC for 1,1-biphenyl.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could produce a change in the WOE.

A literature search conducted for the years 1989 to 2002 identified a 1989 study investigating changes in DNA synthesis levels and morphology in F344 rats following oral administration of biphenyl; a 1989 genotoxicity study using the rat hepatocyte DNA-repair test; a 1992 study investigating liver enzyme-mediated mutagenicity detected in Salmonella typhimurium and Chinese hamster V79 cells; and a 1997 study of the *in vivo* genotoxicity of biphenyl in CD-1 male mouse stomach, liver, kidney, bladder, lung, brain, and bone marrow (positive and negative findings).

Unknown Relevance
Eight documents, three of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Initial Submission: 90-day Inhalation Toxicity Study of Biphenyl (99+% purity) in Cd1 Mice (final report)."

Note: Too many references to download were found while searching Toxline with "word variants" (over 8,500) or "exact words" (over 3,500) with chemical name searching. Therefore, the search was conducted using only the CAS number. Because of the large number of references found in the literature search (approximately 900), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Bis(2-chloroethoxy)methane (CAS No. 111-91-1)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified one subchronic toxicity study (1990) in which bis(2-choroethoxy)methane was administered by gavage in corn oil to Sprague-Dawley rats for 90 days.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Three documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: Bis(2-chloroisopropyl) ether (CAS No. 39638-32-9/108-60-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for bis(2-chloroisopropyl)ether was derived (1989) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for bis(2-chloroisopropyl)ether.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) characterized bis(2-chloroisopropyl)ether as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
Four documents, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Note: The CAS number changed from 39638-32-9 to 108-60-1 on June 6, 2000. Both CAS numbers were considered in the literature search.

Evaluation of the Recent Literature and Determination of Currency for:
Bisphenol A (CAS No. 80-05-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for bisphenol A was derived (1988) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for bisphenol A was derived based on a chronic oral bioassay in rats, published by NTP in 1982. A literature search conducted for the years 1987 to 2002 identified several chronic and subchronic toxicity studies as well as several developmental and reproductive studies. Among these are a 13-week subchronic toxicity study in male and female B6C3F1 mice fed bisphenol A in their diet (1994); a lifetime exposure study in male Sprague-Dawley CD rats fed bisphenol A in their diet (1999); a two-generation reproductive toxicity study in male and female Crj: CD (SD) IGS rats administered bisphenol A via gastric intubation (2001); and a three-generation reproductive, oral toxicity study in Sprague-Dawley rats that reported an adult systemic no-observable-adverse-effect-level (NOAEL) of 5 milligrams per kilogram body weight per day (mg/kg/day) and reproductive/postnatal NOAEL of 50 mg/kg/day (2001). In addition, according to a letter submitted by the Society of the Plastics Industry, Inc. to the IRIS Submission Desk a two-generation reproductive toxicity study (1999) exists.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: According to a letter submitted by the Society of the Plastics Industry, Inc. to the IRIS Submission Desk a 13-week aerosol toxicity study with Fisher 344 rats (1988) exists.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1987 to 2002 identified mutagenicity tests (with both positive and negative findings). Several studies examined the relationship between estrogenicity and cell transforming activity. Among these are studies evaluating sister chromatid exchange and chromosome aberration assays in Chinese hamster ovary cells (1989); *in vivo* DNA adduct formation in CD1 male rats (1995); aneuploidogenic potential in cultured Chinese hamster V79 cells (1997); cellular transformation, aneuploidy, and DNA adduct formation in cultured Syrian hamster embryo cells (1998); cell-transforming activity and estrogenicity in Syrian hamster embryo cells (2001); endocrine disruption in Chinese hamster V79 cells and Sertoli cells in rats (2001); and mutagenicity in human RSa cells (2001).

Evaluation of the Recent Literature and Determination of Currency for:
Bisphenol A (CAS No. 80-05-7)
(continued)

Unknown Relevance
Twenty documents, eleven of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Support: Final Report, 3-Generation Reproductive Toxicity Evaluation of Bisphenol A Administered in Feed to Cd (Sprague-Dawley) Rats," "Support: Evaluation of Reproductive Organ Development in Cf-1 Mice Following Prenatal Exposure to Bisphenol A," "Initial Submission: Bisphenol A: 13-Week Aerosol Toxicity Study with Fischer 344 Rats (Final Report) (1992)," and "Bisphenol A: 13-Week Aerosol Toxicity Study with Fischer 344 Rats (Final Report) (1988)." The literature search also identified two ongoing listed in the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services).

Note: Because of the large number of references found in the literature search (approximately 600), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for: Bromodichloromethane (CAS No. 75-27-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for bromodichloromethane was derived (1987) may contain study data that could potentially produce a change in the RfD.

The IRIS RfD for bromodichloromethane was derived based on a chronic gavage bioassay in mice (1987). ATSDR updated the Toxicological Profile for bromodichloromethane in 1989. ATSDR derived an oral minimal risk level (MRL) based on the same 1987 study used to derive the IRIS oral RfD. A literature search conducted for the years 1988 to 2002, however, identified two 2-year feeding studies in Wistar rats (1992, 1995), a 52-week drinking water study in F344 rats (1995), a prospective study of pregnant women exposed to bromodichloromethane and other trihalomethanes (THMs) in drinking water (1998), two retrospective cohort studies of women exposed to bromodichloromethane and other THMs in drinking water (2000, 2001), and eight reproductive/developmental toxicity studies in rats (1999, 2000, 2001) and rabbits (2001) that could potentially produce a change in the RfD for bromodichloromethane.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1998 to 2002 identified a 1-year bioassay in mice exposed to bromodichloromethane vapor published in 2001.

Oral Slope Factor (CSF)
The literature published since the CSF for bromodichloromethane was derived (1992) may contain study data that could potentially produce a change in the CSF.

The IRIS CSF for bromodichloromethane was derived based on a 2-year carcinogenicity study in mice administered bromodichloromethane in corn oil by gavage (1987). The International Agency for Research on Cancer (IARC) Monograph on bromodichloromethane (1999) cites two 2-year feeding studies in rats (1992, 1995) and a 52-week drinking water study in rats (1995). A literature search conducted for the years 1988 to 2002 identified a 2-year gavage study in rats and mice (1993) not cited in the IARC Monograph. These studies could potentially produce a change in the CSF for bromodichloromethane.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A literature search conducted for the years 1998 to 2002 identified a 1-year bioassay in mice exposed to bromodichloromethane vapor published in 2001.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1992) does not appear to contain study data that could potentially produce a change in the WOE classification. In 1999, consistent with the EPA's WOE designation, IARC classified bromodichloromethane as a Group 2B—possibly carcinogenic to humans.

Evaluation of the Recent Literature and Determination of Currency for:
Bromodichloromethane (CAS No. 75-27-4)
(continued)

A literature search conducted for the years 1988 to 2002 identified no new studies that would likely produce a change in the WOE classification. As was concluded in the IRIS assessment conducted in 1992, there are no adequate epidemiologic studies to assess the carcinogenic potential of bromodichloromethane in humans, and animal bioassays provide some positive evidence of carcinogenic potential. The literature search identified the following additional studies of the carcinogenic and mutagenic potential of bromodichloromethane: two 2-year feeding studies in Wistar rats (1992, 1995); a 2-year gavage study in F344/N rats and B6C3F1 mice (1993); a 52-week drinking water study in rats (1995); a short-term carcinogenicity study (1998); findings of sister-chromatid exchanges (1991, 1993) and chromosomal aberrations (1996); and a study of genotoxic potential (1997). Some negative mutagenicity studies also were identified (1995, 1996, 1997).

Unknown Relevance
Twenty-five studies, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Chronic toxicity studies of Tbm, Dbcm, and Bdcm in Wistar rats" (1988); "Carcinogenic activity of drinking water as related to the tumor initiating and promoting activity of trihalomethanes" (1988); "Public drinking water contamination and birth weight, prematurity, fetal deaths, and birth defects" (1996); "The association of drinking water source and chlorination by-products with cancer incidence among postmenopausal women in Iowa: a prospective cohort study" (1997); and "Evaluation of the potential immunotoxicity of bromodichloromethane in rats and mice" (1999). The literature search also identified one ongoing effort listed in the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services).

Note: A literature search conducted for the years 1988 to 2002 identified two studies carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for bromodichloromethane (1997, 1998).

Note: Because of the large number of references found in the literature search (approximately 450), search results were limited with a secondary search in EndNote to identify references containing common laboratory species or toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
p-Bromodiphenyl ether (CAS No. 101-55-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could potentially produce a change in the WOE classification.

The World Health Organization (WHO) Environmental Health Criteria (1994) did not cite any new studies since the IRIS WOE classification was derived. A literature search conducted for the years 1993 to 2002 identified no new studies that could potentially produce a change in the WOE classification.

Unknown Relevance
One study was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Bromoform (CAS No. 75-25-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for bromoform was derived (1987) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for bromoform was derived based on a subchronic oral gavage bioassay in F344/N rats conducted by the National Toxicology Program (NTP) (1989). ATSDR published a toxicological profile for bromoform in 1990. ATSDR derived an oral minimal risk level (MRL) based on a chronic study in mice and rats published by NTP (1988). A literature search conducted for the years 1989 to 2002 identified the 2-year NTP gavage study in F344 rats and B6C3F1 mice (1989); a reproductive toxicity study in Swiss CD-1 mice administered bromoform in corn oil via gavage (1989); two developmental toxicity studies in F344 rats (1992) and CD-1 mice (2001); and a prospective study of pregnant women exposed to bromoform and other trihalomethanes (THMs) in drinking water (1998).

Note: The IRIS RfD verification date is listed as August 13, 1987, although the principal study (13-week NTP study) was published in 1989. This apparent discrepancy reflects the fact that the IRIS summary was based on a draft form of the NTP bioassay. In 1990, the citation was updated to reflect the final NTP bioassay (NTP 1989).

Inhalation Reference Dose (RfC)
An IRIS RfC is not available because EPA determined that data were inadequate for derivation of an RfC (latest assessment 1993). A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for bromoform.

Oral Slope Factor (CSF)
The literature published since the CSF for bromoform was derived (1989) does not appear to contain study data that could potentially produce a change in the CSF.

The IRIS CSF for bromoform was derived based on a draft 2-year NTP bioassay in rats (1988). [The final bioassay was published in 1989.] The International Agency for Research on Cancer (IARC) Monograph on bromoform (1999) does not cite new study data that would appear to produce a change in the CSF for bromoform. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for bromoform. Two publications (1989, 1993) related to a 2-year gavage study in F344 rates and B6C3F1 mice are reanalyses of data from the NTP bioassay.

Inhalation Unit Risk (IUR)
The literature published since the IUR for bromoform was derived (1989) does not appear to contain study data that could potentially produce a change in the IUR. The IARC Monograph (1999) does not cite new study data that would appear to produce a change in the IUR for bromoform. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of a IUR for bromoform.

Evaluation of the Recent Literature and Determination of Currency for:
Bromoform (CAS No. 75-25-2)
(continued)

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1989) may contain study data that could potentially produce a change in the WOE classification. In 1999, IARC classified bromoform as Group 3—not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1989 to 2002 identified a number of genotoxicity studies; both positive and negative responses were reported.

Unknown Relevance
Twenty-three studies, four of which were submissions to EPA's Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Reproductive risks from contaminants in drinking water" (1993); "Chlorination of drinking water and cancer incidence" (1994); "Reproductive and developmental effects of disinfection by-products in drinking water" (1996); "The association of drinking water source and chlorination by-products with cancer incidence among postmenopausal women in Iowa: a prospective cohort study" (1997); "Exposure to trihalomethanes and adverse pregnancy outcomes" (1998); and "Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review" (2000). For many sources, it was unclear whether bromoform was evaluated individually (many of these sources only note that trihalomethanes were studied).

Evaluation of the Recent Literature and Determination of Currency for:
Bromoxynil octanoate (CAS No. 1689-99-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for bromoxynil octanoate was derived (1987) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for bromoxynil octanoate was derived based on a 2-year dietary study in rats (1982). A Reregistration Eligibility Decision (RED) (for bromoxynil: see note below) was published in 1998. The RfD derived for the RED was based on a 1-year chronic oral toxicity study in dogs (using bromoxynil phenol as the test material) (1988, 1989). A literature search conducted for the years 1986 to 2002 identified developmental toxicity studies (using bromoxynil as the test material) in CD rats and CD-1 mice (1990), in Sprague-Dawley rats and Swiss-Webster mice (1991), and CD-1 mice (1995) not cited in the RED.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: The RED presented a CSF for bromoxynil based on an 18-month dietary study of bromoxynil in mice (1980) and a carcinogenicity study of bromoxynil phenol in mice (1994).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Six studies, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Note: The IRIS summary states the following concerning bromoxynil: "Bromoxynil exists as an acid but also as esters (e.g. octanoate). Subchronic studies indicate that there is no toxicological difference between these different forms of bromoxynil. The RfDs for all bromoxynil compounds will be based on the toxicity of bromoxynil alone, unless evidence to the contrary is found." As a result, the literature search for bromoxynil octanoate was expanded to include bromoxynil (CAS No. 1689-84-5).

Evaluation of the Recent Literature and Determination of Currency for:
Cacodylic acid (CAS. No. 75-60-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A literature search conducted for the years 1990 to 2002 identified a 2-year dietary study of the mechanism of action of bladder tumor induction in rats following a 10-week exposure to cacodylic acid (1999) and a developmental study in Sprague-Dawley rats (oral gavage) (1990).

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1990 to 2002 identified one 50-week drinking water study in mice (1998), a 2-year drinking water bioassay in male F344 rats (1999), and a study of the mechanism of action of bladder tumor induction following 10-week exposure of F344 rats to cacodylic acid (1999).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE (D—not classifiable as to human carcinogenicity) was derived (1991) may contain study data that could potentially produce a change in the WOE classification.

A literature search conducted for the years 1990 to 2002 identified several carcinogenicity bioassays (see description under oral CSF) and a number of genotoxicity studies, including evidence of DNA damage in *in vivo* studies of rats (1997) and mice (1999); genotoxicity in Chinese hamster cells (1992, 1997, 1998); mutagenicity in mouse cells (1993, 1997, 1998); and DNA single-strand breaks, DNA-protein cross-links, and chromosomal aberrations in human cells (1993, 1994, 1995, 1996, 1997).

Unknown Relevance
Twelve studies, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. For many sources, it was unclear whether cacodylic acid (a primary metabolite of arsenic) was evaluated individually (many of these sources only note that arsenic was studied).

Evaluation of the Recent Literature and Determination of Currency for:
Captafol (CAS No. 2425-06-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for captafol was derived (1987) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for captafol was derived based on a 1-year dietary study in dogs (1985). A literature search conducted for the years 1986 to 2002 identified a 1989 study of renal effects in F344 rats exposed to captafol in their diet for 2 years and a 1991 study of F344/DuCrj rats exposed to captafol in their diet for 13 weeks.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: The literature search conducted for the years 1986 to 2002 revealed two studies that might contribute to the development of a CSF for captafol: a 1990 study of dietary exposure to captafol for 104 weeks and a 1996 study of dietary exposure to captafol for 32 weeks.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The Health Effects Division of EPA Office of Pesticide Programs (OPP) assessed the carcinogenicity of captafol and categorized it as a Group 2B—probably human carcinogen (1993). An International Agency for Research on Cancer (IARC) Monograph (1991) listed captafol as Group 2A—probably carcinogenic to humans.

Unknown Relevance
Eight documents were categorized as being of unknown relevance, including four listings in OPP's "Index of Cleared Science Reviews" and two studies (1990, 1992) listed on the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services).

Evaluation of the Recent Literature and Determination of Currency for:
Carbaryl (CAS No. 63-25-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for carbaryl was derived (1985) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for carbaryl was derived based on a chronic dietary study in rats published in 1961. A review of the World Health Organization (WHO) Environmental Health Criteria for carbaryl (1994) identified four toxicity studies published after the derivation of the RfD for carbaryl: a 1-year dietary study in beagles that examined primarily hematological effects (1987); a 1-year dietary study in rats in which changes to body weight, food consumption, total cholesterol, liver weight, and kidney weight were observed (1991); and a developmental toxicity study in mice (1991).

A literature search conducted for the years 1993 to 2002 identified a 1995 study of reproductive effects in male albino rats exposed to carbaryl in their diets for 90 days; two 1997 studies of adult neural, immune, and reproductive function after perinatal exposure to carbaryl; and a 2001 study of bone ossification in juvenile rats exposed to carbaryl during pregnancy and lactation.

Inhalation Reference Concentration (RfC)
An inhalation RfC is not available because EPA determined that data were inadequate for derivation of an RfC (latest assessment 1991). The literature published since 1991 does not appear to contain study data that could be used to develop an RfC for carbaryl. A review of the WHO Environmental Health Criteria for carbaryl (1994) and a literature search conducted for the years 1993 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for carbaryl.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) listed carbaryl as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
Seven documents, including five listings in the EPA Office of Pesticide Programs (OPP) "Index of Cleared Science Reviews," were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Carbaryl (CAS No. 63-25-2)
(continued)

Note: Because of the large number of references found in the literature search (approximately 1,000), search results were limited with a secondary search in EndNote to identify references containing common laboratory species or toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Carbofuran (CAS No. 1563-66-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for carbofuran was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for carbosulfan. The literature search identified two 1997 letters in EPA's public docket relating to a peer review of the carbofuran RfD, as well as two 1998 studies on the pregnancy outcome of rats exposed to carbofuran during days 1 to 5 or days 7 to 14 of gestation.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The literature search conducted for the years 1986 to 2002 identified one study of the genotoxicity of carbofuran in human peripheral blood lymphocytes (1989); a study of non-genotoxic effects of carbofuran in rat liver epithelial cells (1997); a study of the cytotoxicity and genotoxicity of carbofuran in hamster V79 cells (1998); and a study of genotoxicity, cell growth, cell cycle, and apoptosis in hamster lung fibroblast cells (2001).

Unknown Relevance
Fifteen documents were categorized as being of unknown relevance. Among these are "Hepatorenal Toxicity of Nuvacron and Furadan in Mice," "Effect of Carbamates on Some Enzymes of Rat Liver and Kidney," "Carbofuran Toxicity and Clearance in the Isolated Perfused Rat Lung," and "Studies on Carcinogenicity of Furadan in ICR Mice by Chronic Ingestion." Several documents listed in the EPA Office of Pesticide Programs (OPP) "Index of Cleared Science Reviews" also were identified.

Note: Because of the large number of references found in the literature search (approximately 1,800), search results were limited with a secondary search in EndNote to identify references containing common laboratory species or toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Carbon disulfide (CAS No. 75-15-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for carbon disulfide was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. The IRIS RfD was derived based on an inhalation teratology study in rabbits (1981). A review of the Health Canada Assessment (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies of oral exposure to carbon disulfide. New studies of inhalation exposure to carbon disulfide that might be used to derive an oral RfD are discussed below.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for carbon disulfide was derived (1995) appears to contain study data that could potentially produce a change in the RfC.

The IRIS RfC for carbon disulfide was derived based on an occupational study (1983). In 1999, Health Canada derived a tolerable concentration (TC) based on the same principal study used to derive the IRIS RfC. A review of the Health Canada Assessment revealed an epidemiologic study of the effects of carbon disulfide on the peripheral nerves (1995) and an investigation of nerve function in workers exposed to carbon disulfide occupationally.

A literature search conducted for the years 1998 to 2002 identified a number of epidemiology studies of workers occupationally exposed to carbon disulfide (1998, 2000, 2001). The literature search also identified four studies of neurological effects and neurobehavioral effects in F344 rats exposed to carbon disulfide by inhalation for up to 13 weeks (1998), a study of atherogenic effects in C57BL6 mice (1999), and a study of neurotoxic effects in C57BL/6 mice exposed to carbon disulfide by inhalation for up to 20 weeks (2000).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Eleven documents were categorized as being of unknown relevance, including a submission to EPA Office of Toxic Substances (OTS) entitled "Internal Memorandum Regarding Mutagenicity Testing with Attachment" and nine documents pertaining to carbon disulfide and adduct formation, cytotoxicity, artherosclerosis, and inhalation toxicity listed in the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services).

Evaluation of the Recent Literature and Determination of Currency for:
Carbonyl sulfide (CAS No. 463-58-1)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An inhalation RfC is not available because EPA determined that data were inadequate for derivation of an RfC (latest assessment 1991). The literature published since 1991 does not appear to contain study data that could be used to develop an RfC for carbonyl sulfide. A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for carbonyl sulfide.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Nine documents were categorized as being of unknown relevance. Five of these were submissions to EPA Office of Toxic Substances (OTS), and the other four were listed in the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services).

Evaluation of the Recent Literature and Determination of Currency for:
Carbosulfan (CAS No. 55285-14-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for carbosulfan was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for carbosulfan.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: Five genotoxicity studies were identified in a literature search conducted for the years 1985 to 2002. Among these were a study of genotoxicity in an *in vivo* mouse bone marrow assay, two studies of chromosomal aberrations and sister chromatid exchanges in human lymphocytes, a study of *in vivo* chromosomal aberrations in rat bone marrow cells, and a study of mutagenic effects of carbosulfan in the Ames-test and yeast assay.

Unknown Relevance
Four documents were categorized as being of unknown relevance. Among these studies is "A Subchronic Feeding Study with Fmc 35001 in Rats."

Evaluation of the Recent Literature and Determination of Currency for:
Carboxin (CAS No. 5234-68-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for carboxin was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for carboxin.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: One genotoxicity study (1988) was identified.

Unknown Relevance
Two documents were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 280), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for: Chlorimuron-ethyl (CAS No. 90982-32-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for chlorimuron-ethyl was derived (1989) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for chlorimuron-ethyl.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Seven documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 500), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. This search yielded approximately 360 references, so search results were limited with a tertiary search in EndNote to identify references containing the CAS number and any synonym of chlorimuron-ethyl. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Chlorine (CAS No.7782-50-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for chlorine was derived (1993) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for chlorine.

Note: The EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) RfD (1995) for chlorine was derived based on the same National Toxicology Program (NTP) chronic drinking water study in F344/N rats, published in 1992, as the IRIS RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1992 to 2002 identified a 2-year inhalation toxicity study of chlorine gas in mice and rats (1995). In addition, the National Center for Environmental Assessment (NCEA) released an issue paper deriving a chronic RfC in 1999.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: Three studies were identified which examined the carcinogenic potential of chlorinated water in rats and mice (1992, 1993, 1997).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: One study (1995) was identified which evaluated the carcinogenicity of 2-year exposures to chlorine gas in mice and rats.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The 1995 RED for chlorine gas reports a WOE classification of Group D—not classifiable as to human carcinogenicity. An issue paper deriving a subchronic RfC was released by NCEA in 1999 and concluded that chlorine gas is not likely to be a human carcinogen. A 2000 International Agency for Research on Cancer (IARC) Monograph of disinfectants and disinfectant by-products reviewed the carcinogenicity of chlorinated water. A 2001 study of chlorinated water carcinogenicity, through examination of chromosomal aberrations, was also identified.

Evaluation of the Recent Literature and Determination of Currency for:
Chlorine (CAS No.7782-50-5)
(continued)

Unknown Relevance
Eleven documents were categorized as being of unknown relevance. Among these studies are "Letter from the Chlorine Inst Inc to USEPA Regarding a Two-year Chlorine Bioassay in Rats and Mice," "A Chronic Inhalation Toxicity Study of Chlorine in Female and Male B6C3F1 Mice and Fischer 344 Rats," "Support: Information Regarding a Chronic Inhalation Study in Rats and Mice," "Chronic Inhalation Toxicity Study on Chlorine in Non Human Primate," and "Acute and Long Term Pulmonary Toxicity after Accidental Chlorine Exposure."

Note: Because of the large number of references found in the literature search (approximately 3,200), search results were limited with a secondary search in EndNote to identify references containing the CAS number and any synonym of chlorine, yielding approximately 680 references. Because of the continued large number of references, search results were limited with a tertiary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
1-Chlorobutane (CAS No. 109-69-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could potentially produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in establishing a WOE classification. One mutagenicity study (1990) was identified that studied the effects of chlorobutane on chromosome aberration and sister chromatid exchange in Chinese hamster ovary cells.

Unknown Relevance
Nine documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
2-Chlorobutane (CAS No. 78-86-4)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
2-Chlorophenol (CAS No. 95-57-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2-chlorophenol was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. Review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 2-chlorophenol. the ATSDR Toxicological Profile addresses eight chlorophenols. The intermediate minimal risk level (MRL) is based on 1984 and 1985 drinking water studies of 2,4-dichlorophenol in Sprague-Dawley rats.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) classified 2-chlorophenol as Grou 2B—possibly carcinogenic to humans.

Unknown Relevance
Two documents were categorized as being of unknown relevance, both of which were submissions to EPA Office of Toxic Substances (OTS).

Evaluation of the Recent Literature and Determination of Currency for:
p-Chlorophenyl methyl sulfide (CAS No. 123-09-1)

Oral Reference Dose (RfD)
An oral RfD for p-chlorophenyl methyl sulfide is not available because EPA determined that the data were insufficient to support the development of an RfD (latest assessment 1992). The literature published since 1992 does not appear to contain study data that could be useful in the development of an RfD. A literature search conducted for the years 1991 to 2002 identified a 91-day dietary toxicity study in rats and mice (1993). An unpublished version of this study was evaluated by EPA in 1992 and was determined to be inadequate as the basis for the RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1991) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Coke oven emissions (CAS No. 8007-45-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
The literature published since the IUR for coke oven emissions was derived (1989) contains study data that could potentially produce a change in the IUR.

The IRIS IUR for coke oven emissions was derived based on an occupational study examining respiratory cancer in a cohort of steel workers exposed to coke oven emissions (benzene-soluble organics extracted from the particulate phase of coal tar pitch volatiles) (1975, 1976).

A literature search conducted for the years 1988 to 2002 identified nine additional mortality and cancer morbidity studies in aluminum workers (1991, 1994, 1995), coke gas plant workers (1992), steelworkers (1995), carbon workers (1997), and tar distillery workers and roofers (1997) that could potentially produce a change in the IUR; however, the extent to which exposure data are available and causal relationships identified in these studies is unknown.

Nonhuman data include a carcinogenicity study in rats exposed to coal tar pitch (1992), a study of tumor rates in rats exposed to coal tar pitch condensation aerosol (1994), and studies of skin cancer in mice exposed to coal tar pitch smoke (1996, 1997).

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (A—human carcinogen) was derived (1989) does not appear to contain study data that could produce a change in the WOE. The National Toxicology Program (NTP) (1981) and International Agency for Research on Cancer (IARC) Monograph (1987) also classify coke oven emissions as a known human carcinogen. A literature search conducted for the years 1988 to 2002 identified carcinogenicity studies (in humans and animals) as cited above, as well as multiple positive genotoxicity studies.

Unknown Relevance
Thirty-four documents, three of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "Basal cell epitheliomatosis of the face in a man who had handled pitch" and "The influence of the working environment on the respiratory system in coke factory workers."

Evaluation of the Recent Literature and Determination of Currency for:
Coke oven emissions (CAS No. 8007-45-2)
(continued)

Note: Coke oven emissions are a mixture of chemicals that are formed as a result of the distillation of coke from coal and other carbon products. Coke oven emissions include the synonyms coal tar and coal tar pitch. The IRIS summary identifies coal tar pitch volatiles (CASRN 65996-93-2) as the primary synonym for coke oven emissions. Therefore, the literature search reviewed studies related to coke oven emissions, coal tar, coal tar pitch, and coal tar pitch volatiles. Also, researchers quantify the toxicity of coke oven emissions by using exposure concentrations of certain components of coke oven emissions, frequently benzo(a)pyrene (BaP). This literature search includes studies that use BaP as a marker for coke oven emissions exposures, but not studies strictly related to the toxicity of BaP.

Multiple studies were identified evaluating health effects associated with dermal exposure to coal tar in the treatment of psoriasis. While not directly relevant to the IRIS IUR or WOE classification, study data may be useful in supporting IRIS evaluations.

Note: Because of the large number of references found in the literature search (approximately 730), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Cumene (CAS No. 98-82-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for cumene was derived (1997) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1996 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for cumene.

Inhalation Reference Concentration (RfC)
The literature published since the RfC for cumene was derived (1997) does not appear to contain study data that could potentially produce a change in the RfC.

The IRIS RfC for cumene was derived based on a 13-week inhalation study in rats (1995). A literature search conducted for the years 1996 to 2002 identified a 1997 developmental toxicity study in pregnant CD (Sprague-Dawley) rats and pregnant New Zealand white rabbits exposed to cumene vapor. An unpublished version of this study was considered in the 1997 IRIS assessment for cumene.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1997) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1996 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Six documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "Preliminary Results in Mouse Prechronic Inhalation Study of Cumene" and "An Analysis of Genotoxicity Assays Performed on Cumene" and a letter submitting information about a 14-week cumene study in rats.

Evaluation of the Recent Literature and Determination of Currency for:
Cyanazine (CAS No. 21725-46-2)

Oral Reference Dose (RfD)
An oral RfD for cyanazine is not available (latest assessment 1992). The oral RfD and supporting information previously on IRIS were withdrawn in 1992; according to the IRIS summary, a new RfD was in preparation by the RfD/RfC Work Group. A literature search conducted for the years 1991 to 2002 identified study data that may be useful in developing an RfD, specifically, a 2-year dietary study in Sprague-Dawley rats (2000) and a development toxicity study in rats (1999).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1991 to 2002 identified a 2-year dietary study in Sprague-Dawley rats evaluating the oncogenic potential of cyanazine.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1991 to 2002 identified several *in vitro* and *in vivo* mutagenicity studies, reporting no genotoxic effects in most systems tested (1993, 1996, 1998, 2000, and 2001), as well as one animal bioassay (mentioned in the CSF note above).

Unknown Relevance
Three documents, two of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Note: A secondary search in EndNote identified references containing: phytotox*, aquatic*, and ecotox*. References *containing* one of these search terms were coded as N/A.

Note: The EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) for cyanazine was voluntarily canceled in September 1995.

Evaluation of the Recent Literature and Determination of Currency for:
Cyanogen (CAS No. 460-19-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for cyanogen was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for cyanogen.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified a 1984 study investigating behavioral, physiologic, and pathologic effects in male rhesus monkeys and male Charles River rats exposed to cyanogen by inhalation for 6 hours/day, 5 days/week, for 6 months.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Cyclohexanone (CAS No. 108-94-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for cyclohexanone was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for cyclohexanone.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a two-generation reproductive toxicity study in CD Sprague-Dawley albino rats exposed to cyclohexanone vapors (1986) ; two inhalation developmental toxicity studies (1989 and 1992) in pregnant Sprague-Dawley rats and mated CD rats (1989, 1992) ; and a study evaluating development of spines on olfactory granule cells in rats exposed to cyclohexanone vapors (1988).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) assigned cyclohexanone a cancer classification of Group 3—not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1985 to 2002 identified an *in vitro* study of cyclohexanone mutagenicity in Chinese hamster ovary cells (1985).

Unknown Relevance
Eighteen documents, 12 of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Two-generation Rat Reproduction Study with Cyclohexanone via Inhalation," "Inhalation Teratogenicity with Cyclohexanone in Mice,"and "A Summary of the Results of 55 Chemicals Screened for Developmental Toxicity in Mice."

Evaluation of the Recent Literature and Determination of Currency for:
Cyclohexylamine (CAS No. 108-91-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for cyclohexylamine was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for cyclohexylamine was derived based on two chronic studies in rats (1976). A literature search conducted for the years 1986 to 2002 identified a study of morphological changes in male Wistar rats fed cyclohexylamine for up to 13 weeks (1990) and a 13-week dietary study investigating the metabolism and testicular toxicity of cyclohexylamine in rats and mice (1989). Both the 1989 and 1990 studies involved a single study group exposed at 400 milligrams per kilogram body weight per day (mg/kg/day), which was more than 10-fold higher than the lowest dose adminstered in the studies selected as the basis for the current RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1986 to 2002 identified two genotoxicity/mutagenicity studies (1986, 1989).

Unknown Relevance
Eight documents, four of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Initial Submission: Toxicity Studies on Cyclohexylamine (final report)" and "Cyclamate, Cyclohexylamine and Cardiovascular Toxicity in Man: an Initial Population Study."

Evaluation of the Recent Literature and Determination of Currency for:
Dalapon (sodium salt) (CAS No. 75-99-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for dalapon was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for dalapon.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Note: A secondary search in EndNote identified references containing: phytotox*, aquatic*, and ecotox*. References *containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Danitol (CAS No. 39515-41-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for danitol was derived (1993) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for danitol.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted from 1992 to 2002 identified three genotoxicity studies: one study (1995) testing the ability of danitol to induce micronuclei in both whole-blood and isolated human lymphocyte cultures; a second study (1996) testing for genotoxicity in Salmonella typhimurium, chromosome aberrations in Chinese hamster lung fibroblasts, and the induction of micronuclei in mouse cells; and a third study (1997) investigating the induction of micronuclei in rat bone marrow cells. Negative, weak, and positive genotoxic responses were reported.

Unknown Relevance
Nine studies, three of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
2,4-Diaminotoluene (CAS No. 95-80-7)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An inhalation RfC for 2,4-diaminotoluene (2,4-DAT) is not available because EPA determined that the data were inadequate for derivation of an RfC (latest assessment 1990). The literature published since 1990 does not appear to contain study data that could be used to develop an RfC. A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 2,4-DAT.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized 2,4-DAT as Group 2B—possible human carcinogen. The National Toxicology Program (NTP) Ninth Report on Carcinogens (2001) classified 2,4-DAT as "reasonably anticipated to be a human carcinogen." In addition, a literature search conducted for the years 1989 to 2002 identified several genotoxicity and mutagenicity studies, including *in vivo* genotoxicity testing using the rat micronucleus test (1991); analysis of DNA adduct formation (1992, 1993, 1994, 1995, 1996); chromosomal aberration induction studies (1990, 1991); microbial mutagenicity studies (1990, 1992, 2000); and Big Blue transgenic mouse mutation assays (1995, 1996). Overall, reported findings were positive for genotoxicity and mutagenicity. In addition, several studies evaluated possible mechanisms of carcinogenic action of 2,4-DAT (1990, 1992, 1995, 1996).

Unknown Relevance
Twenty documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Determination of the Reproductive Effects in Mice of Nine Selected Chemicals" and "The Carcinogenicity of Hair Dyes and Permanent Wave Preparations."

Evaluation of the Recent Literature and Determination of Currency for:
Dibenzofuran (CAS No. 132-64-9)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A Provisional Assessment deriving a provisional RfD was released by the National Center for Environmental Assessment (NCEA) in 1999. The provisional RfD was based on a 1940 repeat-dose toxicity study in rats. This study was identified as the only available toxicity study of dibenzofuran. A literature search conducted by NCEA for the period 1992 to January 1999 confirmed the absence of current toxicity data for dibenzofuran.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. NCEA released an issue paper in 1999 which concluded that the carcinogenicity of dibenzofuran cannot be determined. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Note: The literature search identified multiple references related to polychlorinated dibenzofurans, however, the IRIS summary specifically stated that polychlorinated dibenzofurans are not appropriate as a surrogate for assessing risks associated with dibenzofuran.

Evaluation of the Recent Literature and Determination of Currency for: Dibromochloromethane (CAS No. 124-48-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for dibromochloromethane was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for dibromochloromethane was derived based on a 13-week gavage bioassay in F344/N rats and B6C3F1 mice (1985). The ATSDR Toxicological Profile (1990) presented an oral minimal risk level (MRL) for dibromochloromethane based on the same study as the IRIS RfD. A literature search conducted for the years 1989 to 2002, however, identified a 90-day oral toxicity study in Sprague-Dawley rats (1990), a short-term reproductive and developmental toxicity screen using Sprague-Dawley rats (1996), and an epidemiologic study of spontaneous abortion in pregnant women exposed to dibromochloromethane and other trihalomethanes (THMs) via chlorinated drinking water (1998) that may be useful in the derivation of an RfD for dibromochloromethane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the oral CSF for dibromochloromethane was derived (1989) does not appear to contain study data that could potentially produce a change in the CSF.

The IRIS CSF for dibromochloromethane was derived based on a 104-week National Toxicology Program (NTP) gavage study in F344/N rats and B6C3F1 mice (1985). An International Agency for Research on Cancer (IARC) Monograph (1999) did not present new study data. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for dibromochloromethane.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1989) may contain study data that could produce a change in the WOE.

The IRIS WOE for dibromochloromethane was derived based on inadequate human data and limited evidence of carcinogenicity in animals (a 104-week gavage study in F344/N rats and B6C3F1 mice [1985]), together with positive mutagenicity data, and structural similarity to other trihalomethanes, which are known animal carcinogens. However, an IARC Monograph (1999) characterized dibromochloromethane as Group 3—not classifiable as to carcinogenicity in humans.

Evaluation of the Recent Literature and Determination of Currency for:
Dibromochloromethane (CAS No. 124-48-1)
(continued)

In addition, a literature search conducted for the years 1989 to 2002 identified new studies not included in the IARC Monograph that may be useful in establishing a WOE classification. These included an analysis of the NTP cancer bioassay findings for various chlorination byproducts (including dibromochloromethane) (1993) and several genotoxicity and mutagenicity studies, mostly reporting positive findings including chromosomal aberration induction studies (1990, 1991), a sister chromatid exchange induction study (1990), a DNA strand break study (1996), microbial mutagenicity studies (1998, 1999), and an *in vitro* genotoxicity study using the Comet assay in human whole blood cultures (1999). In addition, three studies evaluated possible mechanisms of carcinogenic action for dibromochloromethane (1996, 1997, 1998), including a liver tumor induction study (1998) in female B6C3F1 mice exposed to dibromochloromethane via gavage in corn oil for three weeks.

Unknown Relevance

Fifteen documents were categorized as being of unknown relevance. For many studies, it was impossible to determine if dibromochloromethane was tested separately from other THMs. Among these studies are "Assessment of the Toxic and Carcinogenic Potential of Disinfecting Water Supplies, Long-Term Rodent Studies of Chlorine, Chloramine, and Trihalomethanes," "Trihalomethanes in Drinking Water and Cancer Risk Assessment and Integrated Evaluation of Available Data in Animals and Humans," "The Association of Drinking Water Source and Chlorination By-Products with Cancer Incidence Among Postmenopausal Women in Iowa," and "Exposure to Trihalomethanes and Adverse Pregnancy Outcomes."

Evaluation of the Recent Literature and Determination of Currency for: Dibromodichloromethane (CAS No. 594-18-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1991) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Two documents were categorized as being of unknown relevance, "Toxicology of halogenated aliphatic hydrocarbons: Structural and molecular determinants for the disturbance of chromosome segregation and the induction of lipid peroxidation" and "The detection and evaluation of aneugenic chemicals."

Evaluation of the Recent Literature and Determination of Currency for:
p,p'-Dibromodiphenyl ether (CAS No. 2050-47-7)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) for p,p'-dibromodiphenyl ether was derived (1990) does not appear to contain study data that could potentially produce a change in the WOE classification. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of a WOE classification for p,p'-dibromodiphenyl ether.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Dicamba (CAS No. 1918-00-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for dicamba was derived (1988) appears to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for dicamba was derived based on a developmental study in rabbits (1978). A 1999 Federal Register[1] notice published by EPA Office of Pesticide Programs (OPP) related to the pesticide tolerance for dicamba on agricultural commodities includes a summary of the available toxicity studies for dicamba, including several studies not cited in the IRIS summary (a mouse carcinogenicity study, a second rabbit teratology study, and two-generation rat reproduction study). Also in the Federal Register notice, EPA presents an RfD of 0.045 milligrams per kilogram body weight per day (mg/kg/day), based on the 2-generation rat study not apparently considered in the IRIS summary.

A literature search conducted for the years 1987 to 2002 identified a number of studies whose relevance to the derivation of an RfD for dicamba could not be determined because of the limited information contained in each study record. These studies were coded as "unknown relevance."

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In the 1999 Federal Register notice, OPP reached the following conclusion regarding the carcinogenic potential of dicamba:

[1] Two Federal Register notices regarding dicamba were identified:
58 FR 62039, November 24, 1993 [Pesticide Tolerances for Dicamba]
64 FR 759, January 6, 1999 [Dicamba (3,6-dichloro-o-anisic acid); Pesticide Tolerance].

Evaluation of the Recent Literature and Determination of Currency for:
Dicamba (CAS No. 1918-00-9)
(continued)

> "In accordance with the EPA Proposed Guidelines for Carcinogen Risk Assessment (10-APR-1996), the EPA classified dicamba as a "not classifiable" human carcinogen. This was based on the mouse carcinogenicity study and the rat combined chronic toxicity/carcinogenicity study, being classified as supplemental because a [maximum tolerated dose] (MTD) was not achieved in both studies. However, these studies were adequate to indicate that dicamba has either a low or no cancer potential in mammals. A pharmacokinetics study pending EPA review indicates that the MTD for both the rat and mouse studies was reached. If this is corroborated by EPA's review, a quantitative cancer risk will not be made for dicamba and its metabolites, on the other hand, if the review does not corroborate this indication, replacement studies will be required" (64 FR 759, January 6, 1999).

A literature search conducted for the years 1987 to 2002 identified five genotoxicity studies potentially relevant to the derivation of a WOE classification: a structural chromosome aberration study in Chinese hamster ovary cells listed the EPA OPP "Index of Cleared Science Reviews" (1987); two mutagenicity studies using the Ames test and the SOS-Chromotest (1988, 1989, respectively); *in vivo* and *in vitro* test systems in which sister chromatid exchange (SCE) and unscheduled DNA synthesis (UDS) were measured in cultured human peripheral blood lymphocytes and the unwinding rate of liver DNA was measured in intraperitoneally treated rats (1990); and a mutagenicity study using SCE and UDS assays in human peripheral lymphocytes and of chromosome aberration analysis in rat bone marrow (1994). Both positive and negative findings were reported.

Unknown Relevance
Twenty documents were categorized as being of unknown relevance, including nineteen listings in the OPP "Index of Cleared Science Reviews." Among these listings were two memoranda (1993, 1996) regarding "Dicamba: RfD Peer Review Report," a 1996 letter regarding "September 9, 1996, Request for New Chronic Toxicity/Carcinogenicity Study in Rats - RfD Committee Recommendations," a 1998 memorandum titled "Dicamba - Report of the Hazard Identification Assessment Review Committee," and a 1987 memorandum entitled "Banvel Herbicide (Dicamba): Amended Registration."

Also included among these listings were documents entitled "Dicamba: One-year Toxicity Study in Dogs" (1987), "Mutagenicity: *In Vitro* Chromosomal Aberrations" (1987), "Oncogenicity Study in Mice with Dicamba Technical and 21-Day Dermal Toxicity in Rabbits with Banvel Herbicide" (1989), "Dicamba: Developmental Toxicity Study in Rabbits" (1993), "Dicamba: Acute Neurotoxicity Study in Rats" (1993), "Dicamba - Review of Subchronic Neurotoxicity Study (82-7)" (1995), and "Dicamba: Reproductive Toxicity Study Submitted in Response to DCI" (1995).

Note: Because of the large number of references found in the literature search (approximately 500), search results were limited with a secondary search in EndNote to identify references containing common laboratory species or toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for: p,p'-Dichlorodiphenyltrichloroethane (CAS No. 50-29-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for p,p'-dichlorodiphenyltrichloroethane (DDT) was derived (1985) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for DDT was derived based on a 27-week rat dietary study published in 1950. ATSDR updated the Toxicological Profile for DDT in 2000. ATSDR did not derive a chronic oral minimal risk level (MRL) for DDT due to insufficient data. ATSDR derived an intermediate oral MRL for DDT based on the same 1950 rat study used to derive the IRIS RfD in 1985.

A literature search conducted for the years 1999 to 2002 identified a 130-month dietary study in rhesus monkeys (1999), an oral toxicity study in Sprague Dawley rats exposed for up to 18 months (1999), a study of reproductive/developmental toxicity in rabbits (2000), and a teratogenicity study in rats and rabbits (2000).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for DDT was derived (1987) does not appear to contain study data that could produce a change in the CSF. A review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for DDT.

Inhalation Unit Risk (IUR)
The literature published since the IUR for DDT was derived (1987) does not appear to contain study data that could produce a change in the IUR. A review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for DDT.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification for DDT (B2—probable human carcinogen) was derived (1987) contains study data that could potentially produce a change in the WOE classification. In 1991, consistent with the EPA's WOE designation, International Agency for Research on Cancer (IARC) characterized DDT as Group 2B—possibly carcinogenic to humans.

Evaluation of the Recent Literature and Determination of Currency for:
p,p'-Dichlorodiphenyltrichloroethane (CAS No. 50-29-3)
(continued)

The 1987 IRIS WOE classification was based on animal carcinogenicity assays; IRIS concluded that there were inadequate epidemiologic studies to assess the carcinogenic potential of DDT. A review of the ATSDR Toxicological Profile (2000) identified eight studies published in the 1990s evaluating the cancer risk to individuals who may have had relatively high exposures to DDT, four prospective studies characterizing past DDT exposure in groups of cancer patients, five case-control studies of the association between DDT levels in the body and the occurrence of cancer, and several reviews of the role of DDT in the etiology of breast cancer. ATSDR notes, however, that evidence of DDT carcinogenicity in humans is inconclusive. A literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of a WOE classification for DDT.

Unknown Relevance
Three documents were categorized as being of unknown relevance.

Note: The literature search also identified two studies of serum DDT levels in human mothers who had experienced spontaneous abortions (2000, 2001).

Note: Because of the large number of references found in the literature search (approximately 1,000), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. In addition, a synonym for DDT is "Detox." Because both *chemical name* and *word variants* were used as search parameters for the literature search, a number of studies unrelated to DDT were found (due to the common use of the word "detox*"). These studies were identified by a secondary search in EndNote and coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
1,1-Dichloroethane (CAS No. 75-34-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: An issue paper evaluating oral exposures to 1,1-dichloroethane was issued by the National Center for Environmental Assessment (NCEA) in 1998 and concluded that insufficient information was available to derive an RfD. A literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in establishing an RfD for 1,1-dichloroethane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: An issue paper evaluating inhalation exposures to 1,1-dichloroethane was issued by NCEA in 1998 and concluded that insufficient information was available to derive an RfC. A literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in establishing an RfC for 1,1-dichloroethane.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) for 1,1-dichloroethane was derived (1989) does not appear to contain study data that could produce a change in the WOE classification. An NCEA Provisional Assessment (1998) classified 1,1-dichloroethane as Group C—possible human carcinogen. A literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in the derivation of a WOE classification for 1,1-dichloroethane.

Unknown Relevance
Five documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
cis-1,2-Dichloroethylene (CAS No. 75-34-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: In the 1996 Toxicological Profile, ATSDR derived an intermediate minimal risk level (MRL) for cis-1,2-dichloroethylene. A literature search conducted for the years 1995 to 2002 identified a 14- and 90-day gavage study in Sprague-Dawley rats (1995) that appears to be the published version of the study that served as the basis for the ATSDR intermediate MRL.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) for cis-1,2-dichloroethylene was derived (1989) does not appear to contain study data that would produce a change in the WOE classification.

The ATSDR Toxicological Profile (1996) cites several *in vivo* and *in vitro* mutagenicity/genotoxicity studies for cis-1,2-dichloroethylene, with both positive and negative findings reported. A literature search conducted for the years 1995 to 2002 identified no new studies that would be directly useful in the derivation of a WOE classification for cis-1,2-dichloroethylene.

Unknown Relevance
Two documents, both submissions to EPA Office of Toxic Substances (OTS) regarding inhalation studies in rats, were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
trans-1,2-Dichloroethylene (CAS No. 156-60-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for trans-1,2-dichloroethylene was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. Review the ATSDR Toxicological Profile (1996) and a literature search conducted for the years 1995 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for trans-1,2-dichloroethylene. The principle study used to derive the IRIS RfD and the ATSDR oral minimal risk level (MRL) are the same.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: The ATSDR Toxicological Profile for dichloroethylene (1996) includes an intermediate inhalation MRL for trans-1,2-dichloroethylene.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
One document, a submission to EPA Office of Toxic Substances (OTS), was categorized as being of unknown relevance.

Note: A literature search conducted for the years 1995 to 2002 identified one paper presenting a pharmacokinetic model of the kinetics of metabolism of trans-1,2-dichloroethylene, vinyl chloride, and trichloroethylene.

Evaluation of the Recent Literature and Determination of Currency for: Dichloromethane (CAS No. 75-09-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for dichloromethane was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. Review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an RfD. The principal studies used to derive the IRIS RfD and the ATSDR oral minimal risk level (MRL) appear to be unpublished and published versions of the same study.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: ATSDR published a chronic inhalation MRL in the 2000 toxicological profile based on a 2-year inhalation toxicity and oncogenicity study of dichloromethane in rats (1988). In addition, two studies of inhalation exposure to dichloromethane in Fischer 344 rats were identified: a two-generation reproductive toxicity study (produced in 1985) and a 13-week neurotoxicity study (produced in 1988).

Oral Slope Factor (CSF)
The literature published since the CSF for dichloromethane was derived (1989) does not appear to contain study data that could potentially produce a change in the CSF. Review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of a CSF.

Inhalation Unit Risk (IUR)
The literature published since the IUR for dichloromethane was derived (1989) does not appear to contain study data that could potentially produce a change in the IUR. Review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an IUR.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1989) does not appear to contain study data that could produce a change in the WOE. In 1999, consistent with EPA's WOE designation, the International Agency for Research on Cancer (IARC) classified dichloromethane as Group 2B—possibly carcinogenic to humans.

Review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new studies that would likely produce a change in the WOE classification. As was concluded in the IRIS assessment conducted in 1989, there are no adequate epidemiologic studies to assess the carcinogenic potential of dichloromethane in humans, and animal bioassays provide some positive evidence of carcinogenic potential. The literature search identified a positive DNA adduct study (2001).

Evaluation of the Recent Literature and Determination of Currency for:
Dichloromethane (CAS No. 75-09-2)
(continued)

Unknown Relevance
Thirteen documents, most of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
4-(2,4-Dichlorophenoxy)butyric acid (CAS No. 94-82-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 4-(2,4-dichlorophenoxy)butyric acid was derived (1985) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for 4-(2,4-dichlorophenoxy)butyric acid was derived based on a subchronic oral bioassay in dogs (1969). A literature search conducted for the years 1984 to 2002 identified two chronic dietary toxicity studies (1998)—one in rodents and one in dogs. A 1999 publication reported results of developmental toxicity studies in rats and rabbits and a two-generation reproduction study in rats.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified a chronic dietary study in rats reporting no oncogenic response (1998).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified one study that evaluated the *in vitro* genotoxicity of 4-(2,4-dichlorophenoxy)butyric acid in the Ames test, mammalian cell cultures, chromosomal aberration assay, and induction of DNA damage and repair in rat hepatocytes (2000). 4-[2,4-Dichlorophenoxy]butyric acid was found not to be genotoxic in mammals.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
1,2-Dichloropropane (CAS No. 78-87-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: ATSDR derived a chronic oral minimal risk level (MRL) in its 1989 toxicological profile for 1,2-dichloropropane based on a 1986 National Toxicology Program (NTP) bioassay. A literature search conducted for the years 1992 to 2002 identified a 1992 two-generation reproductive toxicity study in male and female Sprague-Dawley rats and a developmental toxicity study in rats and rabbits (1995).

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for 1,2-dichloropropane was derived (1991) does not appear to contain study data that could potentially produce a change in the RfC. Review of the World Health Organization (WHO) Environmental Health Criteria (1993) and a literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 1,2-dichloropropane.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) assigned 1,2-dichloropropane a cancer classification of Group 3—not classifiable as to carcinogenicity in humans. An NTP bioassay revealed no evidence of carcinogenicity in male rats, equivocal evidence in female rats, and some evidence in male and female mice.

Unknown Relevance
Twelve documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
2,3-Dichloropropanol (CAS No. 616-23-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2,3-dichloropropanol was derived (1990) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for chemical.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Three documents were categorized as being of unknown relevance. Among these studies is a submission to EPA Office of Toxic Substances (OTS) titled "A Five Week Feeding Study of Cardura E10 in Rats" (1991).

Evaluation of the Recent Literature and Determination of Currency for:
Dicofol (CAS No. 115-32-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: EPA Office of Pesticide Programs (OPP) derived an oral RfD in its 1998 Reregistration Eligibility Decision (RED) based on a 1-year chronic dietary study in dogs (1988). A literature search conducted for the years 1997 to 2002 identified a reproductive toxicity study in rats following dietary administration (1999).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
A CSF for dicofol is not available because EPA determined that the data were insufficient to support development of a CSF (latest assessment 1992). The CSF and supporting information previously on IRIS were withdrawn. Review of the OPP RED (1998) and a literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for dicofol.

Inhalation Unit Risk (IUR)
An IUR for dicofol is not available because EPA determined that the data were insufficient to support development of an IUR (latest assessment 1992). The IUR and supporting information previously on IRIS were withdrawn. Review of the OPP RED (1998) and a literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for dicofol.

Cancer Weight-of-Evidence (WOE) Classification
A carcinogenicity assessment is not available. The carcinogen assessment summary was withdrawn by the CRAVE Agency Work Group pending further review (latest assessment 1992).

In the 1998 RED, EPA's Carcinogenicity Peer Review Committee classified dicofol as Group C—possible human carcinogen—based on a 1978 National Cancer Institute bioassay in rats and mice (MRID 41037801). A literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
One document, "Dicofol stimulation of cell proliferation," was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Diethyl phthalate (CAS No. 84-66-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for diethyl phthalate was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for diethyl phthalate was derived based on a subchronic oral dietary study in rats (1978). ATSDR derived an intermediate minimal risk level (MRL) in the 1995 Toxicological Profile based on a different 1978 subchronic (3-week) feeding study in rats. A literature search conducted for the years 1994 to 2002 identified a 120-day drinking water study (2000) in Sprague-Dawley rats. Two additional studies (2000) evaluated the effects of perinatal exposures to diethyl phthalate in Sprague-Dawley rats.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1987) does not appear to contain study data that could potentially produce a change in the WOE. A National Toxicology Program (NTP) 2-year dermal cancer bioassay published in 1995 characterized diethyl phthalate as exhibiting equivocal evidence of carcinogenicity in male and female B6C3F1 mice and no evidence of carcinogenicity in male or female F334/N rats. A literature search conducted for the years 1994 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Nine documents, seven of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Determination of Diethyl Phthalate in Blood," "Diethyl Phthalate: Reproduction and Fertility Assessment in Cd-1 Mice When Administered in the Feed," and "Genetic Evaluation of Molykote Pene-Lube, Diethyl Phthalate, in Bacterial Reverse Mutation Assays."

Evaluation of the Recent Literature and Determination of Currency for:
Diethyl-p-nitrophenyl phosphate (paraoxon) (CAS No. 311-45-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1991) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1990 to 2002 identified one mutagenicity study (1995) of metabolites of organothiophosphorus pesticides that included paraoxon.

Unknown Relevance
Three documents were categorized as being of unknown relevance.

Note: The IRIS summary notes that paraoxon has been extensively used as a deacetylase inhibitor in the study of the mechanism of mutagenesis. Several studies identified by the literature search evaluate the inhibition patterns of various esterases following paraoxon exposure, including studies examining cross-species differences.

Note: Paraoxon is a major metabolite of the pesticide, parathion. As a metabolite of parathion, studies and models of parathion poisoning also discuss the effects of paraoxon and include them in the group of effects caused by parathion. Studies identified as such were reviewed during this literature search, and the potential relevance of each study was evaluated individually.

Note: A literature search conducted for the years 1990 to 2002 found one study (1994) carried out to develop, apply, and validate a comprehensive pharmacokinetic model for parathion and its major metabolites (including paraoxon). Another study (1996) examined the interspecies differences in enzymes reacting with organophosphates and their inhibition by paraoxon. A third study (1996) compared parathion and paraoxon toxicokinetics, lung metabolic activity, and cholinesterase inhibition in guinea pigs and rabbit lungs. A fourth study (1993) compared the cytotoxic sensitivities of mouse and human cells to organophosphate insecticides, including paraoxon.

Evaluation of the Recent Literature and Determination of Currency for:
Diethyl-p-nitrophenyl phosphate (paraoxon) (CAS No. 311-45-5)
(continued)

Note: Because of the large number of references found in the literature search (approximately 375), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Dimethipin (CAS No. 55290-64-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for dimethipin was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for dimethipin.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1987) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Seven documents were categorized as being of unknown relevance. All seven documents were listed on the EPA Office of Pesticide Programs (OPP) "Index of Cleared Science Reviews" for dimethipin, including "Harvade: Statistical Tests on Rat (Hazleton, Squire and EPL Evaluations) and Mouse (Hazelton and EPL Evaluations) Data for Selected Tumors," "Harvade: EPA Reg. No. 400-155: Subchronic mouse study," three peer reviews of documents submitted to OPP, and one response to peer review.

Evaluation of the Recent Literature and Determination of Currency for: N,N-Dimethylformamide (CAS No. 68-12-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A continuous breeding dosed-water study was identified in the National Toxicology Program (NTP) Management Status Report.

Inhalation Reference Concentration (RfC)
The literature published since the RfC for N,N-dimethylformamide was derived (1990) contains study data that could potentially produce a change in the RfC.

The IRIS RfC for N,N-dimethylformamide was derived based on two occupational studies (1984). A 2000 Health Canada Assessment reports an inhalation tolerable concentration (TC) based on liver effects as reported in a 1997 occupational study and a 1984 study. [The 1984 study, but not the 1987 study, served as a basis for the current RfC.] In addition, a 13-week inhalation study in Fisher rats and BB63F1 mice was found while searching the NTP Management Status Report.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) characterized N,N-dimethylformamide as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
2,4-Dimethylphenol (CAS No. 105-67-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2,4-dimethylphenol was derived (1990) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for 2,4-dimethylphenol was derived based on a subchronic oral gavage study in mice (1989). A literature search conducted for the years 1989 to 2002 identified one 90-day corn oil gavage study in Sprague-Dawley rats (1993).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
3,4-Dimethylphenol (CAS No. 95-65-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 3,4-dimethylphenol was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 3,4-dimethylphenol.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
One submission to EPA Office of Toxic Substances (OTS) was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
2,4-Dinitrotoluene (CAS No. 121-14-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2,4-dinitrotoluene was derived (1991) does not appear to contain study data that could potentially produce a change in the RfD. Review of the ATSDR Toxicological Profile (1998) and a literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 2,4-dinitrotoluene. ATSDR derived a chronic oral minimal risk level (MRL) for 2,4-dinitrotoluene based on the same 1985 dog study used to derive the IRIS RfD.

Inhalation Reference Concentration (RfC)
An oral RfC for 2,4-dinitrotoluene is not available because EPA determined that the data were insufficient to support development of an RfC (latest assessment 1990). Review of the ATSDR Toxicological Profile (1998) and a literature search conducted for the years 1997 to 2002 identified no new studies that would be directly useful in the derivation of an RfC. According to the ATSDR Toxicological Profile (1998), data were insufficient for the derivation of an acute, intermediate, or chronic inhalation MRL.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1996) characterized 2,4-dinitrotoluene as Group 2B—possibly carcinogenic to humans. A literature search conducted for the years 1997 to 2002 identified one mutagenicity study (1998) and one genotoxicity study (1999), which reported both positive and negative results.

Unknown Relevance
Three submissions to EPA Office of Toxic Substances (OTS) were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Diphenamid (CAS No. 957-51-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for diphenamid was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for diphenamid.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Two documents, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
1,2-Diphenylhydrazine (CAS No. 122-66-7)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An oral RfC for 1,2-diphenylhydrazine is not available because EPA determined that the health effects data were inadequate to support development of an RfC (latest assessment 1991). A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 1,2-diphenylhydrazine.

Oral Slope Factor (CSF)
The literature published since the CSF for 1,2-diphenylhydrazine was derived (1986) does not appear to contain study data that could potentially produce a change in the CSF. Review of the ATSDR Toxicological Profile (1990) and a literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of an CSF for 1,2-diphenylhydrazine.

Inhalation Unit Risk (IUR)
The literature published since the IUR for 1,2-diphenylhydrazine was derived (1986) does not appear to contain study data that could potentially produce a change in the IUR. Review of the ATSDR Toxicological Profile (1990) and a literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for 1,2-diphenylhydrazine.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1986) does not appear to contain study data that could produce a change in the WOE. Review of the ATSDR Toxicological Profile (1990) and a literature search conducted for the years 1989 to 2002 identified one study (2000) investigating the nature of the DNA damage in rats and mice induced by 1,2-diphenylhydrazine.

Unknown Relevance
Two documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Disulfoton (CAS No. 298-04-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for disulfoton was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for disulfoton was derived based on a 2-year oral toxicity (diet) study in F344/N rats (1985). In the Revised Health Effects Risk Assessment (2000) prepared as part of its Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) identified a two-generation reproductive toxicity study in rats administered disulfoton in their diets (1997) and a 1-year toxicity dietary study in dogs (1997). OPP used the 1-year toxicity study in dogs as the basis for its RfD. The RED has not been finalized. ATSDR's minimal risk level (MRL), presented in its 1995 toxicological profile for disulfoton, appears to be based on the same 1985 study used in the derivation of the IRIS RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: ATSDR derived an intermediate inhalation MRL for disulfoton (1995) based on an neurotoxicity study in rats published in 1980.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Endosulfan (CAS No. 115-29-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for endosulfan was derived (1993) does not appear to contain study data that could potentially produce a change in the RfD.

A review of the EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) (2002), the ATSDR Toxicological Profile (2000), and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for endosulfan. The RED RfD and ATSDR's oral minimal risk level (MRL) are based on the same 2-year dietary study in rats (1989) used in the derivation of the IRIS RfD. The literature search did identify two reproductive and developmental toxicity studies in rats (1999, 2000); however, administered dose levels and the only reported observed effect level (decreased sperm production in male offspring) were at levels comparable to those in the 1989 study on which the IRIS RfD is based.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Eight documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Endothall (CAS No. 145-73-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for endothall was derived (1986) may contain study data that could potentially produce a change in the RfD.

The IRIS RfD for endothall was derived based on a 2-year dietary study in dogs (using disodium endothall) (1965). EPA Office of Pesticide Programs (OPP) has initiated a reassessment of the health risks resulting from exposure to endothall; to what extent this reassessment was prompted by new effects information is unknown[2]. A literature search conducted for the years 1985 to 2002 identified a developmental toxicity study in rats (1995) that may be useful in the derivation of an RfD for endothall. Only an abstract with summary findings of this developmental toxicity study has been published.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Nine documents were categorized as being of unknown relevance.

[2]EPA. 2002. *Six-Year Review, Chemical Contaminants, Health Effects Technical Support Document.* Office of Water, Office of Science and Technology. EPA Publication No. 822-R-01-001. February 2002.

Evaluation of the Recent Literature and Determination of Currency for:
Epichlorohydrin (CAS No. 106-89-8)

Oral Reference Dose (RfD)
An oral RfD for epichlorohydrin is not available because EPA determined that the data were inadequate for derivation of an RfD (latest assessment 1992). The oral RfD and supporting information previously on IRIS were withdrawn pending further review by the RfD/RfC work group. The literature made available since 1992 contains study data that could potentially be used to develop an RfD.

A literature search conducted for the years 1991 to 2002 identified a 90-day oral toxicity study in Sprague-Dawley rats (1996) and a 2-year toxicity study (oral gavage) in SPF Wistar RIV:Tox(M) rats (completed in 1982 and later submitted to EPA). A published version of this 1982 2-year study was considered by EPA in the cancer assessment; however, it is not clear if the study was included in the evaluation of noncancer effects.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for epichlorohydrin was derived (1991) contains study data that could potentially produce a change in the RfC.

The IRIS RfC for epichlorohydrin was derived based on a 90-day inhalation study in B6C3F1 mice, F344/N rats, and Sprague-Dawley rats published in 1979. A literature search conducted for the years 1990 to 2002 identified five cohort studies (1990, 1994, 1996) and an occupational exposure study (1993) of workers exposed to epichlorohydrin. The abstracts for the epidemiologic studies are not explicit, however, about the nature and extent of the dose-response data.

Note: Most of the epidemiologic studies identified in this literature search are also cited in the International Agency for Research on Cancer (IARC) Monograph (1999).

Oral Slope Factor (CSF)
The literature published since the oral CSF for epichlorohydrin was derived (1986) does not appear to contain study data that could potentially produce a change in the CSF. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an CSF for epichlorohydrin. No oral carcinogenicity studies were identified in the IARC Monograph (1999).

Inhalation Unit Risk (IUR)
The literature published since the inhalation IUR for epichlorohydrin was derived (1986) contains study data that could potentially produce a change in the IUR.

The IRIS IUR for epichlorohydrin was derived based on a 30-day inhalation study in Sprague-Dawley rats published in 1980 and a retrospective cohort study of workers from epichlorohydrin-producing plants published in 1981. The IARC Monograph (1999) identified six new epidemiologic studies.

Evaluation of the Recent Literature and Determination of Currency for:
Epichlorohydrin (CAS No. 106-89-8)
(continued)

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1986) contains study data that could potentially produce a change in the WOE.

The IRIS WOE for epichlorohydrin was derived based on inadequate human data and sufficient evidence of carcinogenicity in animals. The IARC Monograph (1999) identified six new epidemiologic studies and characterized epichlorohydrin as Group 2A—probably carcinogenic to humans.

In addition, a literature search conducted for the years 1990 to 2002 identified studies not included in the IARC Monograph; however, it does not appear that any of these studies would produce a change in the WOE classification. Studies include: an *in vitro* sister chromatid exchange induction study in human lymphocytes (2000), evaluations of DNA adducts and other genetic effects in workers exposed to epichlorohydrin (1997, 1999, 2000), a DNA adduct induction study in Wistar rats (1999), *in vitro* DNA strand break (and repair) studies in human diploid fibroblasts (1997, 1998), genotoxicity studies using the micronucleus test in mice (1991, 1992), a DNA adduct induction study using calf thymus DNA (1996), and microbial genotoxicity studies (1990, 1991, 1992, 1993 [two studies], 1994). Overall, the studies reported positive findings.

Unknown Relevance
Seventy-eight documents, 39 of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Epichlorohydrin, Subchronic Studies: IV. The Effects of Maternally Inhaled Epichlorohydrin on Rat and Rabbit Embryonal and Fetal Development, 8(d) Submission," "Initial Submission: Inhalation Carcinogenicity of Epichlorohydrin with Cover Letter Dated 10/19/92," "Initial Submission: Carcinogencitiy Study of Epichlorohydrin in Rats (Final Report) with Cover Letter Data 05/27/92," "A Case-Control Study of Lung Cancer and Central Nervous System Neoplasms among Chemical Workers, with Cover Letter Data 10/20/92," and "Epichlorohydrin, Subchronic Studies: I.A. 90-Day Inhalation Study in Laboratory Rodents (Final Report) 8(d) Submission."

Evaluation of the Recent Literature and Determination of Currency for:
1,2-Epoxybutane (CAS No. 106-88-7)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC was derived (1991) does not appear to contain study data that could potentially produce a change in the RfC. A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 1,2-epoxybutane.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) characterized 1,2-epoxybutane as Group 2B—possibly carcinogenic to humans. Carcinogenesis studies published by the National Toxicology Program (NTP) (1988) indicated clear evidence of carcinogenicity in male F344/N rats, equivocal evidence of carcinogenicity in female F344/N rats, and no evidence of carcinogenicity in male or female B6C3F1 mice.

Unknown Relevance
Thirteen documents, four of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Ethephon (CAS No. 16672-87-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ethephon was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A review of the EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) (1995) and a literature search conducted for the years 1994 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for ethephon. The principal study used to derive the RED RfD was considered an additional study in establishing the IRIS RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In the 1995 RED, OPP classified ethephon as Group D—not classifiable as to human carcinogenicity.

Unknown Relevance
Three documents (1997, 1998, 1999) listed in the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services) were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
S-Ethyl dipropylthiocarbamate (CAS No. 759-94-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for S-ethyl dipropylthiocarbamate was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A review of the EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for S-ethyl dipropylthiocarbamate. The RED RfD is based on the same two-generation reproductive toxicity study in rats (1986) that was used to derive the IRIS RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The 1999 RED notes that S-ethyl dipropylthiocarbamate "was not mutagenic and did not exhibit any oncogenic potential in a mouse oncogenicity study and two combined chronic toxicity/oncogenicity studies in rat."

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Ethyl p-nitrophenyl phenylphosphorothioate (CAS No. 2104-64-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ethyl p-nitrophenyl phenylphosphorothioate was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for ethyl p-nitrophenyl phenylphosphorothioate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Seven documents, five of which were submissions to EPA's Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including "Effects of Some Organophosphate Pesticides on the Murine Immune System Following Subchronic Exposure."

Evaluation of the Recent Literature and Determination of Currency for:
Ethylene glycol monobutyl ether (CAS No. 111-76-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ethylene glycol monobutyl ether was derived (1999) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for ethylene glycol monobutyl ether.

Inhalation Reference Concentration (RfC)
The literature published since the RfC for ethylene glycol monobutyl ether was derived (1999) does not appear to contain study data that could potentially produce a change in the RfD. The IRIS RfC for ethylene glycol monobutyl ether was derived based on the application of a benchmark dose assessment and physiologically-based pharmacokinetic (PBPK) model to the results of a subchronic rat inhalation study in which the critical effect was changes in red blood cell count (1998). A literature search conducted for the years 1998 to 2002 identified two publications (1999, 2000) that appear to contain findings from the National Toxicology Program (NTP) subchronic inhalation study considered in the IRIS assessment. The 1999 publication reported disseminated thrombosis and bone infarction in exposed female F344/N rats and the 2000 publication reported dental pulp infarction in female rats.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1999) does not appear to contain study data that could produce a change in the WOE classification. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of a WOE for ethylene glycol monobutyl ether.

Unknown Relevance
Twenty-two documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. These included "Effects of Exposure to Glycol Ethers on Shipyard Painters: Hematologic Effects and Male Production and Evaluation of Exposure to Ethylene Glycol Ether in Shipyard Painting," "Pathology Working Gp Report and Summary Pathology Tables for Ongoing Chronic Inhalation Study on Ethylene Glycol Monobutyl Ether," two reports on "A Teratologic Evaluation of Ethylene Glycol Monobutyl Ether in Fischer 344 Rats & New Zealand White Rabbits Following Inhalation Exposure," "Inhalation Teratologic Potential of Ethylene Glycol Monobutyl Ether in the Rat," and four documents related to studies of reproductive effects.

Evaluation of the Recent Literature and Determination of Currency for:
Ethylene glycol monobutyl ether (CAS No. 111-76-2)
(continued)

Note: A literature search conducted for the years 1998 to 2002 identified a 2000 NTP technical report on "Toxicology and carcinogenesis studies of 2-Butoxyethanol [CAS No. 111-76-2] in F344/N rats and B6C3F1 mice (inhalation studies)." However, the IRIS RfC and WOE classification are based on a 1998 draft publication of the same report, and the 1998 NTP report is cited as an additional study for the IRIS RfD assessment.

Evaluation of the Recent Literature and Determination of Currency for:
Ethylphthalyl ethylglycolate (CAS No. 84-72-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for ethylphthalyl ethylglycolate was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for ethylphthalyl ethylglycolate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Fluridone (CAS No. 59756-60-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for fluridone was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for fluridone.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Five documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Although reported as having a submission date of 1992, these studies were likely part of the series of toxicity studies conducted by Eli Lilly and Company between 1978 and 1986 and considered by EPA in the IRIS assessment.

Note: Because of the large number of references found in the Toxline literature search using standard protocol (over 6,900 results for search: CAS number, toxic*), in the custom search screen, fluridone's CAS number (59756-60-4) and relevant search term were entered and searching was conducted with the "singular and plural forms" search option, rather than the "word variants" search option. Because a synonym of fluridone is "sonar", many of the studies identified were not related to the chemical sonar. Only studies *containing* the CAS number were retained in the EndNote database.

Evaluation of the Recent Literature and Determination of Currency for:
Flurprimidol (CAS No. 56425-91-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for flurprimidol was derived (1989) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for flurprimidol.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Fifteen documents, all of which were submissions to EPA Office of Toxic Substances (OTS) and appear to contain laboratory findings from acute toxicity studies, were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Fluvalinate (CAS No. 69409-94-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for fluvalinate was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for fluvalinate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Ten documents were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 435), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Fomesafen (CAS No. 72178-02-0)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for fomesafen.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1987) contains study data that could potentially produce a change in the WOE.

The IRIS WOE for fomesafen was derived based on a 2-year dietary study in mice (1985). A literature search conducted for the years 1986 to 2002 identified two studies by Czech investigators (1998 [in Czech], 1999) that examined hepatocellular carcinoma and preneoplastic and morphologic changes in the liver of mice administered fomesafen for 3 to 14 months.

Unknown Relevance
Two documents, both submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Formic acid (CAS No. 64-18-6)

Oral Reference Dose (RfD)
An oral RfD for formic acid is not available because EPA determined that the data were insufficient to support development of an RfD (latest assessment 1990). The oral RfD and supporting information previously on IRIS were withdrawn. The literature published since 1990 does not appear to contain study data that could be used to develop an RfD.

A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for formic acid. The literature search identified a study (1995) that examined the role of formate in the development of exencephaly in pregnant and embryonic CD-1 mice, following methanol exposure by gavage[3]. Nine developmental toxicity studies of formic acid on embryos *in culture* were also identified (1993, 1994, 1995, 1996, 1998).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified a National Toxicology Program (NTP) technical report of the toxicity of formic acid on F344/N rats and B6C3F1 mice following 2- and 13-week whole body/inhalation exposures (1992). A 1995 study examined the role of formate in the development of exencephaly in pregnant and embryonic CD-1 mice, following methanol exposure by inhalation[1].

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified three mutagenicity studies of formic acid. None of these studies provided evidence that formic acid is genotoxic.

Unknown Relevance
Five documents were categorized as being of unknown relevance.

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[3]Formic acid, also called formate, is the primary metabolite of methanol and is often the subject of methanol toxicity studies. Therefore, the literature search reviewed studies related to methanol toxicity, generally coding relevant studies as 5, "other toxicity studies not directly useful for establishing IRIS toxicity values."

Evaluation of the Recent Literature and Determination of Currency for:
Formic acid (CAS No. 64-18-6)
(continued)

Note: A biopesticide registration eligibility document (1999) concluded that chronic toxicity tests, "designed to assess mammalian mutagenic potential and impacts on the immune system, chronic feeding studies, and carcinogenicity studies, have been waived because formic acid is a naturally occurring substance in honey and other foods, and is cleared under 21 CFR 172.515 as a Direct Food Additive for use as a flavoring agent in a wide range of processed foods."

Note: A literature search conducted for the years 1989 to 2002 identified one study carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for formic acid (1996).

Note: Because of the large number of references found in the literature search (approximately 800), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Furmecyclox (CAS No. 60568-05-0)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for furmecyclox was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for furmecyclox.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1987) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Glycidaldehyde (CAS No. 765-34-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for glycidaldehyde was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for glycidaldehyde.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1991) does not appear to contain study data that could produce a change in the WOE. An International Agency for Research on Cancer (IARC) Monograph (1999) characterized glycidaldehyde as Group 2B—possibly carcinogenic to humans. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
One document, "Identification of DNA Adducts in Mouse Skin Treated with Glycidaldehyde in-Vivo," was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
n-Heptane (CAS No. 142-82-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1991) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1990 to 2002 identified one genotoxicity study (1992) that investigated the gene mutation, chromosome aberrations, and DNA repair associated with numerous industrial solvents, including n-heptane.

Unknown Relevance
Seven documents, two of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: alpha-Hexachlorocyclohexane (CAS No. 319-84-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: The ATSDR Toxicological Profile (1999) derived a chronic oral minimal risk level (MRL) based on hepatic effects reported in a lifetime dietary study in Wistar rats (1950).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for alpha-hexachlorocyclohexane was derived (1986) does not appear to contain study data that could potentially produce a change in the CSF. Review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for alpha-hexachlorocyclohexane.

Inhalation Unit Risk (IUR)
The literature published since the IUR for alpha-hexachlorocyclohexane was derived (1986) does not appear to contain study data that could potentially produce a change in the IUR. Review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for alpha-hexachlorocyclohexane.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1986) does not appear to contain study data that could produce a change in the WOE. An International Agency for Research on Cancer (IARC) Monograph (1987) classified alpha-hexachlorocyclohexane as Group 2B—possibly carcinogenic to humans—and the National Toxicology Program (NTP) Second Annual Report on Carcinogens (1981) lists alpha-hexachlorocyclohexane as reasonably anticipated to be a human carcinogen. Review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Four documents were categorized as being of unknown relevance. Among these studies are "Organochlorine exposure and risk of breast cancer" and "Differential toxicity and environmental fates of hexachlorocyclohexane isomers."

Evaluation of the Recent Literature and Determination of Currency for: beta-Hexachlorocyclohexane (CAS No. 319-85-7)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: The ATSDR Toxicological Profile (1999) derived an intermediate oral minimal risk level (MRL) based on hepatic effects reported in a 13-week dietary study in Wistar rats (1986).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for beta-hexachlorocyclohexane was derived (1986) does not appear to contain study data that could potentially produce a change in the CSF. The IRIS CSF for beta-hexachlorocyclohexane was derived based on a 110-week dietary study in CF1 mice published in 1973. A review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified two epidemiology studies of beta-hexachlorocyclohexane exposure and breast cancer (1998, 1999). Neither study found statistically significant increases in breast cancer associated with exposure to beta-hexachlorocyclohexane.

Inhalation Unit Risk (IUR)
The literature published since the IUR for beta-hexachlorocyclohexane was derived (1986) does not appear to contain study data that could potentially produce a change in the IUR. A review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for beta-hexachlorocyclohexane.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1986) contains study data that could potentially produce a change in the WOE.

The IRIS WOE for beta-hexachlorocyclohexane was derived based on a 110-week dietary study in CF1 mice published in 1973. An International Agency for Research on Cancer (IARC) Monograph (1987) classified beta-hexachlorocyclohexane as Group 2B—possibly carcinogenic to humans—and the National Toxicology Program (NTP) Second Annual Report on Carcinogens (1981) lists beta-hexachlorocyclohexane as reasonably anticipated to be a human carcinogen. A review of ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified an epidemiology study that found a slight, but not statistically significant, increase in breast cancer associated with exposure to beta-hexachlorocyclohexane (1998). A case-control study comparing beta-hexachlorocyclohexane levels in breast adipose tissue from incident breast carcinoma cases and controls concluded that increasing adipose tissue levels of beta-hexachlorocyclohexane are not associated with increased risk of breast carcinomas (1999).

Evaluation of the Recent Literature and Determination of Currency for:
beta-Hexachlorocyclohexane (CAS No. 319-85-7)
(continued)

Unknown Relevance

Five documents were categorized as being of unknown relevance. Among these studies are "Differential toxicity and environmental fates of hexachlorocyclohexane" and "Partitioning coefficients of organochlorine pesticides between mother blood serum and umbilical blood serum."

Evaluation of the Recent Literature and Determination of Currency for: Hexachlorophene (CAS No. 70-30-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for hexachlorophene was derived (1988) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for hexachlorophene was derived based on a 13-week dietary study in dogs (1974). A literature search conducted for the years 1987 to 2002 identified another subchronic (90-day) oral toxicity study in male weanling Sprague-Dawley rats (1991).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A literature search conducted for the years 1987 to 2002 found one chronic inhalation carcinogenicity study in albino noninbred rats exposed to hexachlorophene (1987; published in Russian).

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized hexachlorophene as Group 3— not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1987 to 2002 identified one chronic inhalation carcinogenicity study in albino noninbred rats exposed to hexachlorophene (1987; published in Russian).

Unknown Relevance
Eight documents, two of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Concerning the Carcinogenicity of Hexachlorophene," "Neurotoxicity of Hexachlorophene in Mice," and "Hexachlorophene Intoxication in F344 Rats."

Evaluation of the Recent Literature and Determination of Currency for:
1,6-Hexamethylene diisocyanate (CAS No. 822-06-0)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
The literature published since the oral RfC for 1,6-hexamethylene diisocyanate was derived (1992) does not appear to contain study data that could potentially produce a change in the RfC.

The IRIS RfC for 1,6-hexamethylene diisocyanate was derived based on a chronic inhalation study in rats published in 1989. Review of the ATSDR Toxicological Profile (1998) and a literature search conducted for the years 1997 to 2002 identified no new chronic toxicity studies, but identified a subchronic, whole-body inhalation study in adult male Sprague-Dawley rats (1998) and two reproductive/developmental/neurotoxicity studies in Sprague-Dawley rats exposed via whole-body inhalation (2000[4]). The two developmental and reproductive toxicity studies reported no developmental toxicity at any dose and maternal effects only at levels above the lowest-observed-adverse-effects-level (LOAEL) found in the principal study for the IRIS RfC. In addition, in its 1998 Toxicological Profile, ATSDR derived a chronic inhalation minimal risk level (MRL) based on the principal study used for the IRIS RfC.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1997 to 2002 identified two genotoxicity studies (1997, 2000).

Unknown Relevance
Twenty-three studies, all of which were either submissions to EPA Office of Toxic Substances (OTS) or to the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services), were categorized as being of unknown relevance. Among these studies are "A Developmental Toxicity Study with 1,6-Hexamethylene Diisocyanate (Hdi) in the Sprague-Dawley Rat,""Chronic Inhalation Study with Hdi (1,6-Hexamethylene Diisocyanate) in the Rat," and "Toxicological Investigations of Desmodur H (Hexamethylene Diisocyanate)."

[4]It is unclear from the abstract whether these are the same or separate studies.

Evaluation of the Recent Literature and Determination of Currency for:
Hexazinone (CAS No. 51235-04-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for hexazinone was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for hexazinone was derived based on a 2-year dietary study in rats completed in 1977. An uncertainty factor was assigned based on the lack of a chronic exposure study in an apparently more sensitive species (dogs). In the 1994 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an RfD based on a chronic (1-year) dietary study in dogs (1991).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In the 1994 RED, the OPP Carcinogenicity Peer Review Committee classified hexazinone as Group D—not classifiable as to human carcinogenicity.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for: Hydrazine/Hydrazine sulfate (CAS No. 302-01-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: ATSDR derived an intermediate inhalation minimal risk level MRL in its 1997 Toxicological Profile.

Oral Slope Factor (CSF)
The literature published since the CSF for hydrazine was derived (1987) contains study data that could potentially produce a change in the CSF.

The IRIS CSF for hydrazine was derived based on a gavage study in mice (1970). An International Agency for Research on Cancer (IARC) Monograph (1999) identified three 2-year drinking-water studies in NMRI mice (1990), Wistar rats (1988), and Syrian hamsters (1987).

Inhalation Unit Risk (IUR)
The literature published since the IUR for hydrazine was derived (1987) contains study data that could potentially produce a change in the IUR.

The IRIS IUR for hydrazine was derived based on a 1-year study in rats published in 1981. An IARC Monograph (1999) identified a subchronic study in Fisher 344 rats (1995) and a cancer mortality study in male workers at a hydrazine plant (1995).

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1987) does not appear to contain study data that could produce a change in the WOE. An IARC Monograph (1999) characterized hydrazine as Group 2B—possibly carcinogenic to humans.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for: Hydroquinone (CAS No. 123-31-9)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A review of the World Health Organization (WHO) Environmental Health Criteria (1994) and a literature search conducted for the years 1993 to 2002 identified a developmental toxicity gavage study in female rats (1992), a reproductive toxicity study in rabbits (1992), a two-generation reproductive toxicity study in CD Sprague-Dawley rats exposed to hydroquinone via gavage (1993), and a 2-year dietary study in male 344 rats (1996).

Inhalation Reference Concentration (RfC)
An inhalation RfC for hydroquinone is not available because EPA determined that the data were insufficient to support development of an RfC (latest assessment 1990). A review of the WHO Environmental Health Criteria (1994) and the literature published conducted for the years 1993 to 2002 identified no new studies that would be directly relevant in the derivation of an RfC.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A review of the WHO Environmental Health Criteria (1994) and a literature search conducted for the years 1993 to 2002 identified a 2-year dietary study in male F344 rats (1996) and a shorter term (6-week) study to better characterize the early development of renal toxicity in male and female F344 rats and male SD rats (1994).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A literature search conducted for the years 1993 to 2002 identified a cancer mortality study of male and female employees exposed to hydroquinone dust and vapor (1995).

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) characterized hydroquinone as Group 3—not classifiable as to carcinogenicity in humans. A review of the WHO Environmental Health Criteria (1994) and a literature search conducted for the years 1993 to 2002 identified the animal assays described under the CSF discussion above, as well as several genotoxicity assays, including studies of DNA adduct formation, induction of micronuclei, sister chromatid exchange, chromosomal loss/breakage, cell transformation, gene mutations, and aneuploidy. Most studies reported positive results; a few studies demonstrated hydroquinone's ability to inhibit the induction of micronuclei.

Evaluation of the Recent Literature and Determination of Currency for:
Hydroquinone (CAS No. 123-31-9)
(continued)

Unknown Relevance
Forty-three documents, 8 of which were submissions to EPA Office of Toxic Substances (OTS) and 25 of which were submissions to the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services), were categorized as being of unknown relevance.

Note: A literature search conducted for the years 1993 to 2002 identified many studies that examined the cytotoxic mechanisms and the mechanisms of tumor induction of hydroquinone and parent compounds (e.g., benzene)[5]. In addition, the search identified one study that developed a physiologically-based pharmacokinetic (PBPK) model for hydroquinone (2000).

Note: Because of the large number of references found in the literature search (approximately 850), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

[5] Hydroquinone is a primary metabolite of benzene and is often the subject of benzene toxicity studies. Therefore, the literature search identified studies related to benzene toxicity; relevant studies were generally assigned a code of 5, "other toxicity studies not directly useful for establishing IRIS toxicity values."

Evaluation of the Recent Literature and Determination of Currency for:
Isobutyl alcohol (CAS No. 78-83-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for isobutyl alcohol was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for isobutyl alcohol was derived based on a subchronic oral toxicity study in rats (1986). A literature search conducted for the years 1985 to 2002 identified one new subchronic toxicity study—a 90-day drinking water study in Wistar rats (1997).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a prenatal inhalation toxicity study in Wistar rats and Himalayan rabbits (1995) and a 90-day neurotoxicity study in Sprague-Dawley rats exposed to isobutyl alcohol vapors (1999).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Thirty-four documents, 23 of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Lymphocyte Subpopulations in Solvent-Exposed Workers," "Mutagenicity Evaluation of Isobutanol Alcohol in the Ames Salmonella/Microsome Plate Test (Final Report)," "Mutagenicity Evaluation of Isobutyl Alcohol in the Mouse Lymphoma Forward Mutation Assay (Final Report)," "Initial Submission: Experimental Investigation of Carcinogenic Effects of Solvents Exemplified by 1-Propanol, 2-Methyl-1-Propanol, and 3-Methyl-1-Butanol," and "Rat Oral Subchronic Toxicity Study with Isobutyl Alcohol (Final Report)."

Evaluation of the Recent Literature and Determination of Currency for:
Lead and compounds (inorganic) (CAS No. 7439-92-1)

Oral Reference Dose (RfD)
An oral RfD is not available because EPA considered deriving an RfD inappropriate since some health effects occur at blood lead levels so low as to be essentially without a threshold (latest assessment 1985). The literature published since 1985 contains study data that could be relevant to the development of an RfD. In its 1999 Toxicological Profile, ATSDR identified numerous studies relating exposure to lead and internal lead doses in humans and several post-1985 systemic, neurological, developmental, and reproductive toxicity studies in rats (primarily) and monkeys. ATSDR did not derive a minimal risk level (MRL) for lead, but did develop an approach for assessing lead exposures using regression analysis with multi-route uptake parameters to estimate blood lead levels. In addition, EPA's Integrated Exposure Uptake Biokinetic Model (IEUBK) was developed and refined since the last IRIS update.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Risk Factor (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1988) does not appear to contain study data that would produce a change in the WOE.

The IRIS WOE for lead and compounds (inorganic) was derived based on sufficient evidence of carcinogenicity in animals (ten rat bioassays and one mouse assay have shown statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble lead salts) and inadequate human evidence. An International Agency for Research on Cancer (IARC) Monograph (1987) characterized lead as Group 2B—possibly carcinogenic to humans. The World Health Organization (WHO) Environmental Health Criteria (1995) and the ATSDR Toxicological Profile (1995) identified no new animal or human carcinogenicity studies.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
d-Limonene (CAS No. 5989-27-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An inhalation RfC for d-limonene is not available because EPA determined that the data were inadequate for derivation of an RfC (latest assessment 1993). The literature published since 1993 does not appear to contain study data that could be used to develop an RfC.

EPA Office of Pesticide Programs (OPP) issued a Reregistration Eligibility Decision (RED) for limonene in 1994 but did not derive an RfC. (The RED considers limonene the same as d-limonene for toxicity assessment purposes.) A literature search conducted for the years 1993 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for d-limonene.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) characterized d-limonene as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
Six documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Malathion (CAS No. 121-75-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for malathion was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for malathion was derived based on a subchronic dietary study in humans (1962). In its 2000 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an RfD for malathion based on a chronic (2-year) oral toxicity/oncogenicity study in Fischer-344 rats (1996; unpublished). In its 2001 Toxicological Profile, ATSDR derived a chronic oral minimal risk level (MRL) based on the same 2-year study. (RED Status: as of February 2001, the 60-day public participation period was completed.)

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) classified malathion as not classifiable as Group 3—to carcinogenicity in humans. In addition, EPA OPP Cancer Assessment Review Committee classified malathion as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential," as reported in the preliminary risk assessment (2000) for the RED.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Maleic anhydride (CAS No. 108-31-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD was derived (1988) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for maleic anhydride was derived based on two chronic studies in rats (1982, 1983). A literature search conducted for the years 1987 to 2002 identified a teratology and multigeneration reproduction study in rats completed by Monsanto Co. in 1991 and submitted to EPA Office of Toxic Substances (OTS) in 1992.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1987 to 2002 identified a 6-month inhalation toxicity study in Engle hamsters, CD rats, and Rhesus monkeys (1988) and a retrospective cohort study of workers at resin and cushion flooring factories exposed to maleic anhydride in the air (1995). The literature search also identified a number of clinical studies related to asthmatic, allergic, and other immune responses following exposure to maleic anhydride.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Thirteen documents, seven of which were submissions to EPA OTS, were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Maleic hydrazide (CAS No. 123-33-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for maleic hydrazide was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for maleic hydrazide was derived based on a 2-year dietary study in SPF Wistar rats (1981). In its 1994 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an oral RfD based on the 1993 recommendations of the OPP RfD/Peer Review Committee. The RED RfD was based on a 104-week chronic feeding study in Sprague-Dawley rats (1991; an addendum to the study was published in 1993) and a co-critical 52-week chronic feeding study in beagle dogs (1991; with supplemental information furnished in 1991). These studies used the potassium salt of maleic hydrazine (which OPP considers equivalent to maleic hydrazine with respect to applicable toxicity study requirements).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized maleic hydrazide as Group 3—not classifiable as to carcinogenicity in humans. The 1994 RED reported both negative and positive mutagenicity assay findings and negative chronic feeding carcinogenicity studies in rats and mice.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Manganese (CAS No. 7439-96-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for manganese was derived (1995) does not appear to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for manganese was derived based three human chronic ingestion studies published in 1973, 1987, and 1989. A review of the ATSDR Toxicological Profile (2000) and a literature search conducted for the years 1999 to 2002 identified no new human chronic studies, but identified developmental and reproductive toxicity studies in rats (1999, 2000) and mice (2001). In the 2000 Toxicological Profile, ATSDR indicated that health effects data are not sufficient to derive a chronic oral minimal risk level (MRL).

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for manganese was derived (1995) contains study data that could potentially produce a change in the RfC.

The IRIS RfC for manganese was derived based on a study of occupational exposure to several different forms of manganese (manganese dioxide, manganese oxides, and manganese salts). In the 2000 Toxicological Profile, ATSDR derived an inhalation MRL based on the same study, but used a benchmark dose (BMD) approach. ATSDR also cites more recent studies: a longitudinal follow-up study by the same author of the principal RfC and MRL study (1999); a study of exposures at a metal producing plant (reporting a no-observed-adverse-effects-level [NOAEL] consistent with the ones derived using the ATSDR BMD approach) (1999); and two studies by the same author of neurobehavioral effects in workers exposed to manganese dusts (1 to 28 years) (1995, 1999). A literature search conducted for the years 1999 to 2002 identified additional human studies: one study of nervous system function and levels of total manganese in blood samples of residents exposed from various environmental sources (1999) and a study of neurological and neurophysiological effects in workers in the ship and electrical industries (2001).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1988) does not appear to contain study data that could produce a change in the WOE classification. A review of (1995, 1999) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in establishing a WOE classification for manganese.

Evaluation of the Recent Literature and Determination of Currency for:
Manganese (CAS No. 7439-96-5)
(continued)

Unknown Relevance
Six documents were categorized as being of unknown relevance, including a 1999 study entitled, "Neurotoxic effects of low level exposure to manganese in human populations."

Note: A literature search conducted for the years 1999 to 2002 identified one study carried out to develop, apply, and validate a biologically-based, dose-response (BBDR) model for manganese (1999), as well as several other studies of the pharmacokinetics of manganese. Several studies evaluated the uptake and distribution of manganese administered within the olfactory system.

Note: Because of the large number of references found in the literature search (approximately 1,250), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. Because the literature search identified a number of studies evaluating the movement of Mn^{+2} within cells, references *containing* the following terms were coded as N/A: MN(2+), Mn(+2), Mn+2, Mn2+, MnDPDP, and MnSOD. In addition, a number of studies *containing* the following terms were also coded as N/A: trace metal, trace element, and nutrition.

Evaluation of the Recent Literature and Determination of Currency for:
Mepiquat chloride (CAS No. 24307-26-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for mepiquat chloride was derived (1988) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for mepiquat chloride was derived based on a 90-day dietary study in dogs (1977). In the 1997 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an oral RfD based on the 1996 recommendations of the OPP RfD/Peer Review Committee. The RED RfD was based on a 1-year dietary study in dogs (1989 and a supplemental 1994 study).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: According to the 1997 RED, OPP's RfD/Peer Review Committee classified mepiquat chloride as Group E—evidence of noncarcinogenicity for humans—in 1996.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Mercuric chloride (CAS No. 7487-94-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for mercuric chloride was derived (1988)[6] does not appear to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for mercuric chloride was derived based on subchronic dietary and subcutaneous studies in Brown Norway rats, as recommended by a 1987 peer review panel. In the 1999 Toxicological Profile, ATSDR derived an intermediate oral minimal risk level (MRL) for mercuric chloride based on a 1993 National Toxicity Program (NTP) assay considered in the IRIS assessment. A literature search conducted for the years 1998 to 2002 identified no chronic toxicity studies, but identified a two-generation reproductive and fertility study in Sprague-Dawley rats (1998; 2001); reproductive toxicity studies in C57/BL6 mice (1999) and in Sprague-Dawley rats (1999); and developmental toxicity studies in MRL/lpr mice (2000) and in post-natal rats (2001). The lowest doses administered in these studies (0.25 to 0.5 milligrams per kilogram body weight per day [mg/kg/day]) were similar to the lowest-observed-adverse-effects-levels (LOAELs) used to derive the IRIS RfD. As such, data from these studies is unlikely to produce a change in the IRIS RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
A CSF for mercuric chloride is not available because EPA determined that the data were insufficient to support development of a CSF (latest assessment 1994). The literature published since 1994 does not appear to contain study data that could potentially produce a change in the CSF status. A review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for mercuric chloride.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1994) does not appear to contain study data that could produce a change in the WOE classification.

A review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no human studies, but identified several genotoxicity studies of mercuric chloride, as well as studies of the mechanisms by which mercuric chloride damages DNA.

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[6]The IRIS RfD verification date is listed in the IRIS summary as 11/16/88. A note is also provided indicating that the IRIS summary was included in the Mercury Study Report to Congress and that peer review and public comments (1995) were evaluated and considered in the revision and finalization of the IRIS summary.

Evaluation of the Recent Literature and Determination of Currency for:
Mercuric chloride (CAS No. 7487-94-7)
(continued)

Unknown Relevance
Eleven documents were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 425), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. In addition, references *containing* the term aquatic were also coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Elemental mercury (CAS No. 7439-97-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
The literature published since the inhalation RfC for elemental mercury was derived (1990)[7] contains study data that could potentially produce a change in the RfC.

The IRIS RfC for elemental mercury was derived based on human occupational studies published between 1983 and 1993. In the 1999 Toxicological Profile, ATSDR derived a chronic inhalation minimal risk level (MRL) for mercury vapor based on one of the studies on which the IRIS RfC is based. A literature search conducted for the years 1998 to 2002, however, identified additional human study data, including several studies of chloralkali workers: studies comparing urinary mercury concentration to effects on thyroid function (2000), renal and immunologic markers (2000), and neuropsychological effects (1999, 2001), as well as an additional study of a variety of long-term health effects in workers whose exposure was assessed with historical measurements and personnel records (2001). Other human studies identified include: a study of reversible color vision loss in workers (1998); a follow-up study of neurological effects to workers who had past occupational exposures (2000); a study of mercury exposures and microdamage to kidneys in Venezuelan workers (2001); a study of changes in the monocyte-macrophage system in workers with low-level exposures (2001); two studies of auditory neuro-sensory responses (1998) and neuro-otological effects (2002) in adults and children in gold mining areas of Ecuador; a study of the effects on the activity of red cell enzymes and peripheral blood indices in workers with chronic exposure (7 months to 32 years) to mercury vapors (2000); and a study of neurobehavioral effects in Zulu chemical workers (2000). The extent to which useful exposure/dose-response data are available for a number of these studies is uncertain based on the information provided in the abstracts.

A review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 also identified developmental toxicity studies (a noted data gap in the IRIS assessment) in rats (1992, 2001), in addition to the two studies of Ecuadorian children noted above.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

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[7]The IRIS RfC verification date is listed in the IRIS summary as 4/19/90. A note is also provided indicating that the IRIS summary was included in the Mercury Study Report to Congress and that peer review and public comments (1995) were evaluated and considered in the revision and finalization of the IRIS summary.

Evaluation of the Recent Literature and Determination of Currency for:
Elemental mercury (CAS No. 7439-97-6)
(continued)

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1994) does not appear to contain study data that could produce a change in the WOE classification. A review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified three genotoxicity studies: a positive micronuclei study in mercury-exposed workers (1999); a study of chromosomal aberrations (positive) and sister-chromatid exchanges (inconclusive) in individuals exposed to mercury and other chemical contaminants (1999); and a positive mutagenicity study that also examined the mechanism by which mutations were induced (1999). The abstracts of the latter two studies do not reveal the form of mercury investigated.

Unknown Relevance
Thirty-three documents were categorized as being of unknown relevance, including 21 records from the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services) and a study entitled "Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort." The documents listed in the CRISP database include descriptions of proposed or ongoing studies of mercury's immunotoxicity, a study of exposure to dentists entitled "Chronic Disease Risks Associated with Mercury Vapor Exposure," and "Cellular and Molecular Toxicity in Human Mammary Cells."

Note: A literature search conducted for the years 1998 to 2002 identified one study carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for inhaled mercury vapor (2001).

Note: Because of the large number of references found in the literature search (approximately 2,050), search results were limited with a secondary search in EndNote to identify references containing terms related to human studies and carcinogenicity assessments, including: human, worker, subject, patient, occupa*, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. In addition, references *containing* the CAS number for mercuric chloride and/or methylmercury, but not the CAS number for elemental mercury were coded N/A. Studies *containing* the terms phytox*, ecotox*, aquatic, sediment, ocean, watershed, ecosystem, patch, or allergy were also coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Merphos oxide (CAS No. 78-48-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for merphos oxide was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for merphos oxide was derived based on a 90-day delayed neurotoxicity study in hens (1979). An uncertainty factor was assigned based on the lack of a complete database. In its 2000 Interim Reregistration Eligibility Decision (IRED) and 2000 Human Health Risk Assessment for Tribufos (merphos oxide), EPA Office of Pesticide Programs (OPP) derived an RfD based on a 1-year dietary study in dogs (1991). In addition, a literature search conducted for the years 1986 to 2002 identified four multi-generational reproductive and developmental dietary toxicity studies of merphos oxide in Sprague-Dawley rats (1996, 1998)[8].

Inhalation Reference Concentration (RfC)
An inhalation RfC for merphos oxide is not available because EPA determined that the data were insufficient to support development of an RfD (latest assessment 1992). A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for merphos oxide.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In its 2000 Interim IRED and 2000 Human Health Risk Assessment for Tribufos, OPP's Cancer Peer Review Committee classified tribufos as an "unlikely human carcinogen" at low doses, but a "likely carcinogen" at high doses. A 1993 hepatocarcinogenicity bioassay in rats found merphos oxide negative in both number and area analyses.

Unknown Relevance
One document was categorized as being of unknown relevance.

[8]Note: A literature search for the years 1986 to 2002 was conducted prior to the identification of the 2000 IRED document for tribufos.

Evaluation of the Recent Literature and Determination of Currency for:
Methamidophos (CAS No. 10265-92-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for methamidophos was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for methamidophos was derived based on a 1-year dietary study in dogs completed in 1984. A Registration Eligibility Decision (RED) is being prepared by EPA Office of Pesticide Programs (OPP), but has not been finalized. In its 2000 Health Effects Risk Assessment, OPP derived an RfD based on an 8-week toxicity study in rats (1991). (The RED status states that a 60-day public participation period for risk management decisions has been completed as of April 2000.)

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In its Health Effects Risk Assessment (2000), OPP's Hazard Identification Assessment Review Committee classified methamidophos as "not likely" to be a human carcinogen.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Methyl isocyanate (CAS No. 624-83-9)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An inhalation RfC for methyl isocyanate is not available because EPA determined that the data were insufficient to support development of an RfC (latest assessment 1990). The literature published since 1990 does not appear to contain study data that could be used to develop an RfC.

A literature search conducted for the years 1989 to 2002, however, identified developmental toxicity studies: a maternal and fetal toxicity study in Swiss-white mice and Sprague-Dawley rats that received a single 3-hour exposure to methyl isocyanate (1990) and two teratological studies in Charles Foster rats that appeared to involve exposure prior to mating only (1994, 1996). In addition, the literature search identified the findings of a survey of the pregnancy outcomes and health status of 200 children whose pregnant mothers were exposed to methyl isocyanate vapor during an accidental factory spill in 1984, in Bhopal, India (1991)[9].

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified six studies of methyl isocyanate genotoxicity and one study of its carcinogenicity. A genotoxicity test of the effects of inhalation exposure on the somatic cells of mice, by means of an *in vivo* micronucleus test and chromosomal analysis of bone marrow cells, revealed few structural and numerical abnormalities (1989). A 1992 study demonstrated the positive genotoxic response of methyl isocyanate-modified DNA in E. coli. A study of germ cell mutagenicity in inhalation-exposed rats concluded that the observed failure of methyl isocyanate to cause germ cell mutagenicity was related to its poor biodistribution to the target sites (1992).

[9]Note: Several follow-up studies (1990 to 1997) report the effects of exposure to high levels of methyl isocyanate accidentally released in 1984, in Bhopal, India.

Evaluation of the Recent Literature and Determination of Currency for:
Methyl isocyanate (CAS No. 624-83-9)
(continued)

Two studies of peripheral blood leucocyte cultures, from people exposed to methyl isocyanate gas at Bhopal, India, were negative for chromosomal aberrations, effects on sister chromatid exchanges, and cell cycle effects (1992, 1996). One chromosomal survey using standard lymphocyte cultures found that people exposed to methyl isocyanate repeatedly showed chromosomal translocations at particular chromosomes (1990). A 1999 study of cancer patterns of the lung, oropharynx, and oral cavity in relation to methyl isocyanate gas exposure at Bhopal, India, concluded that the full potential of excess risk, if any, may not manifest for 15 to 20 years after the accident.

Unknown Relevance

Twenty-seven documents, many of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "An Assessment of Pulmonary Effects from Long Term Low Level Exposure to Methyl Isocyanate" (1992), and five studies related to the effects of a high level accidental release of methyl isocyanate in Bhopal, India, in 1984.

Evaluation of the Recent Literature and Determination of Currency for:
Methyl methacrylate (CAS No. 80-62-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for methyl methacrylate was derived (1997) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1996 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for methyl methacrylate.

Inhalation Reference Concentration (RfC)
The literature published since the oral RfC for methyl methacrylate was derived (1997) does not appear to contain study data that could potentially produce a change in the RfC. A literature search conducted for the years 1996 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for methyl methacrylate.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (E—evidence of non-carcinogenicity for humans) was derived (1997) does not appear to contain study data that could potentially produce a change in the WOE.

The IRIS WOE for methyl methacrylate was derived based on the results of four chronic inhalation studies in three animal species. A literature search conducted for the years 1996 to 2002 identified one negative Ames test conducted with four different Salmonella strains (1996) and one mortality study of workers that found no clear evidence that employment at polymethyl methacrylate production factories or exposure to methyl methacrylate had adversely affected the mortalities of workers (2000). One study of the relation of malignant neoplasm incidence to the dose of methyl methacrylate in workers found a "clear correlation" between the dose of methyl methacrylate and the risk for cancer of the genital system in females and of the lung in males (2000). This study, however, was published only in Russian so the quality of the study cannot be assessed.

An International Agency for Research on Cancer (IARC) Monograph (1994) characterized methyl methacylate as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
Ten documents, most of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Methyl methacrylate (CAS No. 80-62-6)
(continued)

Note: A literature search conducted for the years 1996 to 2002 identified three studies carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for methyl methacrylate (1999, 2001). Two of these studies (1999) are referenced in letters from Methacrylate Producers Association, Inc. to EPA (2001).

Evaluation of the Recent Literature and Determination of Currency for:
2-Methyl-4-chlorophenoxyacetic acid (CAS No. 94-74-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2-methyl-4-chlorophenoxyacetic acid was derived (1988) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for 2-methyl-4-chlorophenoxyacetic acid was derived based on a 1-year dietary study in dogs (1986). An uncertainty factor was assigned based on the lack of a complete database on chronic toxicity (chronic rat and mouse study, and teratogenicity in two species). A literature search conducted for the years 1987 to 2002 identified a 2-year dietary toxicity study in Wistar rats (1999), an 18-month dietary toxicity study in ICR mice (1990), and a two-generation dietary reproductive toxicity study in rats (2001).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1986 to 2002 identified a 2-year dietary oncogenicity study in Wistar rats and an 18-month chronic toxicity study in IRC mice.

Unknown Relevance
Five documents were categorized as being of unknown relevance, two of which were submissions to EPA Office of Toxic Substances (OTS).

Note: Because of the large number of references found in the literature search (approximately 665), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
2-(2-Methyl-4-chlorophenoxy)propionic acid (MCPP) (CAS No. 93-65-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for MCPP was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for MCPP.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Nine documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: Methylmercury (CAS No. 22967-92-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for methylmercury was derived (2001) does not appear to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for methylmercury was derived based on a benchmark dose analysis of epidemiological studies of developmental neuropsychological impairment in a Faroe Islands cohort. The literature search conducted for the years 1998 to 2002 identified a number of epidemiology and developmental toxicity studies (published between 1998 and 2001), including a study describing a biologically-based dose response model for developmental toxicity of methylmercury in rats (2000, 2001) and four developmental toxicity studies in rats and monkeys (2000). Because the IRIS RfD is based on a robust epidemiologic dat set in a sensitive subpopulation, these studies are not likely to result in changes in the current RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1994) does not appear to contain study data that could produce a change in the WOE. Review of the ATSDR Toxicological Profile (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Seventeen documents were categorized as being of unknown relevance, including studies titled "Effects of chronic, intrauterine organic and inorganic mercury intoxication on the epileptogenicity of developing rats" (2000), "Fetal methylmercury syndrome" (2000), "Effect of low-dose developmental methylmercury intoxication on epileptogenicity in rats" (2000), and "Porphyrinurias induced by mercury and other metals" (2001).

Note: Because of the large number of references found in the literature search (approximately 370), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
3-Methylphenol (CAS No. 108-39-4)

Oral Reference Dose (RfD)
Studies made available since the oral RfD for 3-methylphenol was derived (1987) appear to contain data that could potentially produce a change in the RfD. Unpublished developmental toxicity studies (rats and rabbits) and a two-generation reproductive toxicity study (rat) were documented in the EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) (1994), the Toxic Substance Control Act Test Submission (TSCATS) database, submissions by the Chemical Manufacturers' Association (Cresols Panel) (CMA) to the IRIS Submission Desk, and the ATSDR Toxicological Profile (1992). A literature search conducted for the years 1993 to 2002 identified no additional published studies that would be directly useful in the derivation of an RfD for 3-methylphenol.

ATSDR did not derive a chronic or intermediate oral minimal risk level (MRL) in its 1992 Toxicological Profile. The OPP RED (1994) indicated that a reference dose was not required because significant toxicological residues of 3-methylphenol are not expected in food or feed products.

Inhalation Reference Concentration (RfC)
An RfC for 3-methylphenol is not available because EPA determined that the data were insufficient to support development of an RfC (latest assessment 1991). The RfC and supporting information previously on IRIS were withdrawn. Review of the ATSDR Toxicological Profile (1992) and the OPP RED (1994) and a literature search conducted for the years 1993 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 3-methylphenol.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1989) does not appear to contain study data that could produce a change in the WOE. Review of the ATSDR Toxicological Profile (1992) and the OPP RED (1994) and a literature search conducted for the years 1993 to 2002 identified no new studies that would be directly useful in establishing a WOE classification. In submissions to the IRIS Submission Desk, however, CMA presented (1993, 1994) data on genetic assays (generated in response to a Toxic Substance Control Act [TSCA] test rule and from the National Toxicology Program [NTP] [1988, 1989]).

Unknown Relevance
Five documents, two of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Reproductive toxicology, m-/p-cresol" (1997).

Evaluation of the Recent Literature and Determination of Currency for:
4-Methylphenol (CAS No. 106-44-5)

Oral Reference Dose (RfD)
The oral RfD and supporting information for 4-methylphenol previously on IRIS were withdrawn in 1991. Unpublished developmental toxicity studies (rats and rabbits) and a two-generation reproductive toxicity study (rat) not previously considered in the IRIS assessment were documented in the Toxic Substance Control Act Test Submission (TSCATS) database, submissions by the Chemical Manufacturers' Association (Cresols Panel) (CMA) to the IRIS Submission Desk, and the ATSDR Toxicological Profile (1992). These studies could potentially support the development of an RfD for 4-methylphenol. A literature search conducted for the years 1991 to 2002 identified no additional published studies that would be directly useful in the derivation of an RfD for 4-methylphenol.

Inhalation Reference Concentration (RfC)
An RfC for 4-methylphenol is not available because EPA determined that the health effects data were inadequate to support development of an RfC (latest assessment 1991). Review of the ATSDR Toxicological Profile (1992) and a literature search conducted for the years 1991 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 4-methylphenol.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1989) does not appear to contain study data that could produce a change in the WOE. Review of the ATSDR Toxicological Profile (1992) and a literature search conducted for the years 1991 to 2002 identified no new studies that would be directly useful in establishing a WOE classification. In submissions to the IRIS Submission Desk, CMA presented data (1993, 1994) on genetic assays (generated in response to a Toxic Substances Control Act [TSCA] test rule and from the National Toxicology Program [NTP] [1988, 1989]).

Unknown Relevance
Nine documents, three of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "Initial Submission: Developmental Toxicity Evaluation with O-Cresol, M-Cresol, and P-Cresol Administered by Gavage to Sprague-Dawley Rats with Cover Letter Dated 082492" (1992), "Reproductive toxicology, m-/p-cresol" (1997), and "P-cresol and uric acid: two old uremic toxins revisited" (1997), and a letter from the Department of Health and Human Services to EPA (2000) regarding Salmonella assays performed on cresols (with attachments).

Evaluation of the Recent Literature and Determination of Currency for:
4-Methylphenol (CAS No. 106-44-5)
(continued)

Note: Because of the large number of references found in the literature search (approximately 450), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Metribuzin (CAS No. 21087-64-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for metribuzin was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for metribuzin was derived based on a 2-year dietary study in dogs completed in 1974. The EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) (1998) presented an RfD based on a two-generation reproductive toxicity study in Crl:CD BR rats (1988; unpublished) and a 2-year dietary study in Fischer 344 rats (1993; unpublished).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1993) does not appear to contain study data that could produce a change in the WOE. A review of the 1998 RED and a literature search conducted for the years 1997 to 2002 identified three negative carcinogenicity studies, two in rats and one in mice (1998) and one positive DNA adduct study (1997). The 1998 RED reports that in 1995 the OPP/Health Effects Division (HED) RfD Peer Review Committee classified metribuzin as D—not classifiable as to human carcinogenicity—and did not refer it to the OPP/HED Cancer Peer Review Committee.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Nitrate (CAS No. 14797-55-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for nitrate was derived (1990) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for nitrate was derived based on two epidemiological studies showing the incidence of methemoglobinemia (1950, 1951). A literature search conducted for the years 1989 to 2002 identified four epidemiological studies, including studies that evaluated the effect of well-water nitrates on infant health (1991), the correlation between Type-1 diabetes and nitrate in drinking water (1992), the effect of nitrate in drinking water on thyroid function and volume (1994), and the risk factors associated with neural tube defects (1996). The literature search also identified several chronic toxicity studies (1993, 1998) and short-term reproductive and developmental studies (1993, 1996, 1997) in animals.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified several epidemiological studies investigating cancer incidence, including two cohort studies of male nitrate fertilizer workers (1991, 1993), a study investigating the relationship between the intake of nitrates, nitrites, and N-nitrosodimethylamine in adult Finnish men and women (1999), four case-control studies (1993, 1995, 1997, 1998), and a study analyzing the relationship between nitrate levels in drinking water and various cancers (1998). In addition, three studies explored the relationship between nitrate exposure and endogenous formation of carcinogenic nitrosamines (1991, 1998, 1998).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: In addition to the epidemiological studies mentioned above, a literature search conducted for the years 1989 to 2002 identified studies that may be relevant to the establishment of a WOE classification. One study evaluated the peripheral lymphocyte HPRT variant frequency in humans exposed to nitrate in drinking water (1996). Other studies investigated DNA strand break studies in Chinese hamster V79 cells (1990) and human lymphocytes (1993).

Evaluation of the Recent Literature and Determination of Currency for:
Nitrate (CAS No. 14797-55-8)
(continued)

Unknown Relevance
Forty-four documents were categorized as being of unknown relevance. Among these studies are "Correlation Between the Risk of Gastric Cancer in the Province of Soria, Spain and the Nitrate Content of Drinking Water," "Risk Factors of Gastric Precancerous Lesions in High-Risk Colombian Population, II. Nitrate and Nitrite," "Nitrate Content in the Diet of Population, Various Foci of Opisthorchiasis," "Nitrate Contamination of Drinking Water, Evaluation of Genotoxic Risk in Human Populations," "Consumption of Nitrate, Nitrite, and Nitrosodimethylamine and Cancer of the Larynx, Esophagus, and Oral Cavity," "Transplacental Transfer of Nitrates and Their Influence on the Human Fetus," "Dietary Factors and the Risk of Glioma in Adults: Results of a Case-Control Study in Melbourne, Australia," "Impact of Nitrates in Drinking Water on Cancer Mortality in Valencia, Spain," "Risk of Non-Hodgkin's Lymphoma and Drinking Water Nitrate," "Spontaneous Abortions Possibly Related to Ingestion of Nitrate-Contaminated Well Water, Lagrange County, Indiana," "Childhood IDDM is Linked to Nitrate Levels in Drinking Water," "Nitrate Intake and Gastric Cancer Risk Results from the Netherlands Cohort Study," and "Non-Hodgkin's Lymphoma and Nitrate in Drinking Water: A Study in Yorkshire, United Kingdom."

Note: Because of the large number of references found in the literature search (approximately 4,500), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag* Any references *not containing* one of these search terms were coded as N/A. A tertiary search was conducted to eliminate references also containing phytotox*, ecotox*, and aquatic. Any references *containing* one of these search terms were also coded as N/A. Because a large number of references remained (approximately 1,100), search results were limited to the CAS number. Any references *not containing* the CAS number were coded "labanimal/noCAS#." The remaining references (approximately 300) were retained for review.

Evaluation of the Recent Literature and Determination of Currency for:
Nitrite (CAS No. 14797-65-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for nitrite was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for nitrite.

Note: The IRIS RfD for nitrite is based on an epidemiological study that evaluated exposure to nitrate (nitrogen) in contaminated drinking water. A screening-level review of the current health effects literature for nitrate, which was conducted under this Phase II review of the IRIS database, is also available. This evaluation indicated that the literature published since 1990 contains study data that could potentially produce a change in the RfD for nitrate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a follow-up study investigating the relationship between the intake of nitrates, nitrites, and n-nitrosodimethylamine and the risk of colorectal and other gastro-intestinal cancers in Finnish men and women (1999).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a study evaluating the teratogenic and mutagenic effects of nitrite on mouse fetuses (1989) and a cohort study investigating the risk of colorectal and other gastro-intestinal cancers after exposure to nitrite (1999).

Unknown Relevance
Twenty-two documents were categorized as being of unknown relevance. Among these studies are "Nitrite-induced Methemoglobinemia" (1987), "Mammalian Synthesis of Nitrite, Nitrate, Nitric Oxide, and N-Nitrosating Agents" (1992), "Consumption of Nitrate, Nitrite, and Nitrosodimethylamine and the Risk of Upper Aerodigestive Tract Cancer" (1995), "Nitrites caused DNA Adduct Formation as Measured by 32p DNA Radiolabeling and Two-dimensional Thin-layer Chromatography" (1995), and "Induction of Cell Death in the Intestinal Crypt of Mice Following Oral Administration of Nitrate and Nitrite" (1998).

Evaluation of the Recent Literature and Determination of Currency for:
Nitrite (CAS No. 14797-65-0)
(continued)

Note: Because of the large number of references found in the literature search (approximately 3,200), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. A tertiary search was conducted to eliminate references also containing phytotox*, ecotox*, and aquatic. Any references *containing* one of these search terms were also coded as N/A. Because a large number of references remained (approximately 1,200), search results were limited to the CAS number. Any references *not containing* the CAS number were coded "labanimal/noCAS#." The remaining references (approximately 430) were retained for review.

Evaluation of the Recent Literature and Determination of Currency for:
N-Nitrosodimethylamine (CAS No. 62-75-9)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A National Center for Environmental Assessment (NCEA) Provisional Assessment (2001) derived a provisional RfD for N-nitrosodimethylamine based on a developmental drinking water study in CD-1 mice (1978).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the oral CSF for N-nitrosodimethylamine was derived (1986) may contain study data that could potentially produce a change in the CSF.

The IRIS CSF for N-nitrosodimethylamine was derived based on a drinking water study in Colworth rats (1984). A Health Canada Assessment (1999) derived a tumorigenic dose 05 (TD05) for N-nitrosodimethylamine based the same study used to derive the IRIS CSF. A literature search conducted for the years 1998 to 2002 identified a study investigating the relationship between the intake of nitrates, nitrites, and N-nitrosodimethylamine and the risk of cancer in Finnish men and women (1999) that may be useful in the derivation of a CSF for N-nitrosodimethylamine. The nature and extent of exposure data in the human study cannot be fully determined from the abstract.

Inhalation Unit Risk (IUR)
The literature published since the inhalation IUR for N-nitrosodimethylamine was derived (1986) does not appear to contain study data that could potentially produce a change in the IUR. A review of the Health Canada Assessment (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for N-nitrosodimethylamine.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1986) may contain study data that could potentially produce a change in the WOE.

The IRIS WOE for N-nitrosodimethylamine was derived based on the induction of tumors at multiple sites in both rodents and nonrodent mammals exposed by various routes (1967, 1973, 1976, 1984). An International Agency for Research on Cancer (IARC) Monograph published in 1987 characterized N-nitrosodimethylamine as Group 2A—probably carcinogenic to humans. A review of the Health Canada Assessment (1999) and a literature search conducted for the years 1998 to 2002 identified a study that reported a positive relationship between the intake of N-nitrosodimethylamine and the risk of cancer (1999) and eleven studies evaluating mechanisms of carcinogenic action for N-nitrosodimethylamine (1998, 1999, 2000, 2001).

Evaluation of the Recent Literature and Determination of Currency for:
N-Nitrosodimethylamine (CAS No. 62-75-9)
(continued)

Other studies found in the literature search that might be relevant to the WOE classification include many genotoxicity and mutagenicity studies that all reported positive findings. These include microbial mutagenicity studies (1999, 2000); DNA adduct studies (1999, 2001); a DNA strand break study (1998); mutational spectrum studies in human lymphoblastoid cells (1998), the lacI transgene in Big Blue C57BL/6 mice (1998, 1999), and the lacI transgene in B6C3F1 mouse liver (1998); a study of mutagenic effects on human sperm chromosomes (2001); and a renal tumor induction study (2001) in male albino non-inbred rats exposed to a single injection of N-nitrosodimethylamine.

Unknown Relevance

Twenty documents were categorized as being of unknown relevance, seven of which were records from CRISP, a biomedical database of research projects supported by the Department of Health and Human Services, and one of which was a submission to EPA's Office of Toxic Substances (OTS). Among these are "Mechanisms in Perinatal Carcinogenesis," "Necrosis Factor Alpha Induced Hepatotoxicity," "N-nitrosodimethylamine, Toxicologic Significance," and "Mechanisms for Tnf Alpha in Xenobiotic Liver Injury."

Evaluation of the Recent Literature and Determination of Currency for:
N-Nitrosodi-N-propylamine (CAS No. 621-64-7)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: An ATSDR Toxicological Profile (1989) presented an acute oral minimal risk level (MRL) for N-nitrosodi-N-propylamine but derived no intermediate or chronic MRL.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the oral CSF for N-nitrosodi-N-propylamine was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF. The IRIS CSF for N-nitrosodi-N-propylamine was derived based on a lifetime drinking water carcinogenicity study in BD rats (1967). A literature search conducted for the years 1986 to 2002 identified a 50-week carcinogenicity study in C57B1 mice involving twice weekly administration by gastric intubation (1989; published in Russian).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A literature search conducted for the years 1986 to 2002 identified a 15-week intratracheal carcinogenicity study in Syrian golden hamsters (1988).

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1987) does not appear to contain study data that could produce a change in the WOE.

An International Agency for Research on Cancer (IARC) Monograph (1987) characterized N-nitrosodi-N-propylamine as Group 2B—possibly carcinogenic to humans. A literature search conducted for the years 1986 to 2002 identified a 15-week intratracheal carcinogenicity study in Syrian golden hamsters (1988) and 50-week oral carcinogenicity study in C57B1 mice (1989; published in Russian) (see above), as well as several positive genotoxicity and mutagenicity studies, including microbial mutagenicity studies (1992, 2000), mutagenicity studies using Syrian golden hamster hepatocyte V79 cells (1986) and lacZ transgenic mice (MutaMouse) (1999), a genotoxicity study using rodent pancreas (1987), and studies of DNA fragmentation in human and rat hepatocytes (1988) and human and rat kidney cells (1996).

Unknown Relevance
Nineteen documents were categorized as being of unknown relevance. Among these are "Induction of Hepatocellular Carcinoma in Nonhuman Primates by Chemical Carcinogens," and "Integration of Laboratory and Epidemiologic Studies to Evaluate Genotoxic Exposure in Tool and Die Workers."

Evaluation of the Recent Literature and Determination of Currency for:
N-Nitrosodiphenylamine (CAS No. 86-30-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A National Center for Environmental Assessment (NCEA) Provisional Assessment (2001) derived a provisional RfD for N-nitrosodiphenylamine based on a chronic dietary study in rats (1979), which was the same study from which the IRIS CSF was derived.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the oral CSF for N-nitrosodiphenylamine was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF. Review of the ATSDR Toxicological Profile (1993) and a literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for N-nitrosodiphenylamine.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1987) does not appear to contain study data that could produce a change in the WOE. An International Agency for Research on Cancer (IARC) Monograph (1987) characterized N-nitrosodiphenylamine as Group 3—not classifiable as to carcinogenicity in humans. Review of the ATSDR Toxicological Profile (1993) and a literature search conducted for the years 1992 to 2002 identified no new studies that would be directly useful in the derivation of a WOE for N-nitrosodiphenylamine.

Unknown Relevance
Three documents were categorized as being of unknown relevance. Among these studies are "The Genetic Toxicology of N-nitrosodiphenylamine."

Evaluation of the Recent Literature and Determination of Currency for:
Oxyfluorfen (CAS No. 42874-03-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for oxyfluorfen was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for oxyfluorfen was derived based on a 20-month dietary study in Charles River CD-1 mice (1977). In the 2001 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an RfD based on the same study as the IRIS RfD, as well as two 104-week dietary toxicity studies in dogs (1981, 1990) and a chronic carcinogenicity study in mice (1990) that may be useful in the derivation of an RfD for oxyfluorfen.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: In the RED, the EPA OPP Cancer Peer Review Committee classified oxyfluorfen as Group C—possible human carcinogen—based upon combined hepatocellular adenomas/carcinomas in the mouse carcinogenicity study used to derive the OPP RfD.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for: Pentabromodiphenyl ether (CAS No. 32534-81-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for pentabromodiphenyl ether was derived (1986) does not appear to contain study data that could potentially produce a change in the RfD. The IRIS RfD for pentabromodiphenyl ether was derived based on a 90-day gavage bioassay in male Sprague-Dawley rats (1980). A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for pentabromodiphenyl ether.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of a WOE for pentabromodiphenyl ether.

Unknown Relevance
Thirty-seven documents were categorized as being of unknown relevance, 34 of which were submissions to EPA Office of Toxic Substances (OTS). Among these studies are "Chromosome Aberrations in Human Peripheral Blood Lymphocytes with Pentabromodiphenyl Oxide," and "Teratogenic Evaluation of a Polybromodiphenyl Oxide Mixture in New Zealand White Rabbits Following Oral Exposure."

Note: Abstracts of studies using commercial grade pentabromodiphenyl ether, such as DE-71, were included for consideration even though this form is a mixture of several polybromodiphenyl ethers. In the IRIS summary, the primary reference used to derive the RfD is a study that investigated the effects of commercial grade pentabromodiphenyl ether.

Evaluation of the Recent Literature and Determination of Currency for:
Pentachlorocyclopentadiene (CAS No. 25329-35-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Pentafluoroethane (CAS No. 354-33-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An inhalation RfC for pentafluoroethane is not available because EPA determined that the data were inadequate for derivation of an RfC (latest assessment 1993). The literature available since 1993 contains study data that could potentially be used to developed an RfC. A literature search conducted for the years 1992 to 2002 identified a 13-week inhalation study of pentafluoroethane in rats (1993).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: A literature search conducted for the years 1993 to 2002 identified a genotoxicity and carcinogenicity study (1992) and a series of four studies assessing the clastogenic and mutagenic action of pentafluoroethane which were completed in 1991 and 1992 and submitted to EPA Office of Toxic Substances (OTS) in 1993.

Unknown Relevance
Five documents were categorized as being of unknown relevance, two of which were submissions to EPA OTS.

Note: A literature search conducted for the years 1992 to 2002 found two studies that made use of physiologically-based pharmacokinetic (PBPK) models for pentafluoroethane. To evaluate cardiac sensitization potential, one study investigated the relation between air and blood concentrations in humans (1995) under a variety of exposure concentrations and durations. The other study investigated the relation between the cardiac endpoint as assessed in dogs and the target arterial concentration in humans (2000).

Evaluation of the Recent Literature and Determination of Currency for: m-Phenylenediamine (CAS No. 108-45-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for m-phenylenediamine was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for m-phenylenediamine was derived based on a 90-day oral toxicity study in rats (1982). A literature search conducted for the years 1985 to 2002 identified a 78-week oral toxicity and carcinogenicity study in B6C3F1 mice (1988) that may be useful in the derivation of an RfD for m-phenylenediamine.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized m-phenylenediamine as Group 3—not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1985 to 2002 identified several studies that may be relevant to establishing a WOE classification. These included the 78-week oral toxicity and carcinogenicity study in B6C3F1 mice mentioned above (1988) that found no association between exposure and tumor incidences; microbial mutagenicity studies (1985, 1989, 1995, 1997) that mostly reported positive findings; and genotoxicity studies in mice using the bone marrow micronucleus test (1992), in human lymphocytes (1995), and in human DNA fragments (1998), all of which reported positive findings.

Unknown Relevance
Seventy-one documents were categorized as being of unknown relevance, 42 of which were submissions to EPA Office of Toxic Substances (OTS). Among these studies are "Lifetime Toxicity/Carcinogenesis Study in Rats," "Teratological Studies with M-Phenylenediamine on Rats," and "Toxicology of Hairdyes: an Overview."

Evaluation of the Recent Literature and Determination of Currency for: Phenylmercuric acetate (CAS No. 62-38-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for phenylmercuric acetate was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. The IRIS RfD for phenylmercuric acetate was derived based on a chronic oral study in rats (1950). A literature search conducted for the years 1984 to 2002 identified no new chronic animal studies, but identified one study (1986; published in Bulgarian) of the embryotoxic and teratogenic action of phenylmercuric acetate in albino rats in which the administered doses appear to be higher than those doses from which the IRIS RfD was derived.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified two genotoxicity studies (1996, 1997) with positive results.

Unknown Relevance
Eleven documents were categorized as being of unknown relevance. Among these studies are "Comparative studies of 2 organic compounds alone or in combination with ethanol following pre- or post-natal application in mice," "Nephrotoxicity of phenyl-Hg-acetate in alloxan-diabetic rats," "The neurotoxicity and mutagenicity of phenylmercury acetate and nitrate in single and combined applications in animal studies," "A comparative study of the effects of mercury compounds on cell viability and nucleic acid synthesis in hela cells," and "Computerised analysis of pathological findings in longterm trials with phenylmercuric acetate in rats."

Note: The literature search identified approximately 1,000 references because one synonym for phenylmercuric acetate is PMA, and PMA is used as an abbreviation for other chemical substances, such as phenylmercapturic acid and phorbol myristic/myristate acetate. Therefore, a secondary search was conducted in EndNote to identify references containing PMA, but not containing mercur* or the CAS number for phenylmercuric acetate. These references were coded as N/A. In addition, references containing aminophenylmercuric acetate or the keywords "phenylmercuric acetate/analogs & derivatives," but not the CAS number for phenylmercuric acetate were also coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Phenylmercuric acetate (CAS No. 62-38-4)
(continued)

The search results were further limited with a secondary search to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

\Evaluation of the Recent Literature and Determination of Currency for:
Phosmet (CAS No. 732-11-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for phosmet was derived (1986) includes study data that could potentially produce a change in the RfD.

The IRIS RfD was derived based on a 2-year dietary study in rats (1967). In the 2001 Interim Reregistration Eligibility Decision (IRED), EPA Office of Pesticide Programs (OPP) derived an RfD based on a 2-year oral toxicity and carcinogenicity study in rats (1991).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: The 2001 IRED indicates that OPP's Cancer Assessment Review Committee recommended against completing a quantitative cancer risk assessment for phosmet. According to the RED document, this recommendation is "consistent with the previous recommendation to use the reference dose (RfD) approach, in which chronic risks assessed using the RfD are considered to be protective of any carcinogenic effect, in addition to systemic or other chronic effects."

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The 2001 IRED reports the findings of OPP's Cancer Assessment Review Committee (1999), which concluded that phosmet had "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential."

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Phthalic anhydride (CAS No. 85-44-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for phthalic anhydride was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for phthalic anhydride.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A 1998 study entitled "Chromosome aberrations in vitro related to cytotoxicity of nonmutagenic and metabolic poisons" describes phthalic anhydride as a noncarcinogen. A 1987 study entitled "Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells evaluations of 108 chemicals," which has been classified as being of unknown relevance, may include information about the carcinogenicity of phthalic anhydride.

Unknown Relevance
Ten documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a submission titled "Letters regarding adverse health effects suffered by employees exposed to phthalic anhydride."

Evaluation of the Recent Literature and Determination of Currency for:
Picloram (CAS No. 1918-02-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for picloram was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for picloram was derived based on a 6-month dog feeding study completed in 1982.In its 1995 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an RfD for picloram based on a 2-year chronic toxicity study in rats (1986) that is cited in the IRIS assessment. A literature search conducted for the years 1994 to 2002 identified a 2002 Federal Register notice (April 17, 2002) referring to a 1998 OPP updated risk assessment of picloram identified as part of the Six-year Review process[10]. The risk assessment included "relevant studies that had become available on the toxicity of picloram including its potential developmental and reproductive toxicity," but derived the same RfD as the 1995 RED.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1991) classified picloram asGroup 3—not classifiable as to carcinogenicity in humans. The OPP RED (1995)classified picloram as Group E—evidence of non-carcinogenicity for humans—based on the assessment of OPP's Cancer Assessment Review Committee (applies to the picloram acid and potassium salt forms). A 2002 Federal Register notice (April 17, 2002) refers to a 1998 OPP updated risk assessment of picloram that also classifies picloram as Group E—evidence of non-carcinogenicity for humans.

Unknown Relevance
Two documents were categorized as being of unknown relevance.

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[10]EPA. 2002. *Six-Year Review, Chemical Contaminants, Health Effects Technical Support Document.* Office of Water, Office of Science and Technology. EPA Publication No. 822-R-01-001. February 2002.

Evaluation of the Recent Literature and Determination of Currency for:
Pirimiphos-methyl (CAS No. 29232-93-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for pirimiphos-methyl was derived (1986) includes study data that could potentially produce a change in the RfD.

The IRIS RfD was derived based on a 28-day and a 56-day human feeding study (1974, 1976). In the Revised Human Health Risk Assessment and supporting documentation for the Reregistration Eligibility Decision (RED) (1999), EPA Office of Pesticide Programs (OPP) derived an RfD based on a 13-week oral neurotoxicity study in rats (1995).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Potassium silver cyanide (CAS No. 506-61-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for potassium silver cyanide was derived (1985) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for potassium silver cyanide was derived based on a conversion of the no-observed-adverse-effect-level (NOAEL) for dissociated cyanide determined from a chronic oral study and a subchronic to chronic oral bioassay in rats (1955, 1979). A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for potassium silver cyanide. However, the ATSDR Toxicological Profile for dissociated cyanide (1997) considered literature published since 1985 that may be useful in the derivation of an RfD for potassium silver cyanide. The ATSDR Toxicological Profile for dissociated cyanide (1997) provided an intermediate oral minimal risk level (MRL) for cyanide based on a National Toxicology Program (NTP) 13-week drinking water study in F344/N rats and B6C3F1 mice exposed to sodium cyanide (1993).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Prometon (CAS No. 1610-18-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for prometon was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for prometon was derived based on a subchronic dietary study in Sprague Dawley rats (1982). A literature search conducted for the years 1985 to 2002 identified a 2-year dietary study in Sprague-Dawley rats that noted toxicity-related reduced survival; this abstract does not specify administered doses, but suggests effects occurred only at "excessive levels" (1994).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a 2-year dietary study in Sprague-Dawley rats that showed an increased incidence of mammary tumors (1994) and a genotoxicity study (1995).

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Pronamide (CAS No. 23950-58-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for pronamide was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for pronamide was derived based on a 2-year dietary study in dogs (1970). In the 1994 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an RfD for pronamide based on a chronic carcinogenicity feeding study in rats (1990; unpublished).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In 1992, OPP's Carcinogenicity Peer Review Committee classified pronamide as Group B2—probable human carcinogen).

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Propanil (CAS No. 709-98-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for propanil was derived (1987) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for propanil was derived based on a 2-year rat dietary study (1964). An uncertainty factor was assigned based on the lack of an adequate toxicity database. A literature search conducted for the years 1986 to 2002 identified a reproductive toxicity study in rats orally administered propanil during early pregnancy (1997) and a study that evaluated immune parameters in propanil-exposed farm families (with a companion study by the same laboratory that may provide appropriate exposure data) (2001).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1986 to 2002 identified one genotoxicity study that reported propanil was negative in a Salmonella typhimurium reversion assay; propanil produced a dose-dependent hepatocyte toxicity in a Chinese-hamster-ovary-hypoxanthine-guanine-phosphoribosyl-transferase (HGPRT) test (1988).

Unknown Relevance
Thirteen documents were categorized as being of unknown relevance, nine of which were from the Computer Retrieval of Information on Scientific Projects (CRISP) database, a biomedical database of research projects supported by the Department of Health and Human Services.

Note: Because of the large number of references found in the literature search (approximately 670), search results were limited with a secondary search in EndNote to identify references containing the CAS number or synonyms of propanil. Search results were further limited by a tertiary search to identify common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Propargyl alcohol (CAS No. 107-19-7)

Oral Reference Dose (RfD)
The literature published since the oral RfD for propargyl alcohol was derived (1990) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for propargyl alcohol.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1989 to 2002 identified a study that reported propargyl alcohol induced chromosomal aberrations *in vitro*, was clastogenic *in vitro*, did not induce reverse mutations detectable with the Salmonella/mammalian microsome assay, and did not induce micronuclei in the mouse bone-marrow micronucleus assay (1994).

Unknown Relevance
Four documents were categorized as being of unknown relevance, two of which were submissions to EPA Office of Toxic Substances (OTS).

Evaluation of the Recent Literature and Determination of Currency for:
Propham (CAS No. 122-42-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for propham was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for propham.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized propham as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
One documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Propylene glycol monomethyl ether (CAS No. 107-98-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
The literature published since the oral RfD for propylene glycol monomethyl ether was derived (1991) contains study data that could potentially produce a change in the RfC.

The IRIS RfC for propylene glycol monomethyl ether was derived based on a subchronic inhalation study in rats and rabbits (1983). A literature search conducted for the years 1990 to 2002 identified a 2-year inhalation study in B6C3F1-mice and F344-rats (1996) and a 2-generation reproductive study in Sprague-Dawley rats (1999). The Chemical Manufacturers Association (CMA) March 2000 submission to the IRIS Submission Desk presented a 2-year inhalation study in Fischer 344 rats (1998) that has been used by the state of California to derive an inhalation reference exposure level.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Seventeen documents, many of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "Initial Submission: Preliminary P1/F1 Generation Results Only in Two-Generation Reproduction Inhalation Study of Propylene Glycol Monomethyl Ether" (1995), "Reproductive Toxicology. Propylene Glycol Monomethyl Ether" (1997), "Propylene Glycol Monomethyl Ether: Two-Generation Inhalation Reproduction Study in Sprague-Dawley Rats" (1997), "Initial Submission: Inhalation Toxicity Study with Propylene Glycol Monomethyl Ether in Rats & Mice" (date unknown), and "2-Year Vapor Inhalation Chronic/Oncogenicity Study and Hepatic and Renal Cellular Proliferation, P450 Enzyme Induction and Protein Droplet Nephropathy" (1998) (this appears to be the 1998 study presented by CMA [see above]).

Evaluation of the Recent Literature and Determination of Currency for:
Propylene glycol (CAS No. 57-55-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An RfC for propylene glycol is not available because EPA determined that the data were inadequate to support development of an RfC (latest assessment 1991). The literature published since EPA's last review of the health effects literature for propylene glycol appears to contain study data that could potentially produce a change in the RfC.

In the 1997 Toxicological Profile, ATSDR derived an inhalation minimal risk level (MRL) based on a 13-week inhalation toxicity study in Sprague-Dawley rats (1989). This 13-week inhalation study was published prior to the 1991 deliberations of EPA's RfD/RfC Work Group; however, EPA apparently based the assessment of propylene glycol health effects literature on a 1987 review that would not have identified the 13-week inhalation study. A literature search for the years 1996 to 2002 identified no additional studies that would be directly useful in the derivation of an RfC.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Twenty-nine documents, most of which were submissions to EPA Office of Toxic Substances (OTS) were categorized as being of unknown relevance. Among these studies are "Reproductive toxicology. Propylene glycol" (1997), "Propylene glycol toxicity related to high-dose lorazepam infusion: case report and discussion" (1999), "Propylene glycol toxicity in a patient receiving intravenous diazepam" (2000), "Correction and comment: possible toxicity from propylene glycol in injectable drug preparations" (1997), and "Etomidate and propylene glycol toxicity" (1998).

Evaluation of the Recent Literature and Determination of Currency for:
Propyleneimine (CAS No. 75-55-8)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An RfC for propyleneimine is not available because EPA determined that the data were inadequate to support development of an RfC (latest assessment 1991). A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for propyleneimine.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) characterized propyleneimine as Group 2B—possibly carcinogenic to humans.

Unknown Relevance
One document, a submission to EPA's Office of Toxic Substances (OTS), titled "Initial Submission: Mutagenicity Study with 2-Methylaziridine in Salmonella Typhimurium and Saccharomyces Cerevisiae (Final Report)" (1992), was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Pyridine (CAS No. 110-86-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for pyridine was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. Review of the ATSDR Toxicological Profile (1992) and a literature search conducted for the years 1991 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for pyridine.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (2000) characterized pyridine as Group 3—not classifiable as to carcinogenicity in humans. A National Toxicology Program (NTP) Cancer Bioassay (2000) found "clear evidence of carcinogenicity" of pyridine based on a 2-year oral study in rats.

Unknown Relevance
Eleven documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "2-Year Chronic Dosed Water Study of Pyridine (C55301b) in Male and Female F344 Rats and Male Wistar Rats" (1997), "Initial Submission: Mortality Patterns of Workers in the Niagara Plant (Final Report on Mixtures of Chemical Substances) with Attachments" (1992), and "Genotoxicity of Industrial Solvents" (1992).

Note: Because of the large number of references found in the literature search (approximately 1,465), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. An additional secondary search was conducted to identify references that contained neither the word pyridine nor the CAS number for pyridine (110-86-1). Any references *not containing* pyridine or its CAS number were coded as N/A. Finally, 2-amino-1-methyl-6- phenylimidazo[4,5-b]pyridine (Phip) is a carcinogen found in tobacco smoke, automobile exhaust, and cooked food, and has no direct relevance to the toxicity assessment of pyridine. A large number of references were identified by a secondary search for the abbreviation Phip. Any references *containing* the abbreviation Phip were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Quinalphos (CAS No. 13593-03-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for quinalphos was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for quinalphos was derived based on a 2-year dietary study in canines (1980). A literature search conducted for the years 1985 to 2002 identified several studies that could potentially produce a change in the RfD, including a study in which quinalphos was administered orally to pregnant rats and a no-observed-effect-level (NOEL) of 2 milligrams per kilogram body weight (mg/kg) was established (1999). The literature search also identified studies evaluating the effects of quinalphos exposure in neonatal rat pups (1998), the oral toxicity in Wistar rats subchronically gavaged with quinalphos daily for 90 days (1993), the fetotoxicity in pregnant Wistar rats gavaged with quinalphos (1992), and cytogenetic and fetotoxic effects in pregnant mice injected intraperitoneally with Ekalux (quinalphos) (1989).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a dermal study evaluating the tumorigenic potential of quinalphos in Swiss albino mice (2000), a study evaluating mutagenicity in mouse marrow cells *in vivo* and Chinese hamster lung cells *in vitro* (1993), two studies evaluating cytogenetic effects showing a significant increase in chromosomal aberrations (1990, 1991), and a study evaluating cytogenetic and fetotoxic effects in pregnant mice injected intraperitoneally with Ekalux (quinalphos) (1989).

Unknown Relevance
Four documents, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these studies are "Cytological Effects of Some Organophosphorous Pesticides" (1985) and "Cytogenetic and Fetotoxic Effects of Organophosphate Pesticides on Mice" (1989).

Note: Because of the large number of references found in the literature search (approximately 500), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for: Quinoline (CAS No. 91-22-5)

Oral Reference Dose (RfD)
An oral RfD for quinoline is not available because EPA determined that the data were insufficient to support development of an RfD (latest assessment 2001). A literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for quinoline.

Inhalation Reference Concentration (RfC)
An inhalation RfC for quinoline is not available because EPA determined that the data were insufficient to support development of an RfC (latest assessment 2001). A literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for quinoline.

Oral Slope Factor (CSF)
The literature published since the CSF for quinoline was derived (2001) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for quinoline.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (2001) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 2000 to 2002 identified one study (2000) that found that quinoline is genotoxic in its target organ, the liver, and identified the G:C to C:G transversion as the molecular signature of quinoline-induced mutations.

Unknown Relevance
Two documents were categorized as being of unknown relevance, both of which were records listed in the Computer Retrieval of Information on Scientific Projects (CRISP) database (a biomedical database of research projects supported by the Department of Health and Human Services).

Evaluation of the Recent Literature and Determination of Currency for:
Quinone (CAS No. 106-51-4)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An inhalation RfC for quinone is not available because EPA determined that the data were insufficient to support development of an RfC (latest assessment 1990). A literature search conducted for the years 1989 to 2002 does not appear to contain study data that could be used to develop an RfC.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The International Agency for Research on Cancer (IARC) Monograph (1999) characterized quinone as Group 3—not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1989 to 2002 identified multiple genotoxicity studies, including studies of DNA adduct formation, tumor induction, inhibition of DNA synthesis, gene mutations, cell transformation, induction of micronuclei, and clastogenicity. The literature search also identified many studies that examined the cytotoxic mechanisms and the mechanisms of tumor induction of quinone and parent compounds (e.g., benzene)[11].

Unknown Relevance
Twenty-three documents were categorized as being of unknown relevance, three of which were submissions to EPA Office of Toxic Substances (OTS) and three were records from the Computer Retrieval of Information on Scientific Projects (CRISP) database, a biomedical database of research projects supported by the Department of Health and Human Services.

[11] Quinone is a primary metabolite of benzene and is often discussed in benzene toxicity studies. Therefore, the literature search included studies related to benzene toxicity that mentioned quinone, relevant studies were generally coded as 5, "other toxicity studies not directly useful for establishing IRIS toxicity values."

Evaluation of the Recent Literature and Determination of Currency for:
Quinone (CAS No. 106-51-4)
(continued)

Note: Because of the large number of references found in the literature search (approximately 1,700), search results were limited with a secondary search in EndNote to identify references containing the CAS number and synonyms other than "quinone." However, since a large number of references resulted (approximately 750) search results were limited with a tertiary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms and *not containing* the CAS number were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Radium 226, 228 (CAS No. 7440-14-4)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The CSF for radium 226, 228 and supporting information previously on IRIS were withdrawn (latest assessment 1993). Review of the International Agency for Research on Cancer (IARC) Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for radium 226, 228.

Note: The National Center for Environmental Assessment (NCEA) Provisional Assessment (1998) includes cancer slope factors for radium isotopes based on the carcinogenicity of ionizing radiation. No studies examining the non-ionizing radiation effects of radium were identified.

Inhalation Unit Risk (IUR)
The IUR for radium 226, 228 and supporting information previously on IRIS were withdrawn (latest assessment 1993). Review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for radium 226, 228.

Note: The NCEA Provisional Assessment (1998) includes inhalation slope factors for radium isotopes based on the carcinogenicity of ionizing radiation. No studies examining the non-ionizing radiation effects of radium were identified.

Cancer Weight-of-Evidence (WOE) Classification
The WOE for radium 226, 228 and supporting information previously on IRIS were withdrawn (latest assessment 1993). Review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation a WOE for radium 226, 228. The literature search identified a study that examined radium-induced eye melanomas in canines (2000) and a study that examined the effective thresholds for induction of skeletal malignancy in canines by radionuclides (2000).

Unknown Relevance
Five documents were categorized as being of unknown relevance, one of which was a record from the Computer Retrieval of Information on Scientific Projects (CRISP) database, a biomedical database of research projects supported by the Department of Health and Human Services. Also included were studies titled "Cancer Incidence After Childhood Nasopharyngeal Radium Irradiation" and "A Mortality Follow-up Study of WWII Submariners Who Received Nasopharyngeal Radium Irradiation Treatment."

Evaluation of the Recent Literature and Determination of Currency for:
Radon 222 (CAS No. 14859-67-7)

Note: The International Agency for Research on Cancer (IARC) Monograph for radon 222 lists the CAS No. for radon as 10043-92-2. A literature search was conducted for the years 2000 to 2002 using the CAS No. 1004-92-2, as well as the CAS No. 14859-67-7. However, none of the studies identified through the literature search using CAS No. 1004-92-2 contained information relevant to radon 222 toxicity; therefore, these studies were coded as N/A.

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The CSF for radon 222 and supporting information previously on IRIS were withdrawn in 1993 pending further review. Review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation a CSF for radon 222.

Inhalation Unit Risk (IUR)
The IUR for radon 222 and supporting information previously on IRIS were withdrawn in 1993 pending further review. Review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation an IUR for radon 222.

Cancer Weight-of-Evidence (WOE) Classification
The WOE for radon 222 and supporting information previously on IRIS were withdrawn in 1993 pending further review. Review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation a WOE for radon 222.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Resmethrin (CAS No. 10453-86-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for resmethrin was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. Review of the World Health Organization (WHO) Environmental Health Criteria on resmethrins (1989) and a literature search conducted for the years 1988 to 2002, identified no new studies that would be directly useful in the derivation of an RfD for resmethrin.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: A literature search conducted for the years 1988 to 2002 identified a mutagenicity study using Salmonella typhimurium that reported negative results (1988).

Unknown Relevance
Seventeen documents were categorized as being of unknown relevance, six of which were included in the "Index of Cleared Science Reviews" on the EPA Office of Pesticide Programs (OPP) Web site. Among the studies identified were "Evaluation of New Mouse Dietary Carcinogenicity Study and Reevaluation of Previously Submitted Mouse Carcinogenicity Study on Resmithrin (SBP 1: 52)," "SBP-1382 (Resmethrin, Technical Manufacturing Use Product). Evaluation of 2-Generation Reproduction Study in Rat and Reevaluation of the following Previously Submitted Studies: 3-Generation Reproduction Study in Rat, Six Month Dog, Rat Developmental and Rabbit Developmental Toxicity Studies," "Memorandum: Resemthrin (SB-1382). Review of Chronic Rat Feeding/Carcinogenicity Study Submitted as 6(a)(2) Data," and "Household Pesticides and Risk of Pediatric Brain Tumors."

Evaluation of the Recent Literature and Determination of Currency for:
Savey (CAS No. 78587-05-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for savey was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for savey.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Four documents were categorized as being of unknown relevance, all of which were submissions to EPA Office of Toxic Substances (OTS).

Evaluation of the Recent Literature and Determination of Currency for:
Selenious acid (CAS No. 7783-00-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for selenious acid was derived (1991) does not appear to contain study data that could potentially produce a change in the RfD. Review of the ATSDR draft Toxicological Profile for selenium (2001), which includes selenious acid, and a literature search conducted for the years 2000 to 2002, identified no new studies that would be directly useful in the derivation of an RfD for selenious acid.

Note: The RfD for selenious acid was derived from a follow-up study of approximately 400 individuals residing in an area of China with high environmental concentrations of selenium (1989). This study was also used to derive an RfD for selenium (CAS No. 7782-49-2). the ATSDR draft Toxicological Profile for selenium (2001) presents a minimal risk level (MRL) for selenium derived from a second follow-up study in the same area of China (1994). This second study may be relevant to the derivation of an RfD for selenious acid.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could potentially produce a change in the WOE. Review of the ATSDR draft Toxicological Profile on selenium (2001), which includes selenious acid, and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Selenium sulfide (CAS No. 7446-34-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A draft ATSDR Toxicological Profile on selenium, which includes selenium sulfide, was published in 2001.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A review of the ATSDR draft Toxicological Profile on selenium (2001), which includes selenium sulfide, and a literature search conducted for the years 2000 to 2002, identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Selenium and compounds (CAS No. 7782-49-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for selenium and compounds was derived (1991) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for selenium and compounds was derived based on a follow-up study of approximately 400 individuals residing in an area of China with high environmental concentrations of selenium (1989). The ATSDR draft Toxicological Profile for selenium (2001) derived a minimal risk level (MRL) based on a second follow-up study of the same area in China (1994). A literature search conducted for the years 2000 to 2002 identified several epidemiological studies that may be useful in the derivation of an RfD for selenium and compounds. The first study evaluated toxic and carcinogenic health outcomes (2000) and the second study evaluated reproductive health outcomes (2000) for a cohort of residents of an Italian municipality who had been chronically exposed to drinking water with a high content of inorganic selenium. The literature also identified an epidemiological study evaluating the effects of selenium in food on semen quality in men (2001). Also, the literature search identified a reproductive and a developmental toxicity study in rats (dietary exposures for 9 weeks) (2000) and pigs (dietary exposures through one reproductive cycle) (2001).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A review of the ATSDR draft Toxicological Profile on selenium and compounds (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Six documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Selenourea (CAS No. 630-10-4)

Oral Reference Dose (RfD)
The oral RfD for selenourea and supporting information were withdrawn from IRIS by EPA pending further review (1991). A literature search conducted for the years 1990 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for selenourea.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Four documents, two of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Silver cyanide (CAS No. 506-64-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for silver cyanide was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for silver cyanide.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Simazine (CAS No. 122-34-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for simazine was derived (1991) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for simazine was derived based on a 2-year dietary study in rats (1988). A literature search conducted for the years 1990 to 2002 identified a study of immunomorphological effects in rats exposed to simazine in their diets for 6 months (1991), a developmental toxicity study in Sprague-Dawley rats (1992), and a reproductive toxicity study in Sprague-Dawley rats exposed orally to simazine (exposure duration unspecified) (1994).

Note: In April 2002, EPA announced the preliminary determination that three triazine pesticides–simazine, atrazine, propazine–and three metabolites share a common mechanism of toxicity and could be grouped together for purposes of a cumulative risk assessment and as part of the tolerance reassessment process for triazine pesticides.EPA expects the risk assessment to be completed in 2003 or 2004.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1990 to 2002 identified a study of mammary tumorigenesis in Sprague-Dawley rats exposed to simazine in their diets for 2 years (1994).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1999) assigned simazine a cancer classification of Group 3—not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1990 to 2002 identified five studies evaluating genotoxic effects (1992, 1994), chromosomal damage induced by exposure to simazine in drinking water (1995), and clastogenic potential on Chinese hamster ovary cells (1996, 1999).

Evaluation of the Recent Literature and Determination of Currency for:
Simazine (CAS No. 122-34-9)
(continued)

Unknown Relevance
Nineteen documents were categorized as being of unknown relevance. Five of these documents were submissions to EPA Office of Toxic Substances (OTS), including: "Teratology study of simazine technical in New Zealand white rabbits," "Reproduction study G 27692 tech. rat seg. ii (test for teratogenic or embryotoxic effects) (final report)," "Letter from Ciba-Geigy Corporation to USEPA submitting a summary on simazine 104-week chronic toxicity and carcinogenicity study in rats," and "Subacute oral 13-week toxicity study of simazine in rats." Three of the documents were referenced in the EPA report "The grouping of a Series of Triazine Pestcides Based on a Common Mechanism of Toxicity," including: "Comparison of LH surge in female rats exposed to atrazine, simazine, and diaminochlorotriazine (DACT) via oral gavage for one month" (2001) and "52-Week toxicity study of simazine, atrazine, and DACT administered in the diet to female rats" (2002).

The EPA Office of Pesticide Programs (OPP) Web site provides an "Index of Cleared Science Reviews" for simazine, including "Carcinogenic risk for simazine-registered commodities" (1991), "Review of simazine 2-generation reproduction study in rats," two data reviews for simazine reregistration (January and February 1993), "Reference dose for chronic oral exposure (RfD) for simazine" (1993), and "Atrazine and simazine–reviews of five studies examining: 1) short-term effects on the rat estrus cycle; 2) antiestrogenicity in rats; 3) in vitro antagonism of estrogen action and in vitro binding with the estrogen receptor; 4) estrogenic responses in MCF-7 human breast cancer cells; 5) estrogenic responses in vivo (rat) and in vitro" (1999).

Note: Because of the large number of references found in the literature search (approximately 950), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Sodium diethyldithiocarbamate (CAS No. 148-18-5)

Oral Reference Dose (RfD)
The literature published since the oral RfD for sodium diethyldithiocarbamate was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. The IRIS RfD for sodium diethyldithiocarbamate was derived based on 90-day subchronic oral toxicity study in albino rats (1967) and a 2-year dietary study in F344 rats (1979). A literature search conducted for the years 1984 to 2002 identified a study of the effects of sodium diethyldithiocarbamate on developing mouse embryos (1994). This study was conducted using histological preparations, rather than by administering sodium diethyldithiocarbamate to pregnant mice.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: In 1984, EPA Office of Solid Waste reported a human carcinogen potency factor for sodium diethyldithiocarbamate of 0.25 (milligrams per kilogram body weight per day)$^{-1}$ ([mg/kg/day]$^{-1}$).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A 1991 British Industrial Biological Research Association (BIBRA) working group toxicity profile for sodium diethyldithiocarbamate notes that mutagenic activity has been seen in Ames bacterial tests and in mammalian cells in culture. A literature search conducted for the years 1984 to 2002 identified seven studies of the genotoxicity and mutagenicity of sodium diethyldithiocarbamate.

Unknown Relevance
Four documents, including one submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. Among these documents was a study titled, "Diethyldithiocarbamate inhibits scheduled and unscheduled DNA synthesis of rat thymocytes in vitro and in vivo: Dose-effect relationships and mechanisms of action."

Evaluation of the Recent Literature and Determination of Currency for:
Strychnine (CAS No. 57-24-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for strychnine was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for strychnine.

Note: A Reregistration Eligibility Decision (RED) for strychnine (1996) stated that "based on the severe oral toxicity of this chemical and the nonfood use status, a reference dose and carcinogenicity classification has not been determined at this time."

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Thirteen documents were categorized as being of unknown relevance, including "Effect of strychnine on the reactivity of neurons of the sensorimotor cortex and temporary connection in rabbits" (1988).

Note: Because of the large number of references found in the literature search (approximately 950), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.In addition, several hundred references were identified that either did not address strychnine or did not address the toxicity of strychnine.Therefore, a secondary search was conducted in EndNote to identify references containing "strychnine-binding" or the keywords "strychnine/analogs & derivatives," "strychnine/therapeutic use," or "strychnine/pharmacology."These references were coded as N/A.In addition, references *containing* the keyword "strychnine/administration & dosage," but not "metabolism" or "toxicity" were also coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Systhane (CAS No. 88671-89-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for systhane was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for systhane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Five documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Teratology Study of 1h-1,2,4-Triazole-1-Propanenitrile, Apha-Butyl-Alpha-(-4-Chlorophenyl)- in Rats" (1992).

Evaluation of the Recent Literature and Determination of Currency for:
Tebuthiuron (CAS No. 34014-18-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for tebuthiuron was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for tebuthiuron.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1987 to 2002 identified one study of genotoxic activities of pesticides, including tebuthiuron, using a modified SOS microplate assay (1995). The results of the study were not reported in the abstract.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Terbutryn (CAS No. 886-50-0)

Oral Reference Dose (RfD)
The literature published since the oral RfD for terbutryn was derived (1988) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for terbutryn was derived based on a 2-year dietary study in rats (1980). A literature search conducted for the years 1987 to 2002 identified one 2-year dietary study in Sprague-Dawley rats that noted toxicity-related reduced survival (1994).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1987 to 2002 identified a 2-year dietary study in Sprague-Dawley rats that found an increased incidence of mammary tumors (1994) and two genotoxicity studies that found terbutryn induced primary DNA damage (2000 and 2002), but failed to produce any significant increases in sister-chromatid exchanges or micronucleus in freshly isolated human peripheral blood leukocytes (2002).

Unknown Relevance
Two documents, both of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance. The studies were titled "Chronic Dietary Toxicity Study of Terbutryn Technical, 2-(Tert-Butylamino-)-4-)Ethylamino)-6-(Methyltio)-S-Triazine in Dogs" (1994) and "Toxicological Investigation of: Cp 99386" (1992).

Evaluation of the Recent Literature and Determination of Currency for:
Tetrabromodiphenyl ether (CAS No. 40088-47-9)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1990) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1989 to 2002 identified no new studies that would be directly useful in establishing a WOE classification for tetrabromodiphenyl ether.

Unknown Relevance
One document was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
1,2,4,5-Tetrachlorobenzene (CAS No. 95-94-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,2,4,5-tetrachlorobenzene was derived (1985) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for 1,2,4,5-tetrachlorobenzene was derived based on an oral subchronic study in rats (1984). In its 1992 assessment, Health Canada derived a tolerable daily intake (TDI) based on a subchronic (13-week) dietary study in rats (1991).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In its 1992 assessment, Health Canada classified 1,2,4,5-tetrachlorobenzene as Group VI—unclassifiable with respect to carcinogenicity in humans.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Tetrachlorocyclopentadiene (CAS No. 695-77-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: 1,1,1,2-Tetrachloroethane (CAS No. 630-20-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,1,1,2-tetrachloroethane was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 1,1,1,2-tetrachloroethane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for 1,1,1,2-tetrachloroethane was derived (1988) does not appear to contain study data that could potentially produce a change in the CSF. Review of the International Agency for Research on Cancer (IARC) Monograph (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for 1,1,1,2-tetrachloroethane.

Inhalation Unit Risk (IUR)
The literature published since the IUR for 1,1,1,2-tetrachloroethane was derived (1988) does not appear to contain study data that could potentially produce a change in the IUR. Review of the IARC Monograph (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for 1,1,1,2-tetrachloroethane.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1988) does not appear to contain study data that could produce a change in the WOE. The IARC Monograph (1999) characterized 1,1,1,2-tetrachloroethane as Group 3—not classifiable as to carcinogenicity in humans. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in establishing a WOE classification. The literature search identified three studies of 1,1,1,2-tetrachloroethane genotoxicity, including two *in vivo* assays (involving intraperitoneal injection in the rat and mouse) (1989, 1991) and an *in vitro* chromosomal aberration assay using Chinese hamster lung fibroblast cells (1996). At least two of the three studies reported positive evidence of genotoxicity.

Unknown Relevance
Fifteen documents, ten of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "Comparison of the Inhalation Toxicity of 1,1,1,2-Tetrachloroethane and Perchloroethylene in the Rat" (1987), "Mortality among Dow Chemical Employees of a Texas Operations Per-Tet Manufacturing Plant" (1989), and "Genotoxic and Biochemical Activities of Some Chlorinated Ethanes" (1989).

Evaluation of the Recent Literature and Determination of Currency for: 1,1,2,2-Tetrachloroethane (CAS No. 79-34-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: The ATSDR Toxicological Profile (1996) presents a chronic oral minimal risk level (MRL) derived from a 1978 respiratory study in rats. The National Center for Environmental Assessment (NCEA) Provisional Assessment (2000) presents an RfD derived from a 1994 subchronic dietary study in rats and mice.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for 1,1,2,2-tetrachloroethane was derived (1986) does not appear to contain study data that could potentially produce a change in the CSF. Review of the NCEA "Risk Assessment Issue Paper for: Evaluation of Deriving a Provisional Carcinogenicity Assessment for 1,1,2,2-Tetrachloroethane" (2000), and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for 1,1,2,2-tetrachloroethane.

Inhalation Unit Risk (IUR)
The literature published since the IUR for 1,1,2,2-tetrachloroethane was derived (1986) does not appear to contain study data that could potentially produce a change in the IUR. Review of the NCEA "Risk Assessment Issue Paper for: Evaluation of Deriving a Provisional Carcinogenicity Asssessment for 1,1,2,2-Tetrachloroethane" (2000), and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for 1,1,2,2-tetrachloroethane.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1986) does not appear to contain study data that could produce a change in the WOE. An IARC Monograph (1999) characterized 1,1,2,2-tetrachloroethane as Group 3—not classifiable as to carcinogenicity in humans. A Health Canada Assessment (1992) classified 1,1,2,2-tetrachloroethane as Group III—possibly carcinogenic to humans. The NCEA Provisional Assessment (2000) recommended no changes to the WOE classification. A literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
Six documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Observations on the Toxicity of Various Halogenated Hydrocarbons Used or Projected for Use in Ethyl Fluid" (2000).

Evaluation of the Recent Literature and Determination of Currency for: 2,3,4,6-Tetrachlorophenol (CAS No. 58-90-2)

Note: A number of epidemiological studies of soft cell sarcomas were identified during the literature search. These studies were coded 8 because they primarily focused on chlorophenol and dioxin exposures. However, they may contain data regarding 2,3,4,6-tetrachlorophenol because they were identified during the literature search for 2,3,4,6-tetrachlorophenol.

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2,3,4,6-tetrachlorophenol was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 2,3,4,6-tetrachlorophenol.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1986 to 2002 identified studies of 2,3,4,6-tetrachlorophenol's potential to cause mutations in Salmonella (1990) and hamster cells (1986) and to cause DNA damage in mouse embryos (1995).

Unknown Relevance
Six documents, one of which was a submission to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Teratological Evaluation of 2,3,4,6-Tetrachlorophenol (Tcp) in Rats" (1987).

Note: Because of the large number of references found in the literature search (approximately 1,150), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Tetraethyl lead (CAS No. 78-00-2)

Note: Triethyl lead is a metabolite of tetraethyl lead. A number of references studying the effects of triethyl lead to determine the toxicity of exposure to tetraethyl lead were identified by the literature search conducted for the years 1984 to 2002. These studies were coded 8 because the levels of tetraethyl lead that would lead to the exposure levels of triethyl lead studied were not determined.

Oral Reference Dose (RfD)
The literature published since the oral RfD for tetraethyl lead was derived (1985) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for tetraethyl lead was derived based on a subchronic study in rats (1964). A 1995 submission to the IRIS Submission Desk (by the International Technology Corporation) identified a subchronic oral toxicity study of organic lead compounds (including tetraethyl lead) in rats (1987). A literature search conducted for the years 1984 to 2002 identified no additional studies that would be directly useful in establishing an RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: Two occupational studies evaluating the inhalation toxicity of tetraethyl lead were identified by the literature search conducted for the years 1985 to 2002. One study found increased tremors and sinus bradycardia among gasoline workers (1994). The second study found evidence for obstructive and restrictive lung pathology among tetraethyl lead handlers and petrol tanker fillers (1999).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A case-control study (1997) investigating cancer risk among workers in a tetraethyl lead manufacturing area found limited evidence of a link between tetraethyl lead exposure and colorectal cancer (1997).

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: An International Agency for Research on Cancer (IARC) Monograph (1987) characterized tetraethyl lead as Group 3—not classifiable as to carcinogenicity in humans. In addition, an investigation of mortality from cancer in chemical plant workers (1984, 1986) found no statistically significant increase in site specific mortality from cancer among workers primarily exposed to tetraethyl lead; however, these exposure levels were not measured.

Evaluation of the Recent Literature and Determination of Currency for:
Tetraethyl lead (CAS No. 78-00-2)
(continued)

Unknown Relevance

Twenty-one documents, nine of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including studies titled "Initial Submission: Preliminary Comparative Toxicity Studies with Tetramethyl Lead and Tetraethyl Lead" (1992), "Initial Submission: Department of Transportation Inhalation Toxicity Studies of Tetraethyllead in Rats" (1992), "Initial Submission: Special Oral Test of Tetraethyl Lead in Rats" (1992), "Initial Submission: An Epidemiologic Study of Cancer Risk Following Exposure to Organic Lead among the Dupont Company's Chambers Works Employees" (1991), "Tetraethyl lead" (1993), "Critical Periods of Exposure and Developmental Effects of Lead" (1984), and "Biomonitoring and Subclinical Effect in Tetraethyl Lead Exposed Persons in Hubei China" (1993).

Evaluation of the Recent Literature and Determination of Currency for:
Thallic oxide (CAS No. 1314-32-5)

Oral Reference Dose (RfD)
In 1989, the oral RfD for thallic oxide and supporting information previously on IRIS were withdrawn pending further review. In 1993, EPA confirmed the decision to withdraw the IRIS assessment for thallic oxide. A literature search was conducted for the years 1988 to 2002. The literature published since 1988 does not appear to contain study data that could be used to develop an RfD.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
One submission to EPA Office of Toxic Substances (OTS) was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Thallium carbonate (CAS No. 6533-73-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for thallium carbonate was derived (1988) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for thallium carbonate was derived based on an EPA 90-day study in rats exposed to thallium sulfate (1986). Review of the World Health Organization (WHO) Environmental Health Criteria for thallium (1996) and a literature search conducted for the years 1995 to 2002 identified a 6-month study in mice exposed to thallium carbonate in their drinking water (1987; published in Chinese). This study found decreases in male reproductive endpoints.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. Review of the WHO Environmental Health Criteria for thallium (1996) and a literature search conducted for the years 1995 to 2002 identified a 1988 study that induced sister-chromatid exchange, chromosomal aberrations, and gene mutations when cell lines were exposed to thallium carbonate.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Thallium nitrate (CAS No. 10102-45-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for thallium nitrate was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. Review of the World Health Organization (WHO) Environmental Health Criteria for thallium (1996) and a literature search conducted for the years 1995 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for thallium nitrate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. Review of the WHO Environmental Health Criteria for thallium (1996)and a literature search conducted for the years 1995 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Thallium sulfate (CAS No. 7446-18-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for thallium sulfate was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD. Review of the World Health Organization (WHO) Environmental Health Criteria for thallium (1996) and a literature search conducted for the years 1995 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for thallium sulfate.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. Review of the WHO Environmental Health Criteria for thallium (1996) and a literature search conducted for the years 1995 to 2002 identified a cytogenetic study that did not result in a significant modification of structural chromosome aberrations nor sister chromatid exchanges (1997) and a study investigating micronuclei induction in human lymphocytes (1999).

Unknown Relevance
One document was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: Thiobencarb (CAS No. 28249-77-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for thiobencarb was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A review of the EPA Office of Pesticide Programs Reregistration Eligibility Decision (RED) (1997) and a literature search conducted for the years 1996 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for thiobencarb.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: The OPP RED (1997) categorizes thiobencarb as Group D—not classifiable as to human carcinogenicity.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Thiophanate-methyl (CAS No. 23564-05-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for thiophanate-methyl was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for thiophanate-methyl was derived based on a 2-year dietary study in Sprague-Dawley rats (1972). The EPA Office of Pesticide Programs (OPP) Revised Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) (2001) presented an RfD for thiophanate-methyl based on a 1-year oral capsule study in dogs (1992).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: The OPP Revised Preliminary Risk Assessment for the RED (2001) presented a CSF for thiophanate-methyl based on an 18-month dietary carcinogenicity study in CD-1 mice (1992).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Note: The OPP Revised Preliminary Risk Assessment for the RED (2001)stated that thiophanate-methyl was classified as "likely to be carcinogenic to humans."

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for:
Toxaphene (CAS No. 8001-35-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: In the 1996 Toxicological Profile, ATSDR derived an intermediate oral minimal risk level (MRL) for toxaphene based on a toxicity study in rats (1986). In addition, a review of the International Agency for Research on Cancer (IARC) Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified a number of studies demonstrating hepatotoxicity and immunotoxicity in a variety of animal species (1957, 1971, 1986, 2000, 2001) and three multigeneration studies in rats that showed no reproductive or developmental effects (1976, 1988, 1990).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the oral CSF for toxaphene was derived (1987) contains study data that could potentially produce a change in the CSF.

The IRIS CSF for toxaphene was derived based on an 18-month dietary study in B6C3F1 mice (1978). A review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified a case-control study of non-Hodgkin lymphoma and a case-control study of leukemia that both showed no significant increase in risk associated with exposure to toxaphene (1992) and a study demonstrating an increase in hepatocellular adenomas and carcinomas in B6C3F1 mice (2000).

Inhalation Unit Risk (IUR)
The literature published since the inhalation IUR for toxaphene was derived (1987) does not appear to contain study data that could produce a change in the IUR. A review of the IARC Monograph (2001) and a literature search conducted for the years 2000 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for toxaphene.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1987) does not appear to contain study data that could produce a change in the WOE.

The IRIS WOE for toxaphene was derived based on an 18-month dietary study in B6C3F1 mice (1978). The IARC Monograph (2001) characterized toxaphene as Group 2B—possibly carcinogenic to humans. A review of the IARC Monograph (2001)and a literature search conducted for the years 2000 to 2002 identified several genotoxicity and mutagenicity studies, including microbial mutagenicity studies (1978, 1979, 1986, 1987, 1998) and sister chromatid induction studies (1983, 1990, 1999). The majority of the mutagenicity studies reported positive findings.

Evaluation of the Recent Literature and Determination of Currency for:
Toxaphene (CAS No. 8001-35-2)
(continued)

Unknown Relevance
One document was categorized as being of unknown relevance.

Note: According to information available through the IRIS Submission Desk, a March 3, 1998 letter from Hercules Incorporated noted that new studies were available since the most recent IRIS update; however, the references for these studies were not provided.

Note: A literature search conducted for the years 2000 to 2002 identified a study describing the development of a pharmacokinetic model for predicting absorption, elimination, and tissue burden of toxaphene in rats (2000).

Evaluation of the Recent Literature and Determination of Currency for:
1,2,4-Tribromobenzene (CAS No. 615-54-3)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,2,4-tribromobenzene was derived (1986) does not appear to contain study data that could produce a change in the RfD. A literature search conducted for the years 1985 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 1,2,4-tribromobenzene.

Inhalation Reference Dose (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE is included in IRIS.

Unknown Relevance
Three documents were categorized as being of unknown relevance, one of which was a submission to EPA Office of Toxic Substances (OTS).

Evaluation of the Recent Literature and Determination of Currency for:
Tributyltin oxide (CAS No. 56-35-9)

Oral Reference Dose (RfD)
The literature published since the oral RfD for tributyltin oxide was derived (1997) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for tributyltin oxide was derived based on an 18-month immunotoxicity study in Wistar rats (1990). A literature search conducted for the years 1996 to 2002 identified a short-term developmental toxicity screen using Han:NMRI mice gavaged with tributyltin oxide (1996 [abstract], 1997) that may be useful in the derivation of an RfD for tributyltin oxide.

Inhalation Reference Concentration (RfC)
An inhalation RfC for tributyltin oxide is not available because EPA determined that the data were inadequate for derivation of an RfC (latest assessment 1997). A literature search conducted for the years 1996 to 2002 does not appear to contain study data that could be used to develop an RfC.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1997) does not appear to contain study data that could produce a change in the WOE. A literature search for the years 1996 to 2002 identified no new studies that would be directly useful in establishing a WOE classification.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: Trichloroacetic acid (CAS No. 76-03-9)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: A review of the International Agency for Research on Cancer (IARC) Monograph (1995) and a literature search conducted for the years 1992 to 2002 identified two chronic toxicity studies in which male Fischer 344/N rats and both male and female B6C3F1 mice were exposed to trichloroacetic acid in drinking water for 104 weeks and 52 weeks, respectively (1990, 1993, 1997); a study evaluating the toxic effects on in vitro fertilization in B6D2F-1 mice exposed via oral gavage (1992); and several developmental toxicity studies in pregnant rats exposed orally, whole embryo rat cultures, and whole embryo mouse cultures (1995, 1996, 1998, 2001, 2002).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A review of the IARC Monograph (1995) and a literature search conducted for the years 1992 to 2002 identified one chronic toxicity study in which male Fischer 344/N rats were exposed to trichloroacetic acid in their drinking water for 104 weeks (1997) and several studies that investigated the carcinogenic activity and hepatic tumor promotion of trichloroacetic acid administered to female B6C3F1 mice in drinking water (1996, 1997, 1998).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1993) does not appear to contain study data that could produce a change in the WOE. A review of the IARC Monograph (1995) and a literature search conducted for the years 1992 to 2002 identified several studies investigating cytotoxicity and genotoxicity of trichloroacetic acid, including the induction of DNA strand breaks, protein synthesis inhibition, micronuclei induction, mutations, chromosomal damage, cell replication (1992, 1995, 1996, 1997, 1998) and several studies investigating the mechanism of liver tumor induction (1994, 1995, 1997, 1999, 2000). The IARC Monograph (1995) characterized tetraethyl lead as Group 3—not classifiable as to carcinogenicity in humans.

Unknown Relevance
Four documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Trichloroacetic acid (CAS No. 76-03-9)
(continued)

Note: A review of the 1995 IARC Monograph and a literature search conducted for the years 1992 to 2002 found five studies carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for trichloroacetic acid (1993, 1997, 1998, 1999).

Note: Because of the large number of references found in the literature search (approximately 700), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A. Because a large number of references remained (approximately 430), a tertiary search was conducted to identify references containing chemexfoliation, therapeutic, pharmacology, chemistry, condylomata, genital warts, and dental in the keywords. References *containing* one of these search terms were also coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for: Trichlorocyclopentadiene (CAS No. 77323-84-3)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1989) does not appear to contain study data that could produce a change in the WOE. A literature search conducted for the years 1988 to 2002 identified no new studies that would be directly useful in the derivation of a WOE classification for trichlorocyclopentadiene.

Unknown Relevance
No documents were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for: Trichlorofluoromethane (CAS No. 75-69-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for trichlorofluoromethane was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for trichlorofluoromethane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A World Health Organization (WHO) Environmental Health Criteria on fully halogenated compounds (1990) includes an assessment of trichlorofluoromethane and identified negative that long-term carcinogenicity studies of trichlorofluoromethane (by oral and inhalation routes). WHO concluded that trichlorofluoromethane has "little or no mutagenic or carcinogenic potential."

Unknown Relevance
Eight documents, were categorized as being of unknown relevance. Among these documents were seven submissions to EPA Office of Toxic Substances (OTS). One of the submissions to OTS was titled "Inhalation Toxicity of Freon 11 and of Freon 11 + 0.3% Nitromethane in Rats." Four 1992 OTS submissions pertain to cardiac effects of trichlorofluoromethane (and other chlorofluorocarbons) in dogs.

Note: A literature search conducted for the years 1984 to 2002 found one study carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for trichlorofluoromethane (2001).

Note: Because of the large number of references found in the literature search (approximately 350), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
2,4,5-Trichlorophenol (CAS No. 95-95-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2,4,5-trichlorophenol was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. Review of the ATSDR Toxicological Profile for chlorophenols (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 2,4,5-trichlorophenol.

Note: The ATSDR Toxicological Profile (1999) included an intermediate oral minimal risk level (MRL) for chlorophenols, based on a study of 2,4-dichlorophenol. No chronic MRL was derived because the no-observed-adverse-effect levels (NOAELs) identified in the chronic studies were greater than the lowest-observed-adverse-effect levels (LOAELs) identified in the intermediate duration studies.

Inhalation Reference Concentration (RfC)
An inhalation RfC for 2,4,5-trichlorophenol is not available because EPA determined that the data were inadequate for derivation of an RfC (latest assessment 1991). Review of the ATSDR Toxicological Profile for chlorophenols (1999) and a literature search conducted for the years 1999 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for 2,4,5-trichlorophenol.

Note: The ATSDR Toxicological Profile for chlorophenols (1999) includes no inhalation MRLs for 2,4,5-trichlorophenol. The only available study (an acute inhalation study in rats exposed to 2-chlorophenol) was determined to be inadequate for deriving an inhalation MRL.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: In the 1999 Toxicological Profile for chlorophenols, ATSDR cited a number of epidemiological studies published between 1981 and 1991 that assessed the carcinogenic potential of chlorophenol-based pesticides. Most of the studies evaluated exposures of farm workers or workers involved in chlorophenol-based pesticide production; these individuals may also have been exposed to other chlorophenols, dioxins, and chlorophenoxy pesticides. ATSDR determined that the data were not sufficient to support a causal relationship, but suggested a possible concern.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A International Agency for Research on Cancer (IARC) Monograph (1999) lists "polychlorophenols and their sodium salts (mixed exposures)" as Group 2B—possibly carcinogenic to humans. A literature search conducted for the years 1998 to 2002 identified a single study of the cytogenetic characteristics of peripheral blood lymphocytes of herbicide plant workers (1998). The study found that 2,4,5-trichlorophenol had mutagenic effects in humans.

Evaluation of the Recent Literature and Determination of Currency for:
2,4,5-Trichlorophenol (CAS No. 95-95-4)
(continued)

Unknown Relevance
One documents, a submission to EPA Office of Toxic Substances (OTS), was categorized as being of unknown relevance

Evaluation of the Recent Literature and Determination of Currency for:
2,4,6-Trichlorophenol (CAS No. 88-06-2)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Note: The ATSDR Toxicological Profile for chlorophenols (1999) includes an intermediate oral minimal risk level (MRL) for chlorophenols, based on a study of 2,4-dichlorophenol. No chronic MRL was derived because the no-observed-adverse-effect levels (NOAELs) identified in the chronic studies were greater than the lowest-observed-adverse-effect levels (LOAELs) identified in the intermediate duration studies.

Inhalation Reference Concentration (RfC)
An RfC for 2,4,6-trichlorophenol is not available because EPA determined that the data were insufficient to support development of a RfC (1991). Based on a review of the ATSDR Toxicological Profile for chlorophenols (1999) and a literature search conducted for the years 1998 to 2000, the literature published since 1991 does not appear to contain study data that could be used to develop a RfC.

Oral Slope Factor (CSF)
The literature published since the CSF for 2,4,6-trichlorophenol was derived (1989) does not appear to contain study data that could potentially produce a change in the CSF. Review of the ATSDR Toxicological Profile for chlorophenols (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of a CSF for 2,4,6-trichlorophenol.

Inhalation Unit Risk (IUR)
The literature published since the IUR for 2,4,6-trichlorophenol was derived (1989) does not appear to contain study data that could potentially produce a change in the IUR. Review of the ATSDR Toxicological Profile for chlorophenols (1999) and a literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of an IUR for 2,4,6-trichlorophenol. ATSDR cited a number of epidemiological studies published between 1981 and 1991 that assessed the carcinogenic potential of chlorophenol-based pesticides. Most of the studies evaluated exposures of farm workers or chlorophenol-based pesticide production worker. These individuals may also have been exposed to other chlorophenols, dioxins, and chlorophenoxy pesticides. ATSDR determined that the data were not sufficient to support a causal relationship, but suggested a possible concern.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (B2—probable human carcinogen) was derived (1989) does not appear to contain study data that could produce a change in the WOE classification. A International Agency for Research on Cancer (IARC) Monograph (1999) lists "polychlorophenols and their sodium salts (mixed exposures)" as Group 2B—possibly carcinogenic to humans. A literature search conducted for the years 1998 to 2002 identified no new studies that would be directly useful in the derivation of a WOE classification for 2,4,6-trichlorophenol.

Evaluation of the Recent Literature and Determination of Currency for:
2,4,6-Trichlorophenol (CAS No. 88-06-2)
(continued)

Unknown Relevance
One submission to EPA Office of Toxic Substances (OTS) was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP) (CAS No. 93-72-1)

Note: A number of epidemiological studies of occupational exposure to chlorophenoxy herbicides were identified during the literature search. These studies were coded 8 because they primarily focused on exposures to mixtures of chlorophenoxy herbicides, dioxins, and/or trichlorophenols. However, they may contain data regarding 2 (2,4,5-trichlorophenoxy) propionic acid (2,4,5-TP) because they were identified during the literature search for 2,4,5-TP.

Oral Reference Dose (RfD)
The literature published since the oral RfD for 2,4,5-TP was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD.

The IRIS RfD for 2,4,5-TP was derived based on a 2-year chronic dietary study in dogs (1978) and a 2-year dietary study in rats (1966) in which both species were fed the same formulation containing the potassium salt of 2,4,5-TP. A literature search conducted for the years 1987 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 2,4,5-TP. A literature review conducted by the EPA Office of Water (OW) (2002) as part of its 6-year review of the National Primary Drinking Water Standards concluded that a "literature search did not identify any new studies that warrant a review of the RfD or the cancer classification".[12]

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (D—not classifiable as to human carcinogenicity) was derived (1987) may contain study data that could produce a change in the WOE classification.

A literature search conducted for the years 1986 to 2002 identified two International Agency for Research on Cancer (IARC) Monographs on chlorophenoxy herbicides (1986, 1987). The 1987 IARC Monograph classifies them as Group 2B—possibly carcinogenic to humans. A literature review conducted by OW (2002) as part of its 6-year review of the National Primary Drinking Water Standards concluded that a "literature search did not identify any new studies that warrant a review of the RfD or the cancer classification."

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[12]EPA. 2002. *Six-Year Review, Chemical Contaminants, Health Effects Technical Support Document.* Office of Water, Office of Science and Technology. EPA Publication No. 822-R-01-001. February 2002.

Evaluation of the Recent Literature and Determination of Currency for:
2 (2,4,5-Trichlorophenoxy) propionic acid (2,4,5-TP) (CAS No. 93-72-1)
(continued)

The literature search also identified a negative mutagenicity study of 2,4,5-TP (1988, 1989) and a study titled "Phenoxy Herbicides and Cancer Insufficient Epidemiologic Evidence for a Causal Relationship" (1989).

Unknown Relevance
Three documents were categorized as being of unknown relevance, including a study titled "Cause Specific Mortality among Employees Engaged in the Manufacture Formulation or Packaging of 2,4-D and Related Salts."

Evaluation of the Recent Literature and Determination of Currency for: 1,2,3-Trichloropropane (CAS No. 96-18-4)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,2,3-trichloropropane was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for 1,2,3-trichloropropane was derived based on a 120-day gavage study in rats (1983). In the 1999 Provisional Assessment, the National Center for Environmental Assessment (NCEA) derived an RfD based on a 17-week subchronic gavage study in rats and mice (1993).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: In its 1999 Provisional Assessment, NCEA derived an RfC based on a 13-week inhalation study in rats (1988).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: In its 1999 Provisional Assessment, NCEA derived a CSF based on a 17-week subchronic gavage study in mice (1993).

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In the 1999 Provisional Assessment, NCEA classified 1,2,3-trichloropropane as Group B2—probable human carcinogen. In addition, the International Agency for Research on Cancer (IARC) classified 1,2,3-trichloropropane as Group 2B—possibly carcinogenic to humans—in its 1995 Monograph. Also, the National Toxicology Program (NTP) classified 1,2,3-trichloropropane as exhibiting clear evidence of carcinogenicity in a 1993 cancer bioassay. In its Eighth Report on Carcinogens, NTP classified 1,2,3-trichloropropane as reasonably anticipated to be a human carcinogen.

Unknown Relevance
No literature search was necessary.

Note: An NCEA Superfund Technical Support Center (STSC) memo dated 1/4/02 included as attachments "Draft Risk Assessment Issue Papers for: Derivation of the Systemic Toxicity of 1,2,3-trichloropropane (CAS No. 96-18-4)" and "Evaluation of Carcinogenicity of 1,2,3-trichloropropane (CAS No. 96-18-4) (99-014/8-13-99)."

Evaluation of the Recent Literature and Determination of Currency for:
1,2,3-Trichloropropane (CAS No. 96-18-4)
(continued)

Note: Letters dated April 17, 1992 and February 4, 1994 from Ciba-Geigy Corporation (Ciba) to the IRIS Submission Desk noted that new studies were available since the most recent IRIS update. In its 1992 letter, Ciba referenced an issue paper addressing the relevance of gavage-induced response to responses in humans, citing NTP 1991 and Merrick et al. 1991. In its 1994 submission, Ciba cited work by Swenberg et al. (1993) on DNA adduct formation from exposure to 1,2,3-trichloropropane in rats.

Evaluation of the Recent Literature and Determination of Currency for: 1,1,2-Trichloropropane (CAS No. 598-77-6)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,1,2-trichloropropane was derived (1987) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1986 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 1,1,2-trichloropropane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
One document, a submission to EPA Office of Toxic Substances (OTS), was categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
1,1,2-Trichloro-1,2,2-trifluoroethane (CAS No. 76-13-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for 1,1,2-trichloro-1,2,2-trifluoroethane was derived (1985) does not appear to contain study data that could potentially produce a change in the RfD. A literature search conducted for the years 1984 to 2002 identified no new studies that would be directly useful in the derivation of an RfD for 1,1,2-trichloro-1,2,2-trifluoroethane.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified one submission to EPA Office of Toxic Substances (OTS) that contained inhalation toxicity study information: a two 2-year inhalation toxicity/carcinogenicity study in rats (1985; unpublished). Results from this study were published in 1988.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified a 2-year inhalation carcinogenicity study in rats (1988).

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1984 to 2002 identified a negative 2-year inhalation carcinogenicity study (1988). One study also reported no evidence of mutagenicity in a Salmonella-typhimurium assay, but evidence for enhancement of the mutagenic response of aromatic hydrocarbons (1988).

Unknown Relevance
Twenty-five documents, most of which were submissions to EPA OTS, were categorized as being of unknown relevance.

Note: A literature search conducted for the years 1984 to 2002 found one study carried out to develop, apply, and validate a physiologically-based pharmacokinetic (PBPK) model for 1,1,2-trichloro-1,2,2-trifluoroethane (1991).

Evaluation of the Recent Literature and Determination of Currency for:
Tridiphane (CAS No. 58138-08-2)

Oral Reference Dose (RfD)
The literature published since the oral RfD for tridiphane was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for tridiphane was derived based on a dietary 2-generation reproduction study in rats conducted by Dow Chemical (1984). A literature search conducted for the years 1985 to 2002 identified a dietary 2-generation reproduction study in Fischer 344 rats (1987) and a oral administration embryotoxicity and fetotoxicity study in CF-1 mice and Sprague-Dawley rats (1987).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a dietary 2-generation reproduction study in Fischer 344 rats (1987) that included examinations for hepatic lesions.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
One document was categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 860), search results were limited with a secondary search in EndNote to identify references containing tridiphane's CAS number (58138-08-2) or a synonym. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Triethylene glycol monobutyl ether (CAS No. 143-22-6)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An RfC for triethylene glycol monobutyl ether is not available because EPA determined that the data were inadequate for derivation of an inhalation RfC (1992). The literature published since the inhalation RfC for triethylene glycol monobutyl ether was reviewed (1992) does not appear to contain study data that could potentially produce a change in the RfC. A literature search conducted for the years 1991 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for triethylene glycol monobutyl ether.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Four documents, three of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Triethylene glycol monoethyl ether (CAS No. 112-50-5)

Oral Reference Dose (RfD)
No assessment of the RfD is included in IRIS.

Inhalation Reference Concentration (RfC)
An RfC for triethylene glycol monoethyl ether is not available because EPA determined that the data were inadequate for derivation of an inhalation RfC (1992). The literature published since the inhalation RfC for triethylene glycol monoethyl ether was reviewed (1992) does not appear to contain study data that could potentially produce a change in the RfC. A literature search conducted for the years 1991 to 2002 identified no new studies that would be directly useful in the derivation of an RfC for triethylene glycol monoethyl ether.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
Five documents, all of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance, including a study titled "Triethylene Glycol Ether: An Evaluation of Teratogenic Potential and Developmental Toxicity Using an *in vivo* Screen in Rats."

Evaluation of the Recent Literature and Determination of Currency for:
Trifluralin (CAS No. 1582-09-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for trifluralin was derived (1989) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for trifluralin was derived based on a 12-month dietary study in dogs (1984). Review of the EPA Office of Pesticide Programs Reregistration Eligibility Decision (RED) (1996) and a literature search conducted for the years 1991 to 2002 identified a 2-year dietary toxicity study in B6C3F1 mice (1991) and two developmental toxicity studies, with administration by gavage, in rats and rabbits (1990, 1995). In the 1996 RED, OPP derived an RfD based on a chronic (1-year) toxicity feeding study in dogs (1992).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
The literature published since the CSF for trifluralin was derived (1987) does not appear to contain study data that could potentially produce a change in the CSF.

The IRIS CSF for trifluralin was derived based on a rat study that showed an increased incidence of renal pelvis carcinomas, urinary papillomas, and thyroid adenomas and carcinomas (1980). Review of the International Agency for Research on Cancer (IARC) Monograph (1991), the OPP RED (1996), and a literature search conducted for the years 1991 to 2002 identified a 2-year dietary oncogenicity study in B6C3F1 mice (1991). This study found no treatment-related increase in the incidence of benign or malignant neoplasms.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
The literature published since the WOE classification (C—possible human carcinogen) was derived (1987) does not appear to contain study data that could potentially produce a change in the WOE.

The IRIS WOE for trifluralin was derived based on a rat study that showed an increased incidence of renal pelvis carcinomas, urinary papillomas, and thyroid adenomas and carcinomas (1980). Review of the IARC monograph (1991), the OPP RED (1996), and a literature search conducted for the years 1991 to 2002 suggests that studies in the more recent literature are not likely to produce a change in the WOE classification.

The IARC Monograph (1991) characterized trifluralin as Group 3—not classifiable as to carcinogenicity in humans. The OPP RED (1996) stated that the Carcinogenicity Peer Review Committee classified trifluralin as Group C—possible human carcinogen—based on limited evidence of carcinogenicity in male and female rats (long-term rodent carcinogenicity studies, rat and mouse bioassays, and genotoxicity tests).

Evaluation of the Recent Literature and Determination of Currency for:
Trifluralin (CAS No. 1582-09-8)
(continued)

Also, A literature search conducted for the years 1991 to 2002 identified a negative carcinogenicity bioassay in the mouse (1991), mouse bone-marrow micronucleus test (1997) in which trifluralin caused a significant increase in the number of micronuclei in female mice only, and a bioassay in human peripheral blood lymphocytes (1996) where trifluralin exhibited a weak cytotoxic effect. For example, in this study trifluralin caused a reduction in the proliferative rate index and cytokinesis block proliferation index and induced a slight increase in the frequency of sister chromatid exchanges. However, there were no genotoxic effects observed in the chromosomal aberration and micronuclei tests. In addition, a genotoxicity study (1991) reported trifluralin-induced cytotoxicity in the mouse lymphoma assay, without forward mutations. This study also showed no reverse mutation in Salmonella-typhimurium, no increase in the frequency of sister chromatid exchanges in Chinese hamster cells, and a negative result in a dominant lethal assay in male Wistar-rats. An additional study (1998) showed that the effect of trifluralin on microtubules in a Chinese hamster fibroblast cell bioassay was negligible and few spindles were disrupted in association with aberrant mitotic figures.

Unknown Relevance
Three documents, two of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Note: Because of the large number of references found in the literature search (approximately 710), search results were limited with a secondary search in EndNote to identify references containing common laboratory species and toxicological terms, including: rat, mouse/mice, gerbil, hamster, beagle, dog, human, rabbit, pig, monkey, primate, worker, subject, patient, inhalation, epidemiol*, genotox*, mutat*, and mutag*. Any references *not containing* one of these search terms were coded as N/A.

Evaluation of the Recent Literature and Determination of Currency for:
Uranium, soluble salts (CAS No. not available)

Oral Reference Dose (RfD)
The literature published since the oral RfD for soluble uranium salts was derived (1989) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for soluble uranium salts was derived based on a 30-day dietary bioassay in rabbits (1949). In the 1999 Toxicological Profile, ATSDR derived an intermediate oral minimal risk level (MRL) for soluble uranium salts based on renal effects exhibited in rabbits (1998). However, ATSDR did not derive a chronic oral MRL because of lack of sufficient data. ATSDR noted that the intermediate MRL for soluble uranium salts would likely be protective for chronic duration exposure.

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: In the 1999 Toxicological Profile, ATSDR derived a chronic MRL for non-cancer inhalation exposure for soluble uranium salts based on kidney effects exhibited in dogs in 2-year inhalation study (1953).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Unknown Relevance
No literature search was necessary.

Evaluation of the Recent Literature and Determination of Currency for: Vanadium pentoxide (CAS No. 1314-62-1)

Oral Reference Dose (RfD)
The literature published since the oral RfD for vanadium pentoxide was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for vanadium pentoxide was derived based on a chronic dietary study in rats (1953). A literature search conducted for the years 1985 to 2002 identified a reproductive/developmental toxicity study in male mice (1996), a 6-month immunotoxicity drinking water study in Wistar rats (1993), two teratogenicity/developmental toxicity studies in pregnant Wistar rats (1993; published in Chinese), a fetotoxicity study in pregnant Wistar rats (1993; published in Chinese), and a developmental toxicity study in NIH mice (1991; published in Chinese).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Note: A literature search conducted for the years 1985 to 2002 identified a 26-week inhalation study of pulmonary reactivity in male cynomolgus monkeys (1992).

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: A literature search conducted for the years 1991 to 2002 identified a study in which histopathological lung lesions developed following an intratracheal administration of vanadium pentoxide powder (2001); a single cell gel electrophoresis assay that found an increased number of cells with damage in the liver, kidney, lung, spleen, and heart, but not bone marrow following vanadium pentoxide exposure (1999); a single cell gel electrophoresis assay that found clear dose-response DNA migration in whole blood leukocytes and a significant positive effect with the highest tested concentration in human lymphocyte cultures (1996); and a genotoxicity study that found no significant increases in the frequency of sister chromatid exchanges or gene mutations, but reported dose-related increases of micronucleated cells in culture and decreases in the number of binucleated cells in the presence of cytochalasin B (1994).

Unknown Relevance
Eight documents, five of which were submissions to EPA Office of Toxic Substances (OTS), were categorized as being of unknown relevance.

Evaluation of the Recent Literature and Determination of Currency for:
Vinclozolin (CAS No. 50471-44-8)

Oral Reference Dose (RfD)
The literature published since the oral RfD for vinclozolin was derived (1986) contains study data that could potentially produce a change in the RfD.

The IRIS RfD for vinclozolin was derived based on a 6-month dietary study in dogs (1982). In the 2000 Reregistration Eligibility Decision (RED), EPA Office of Pesticide Programs (OPP) derived an RfD for vinclozolin based on a chronic (2-year) dietary toxicity study in rats (1994).

Inhalation Reference Concentration (RfC)
No assessment of the RfC is included in IRIS.

Oral Slope Factor (CSF)
No assessment of the CSF is included in IRIS.

Note: In the 2000 RED, OPP derived a CSF for vinclozolin based on a 1994 study that repored an increased incidence of spleen sarcomas in rats. The CSF is based on a low-dose linear extrapolation of 3,5-dichloroaniline resulting solely from the use of vinclozolin. OPP assumed that the carcinogenic potential of 3,5-dichloroaniline represented the carcinogenicity of all chloroanilines, unless sufficient evidence is otherwise available.

Note: The chronic population adjusted dose provided in the OPP RED (2000) was considered protective of possible cancer effects because this dose was protective of the precursor anti-androgen effects that lead to tumors. OPP also determined that a nonlinear (margin-of-exposure) approach was appropriate for vinclozolin.

Inhalation Unit Risk (IUR)
No assessment of the IUR is included in IRIS.

Cancer Weight-of-Evidence (WOE) Classification
No assessment of the WOE classification is included in IRIS.

Note: In the 2000 RED, OPP classified vinclozolin as Group C—possible human carcinogen—based on Leydig (interstitial testicular) cell tumors in rats in chronic and carcinogenicity studies.

Unknown Relevance
No literature search was necessary.

Appendix G: Summary of Findings

Appendix G: Summary of Findings

Chemical	CAS Number	RfD	RfC	CSF	IUR	WOE	UR
Acetonitrile	75-05-8	C	C	--	--	C	3
Acrylonitrile	107-13-1	O	C	N	N	N	8
Adiponitrile	111-69-3	--	O	--	--	C	24
Aldicarb	116-06-3	N	--	--	--	C	7
Aldrin	309-00-2	C	--	C	N	N	1
Ally	74223-64-6	C	--	--	--	--	5
Allyl alcohol	107-18-6	N	--	--	--	--	11
Ametryn	834-12-8	C	--	--	--	O	5
4-Aminopyridine	504-24-5	--	--	--	--	C	4
Amitraz	33089-61-1	C	--	--	--	O	4
Ammonium acetate	631-61-8	--	--	--	--	C	4
Ammonium sulfamate	7773-06-0	C	--	--	--	--	0
Aniline	62-53-3	O	C	C	--	C	4
Antimony	7440-36-0	N	O	--	O	O	5
Antimony trioxide	1309-64-4	O	C	--	--	O	2
Apollo	74115-24-5	C	--	--	--	C	1
Arsenic (inorganic)	7440-38-2	N	--	N	N	C	0
Arsine	7784-42-1	--	N	--	--	O	3
Assure	76578-14-8	C	--	--	--	C	7
Azobenzene	103-33-3	O	--	C	C	C	1
Barium cyanide	542-62-1	C	--	--	--	--	0
Baythroid	68359-37-5	C	--	--	--	--	11
Benefin	1861-40-1	C	--	--	--	--	0
Benomyl	17804-35-2	N	--	--	--	O	N/A
Bidrin	141-66-2	N	--	--	--	--	0
Biphenthrin	82657-04-3	C	--	O	--	--	3
1,1-Biphenyl	92-52-4	C	C	--	--	C	8
Bis(2-chloroethoxy)methane	111-91-1	O	--	--	--	C	3
Bis(2-chloroisopropyl) ether	39638-32-9	C	--	--	--	O	4
Bisphenol A	80-05-7	N	O	--	--	O	20
Bromodichloromethane	75-27-4	N	O	N	O	C	25
p-Bromodiphenyl ether	101-55-3	--	--	--	--	C	1
Bromoform	75-25-2	N	C	C	C	N	23
Bromoxynil octanoate	1689-99-2	N	--	O	--	--	6
Cacodylic acid	75-60-5	O	--	O	--	N	12
Captafol	2425-06-1	N	--	O	--	O	8

Chemical	CAS Number	RfD	RfC	CSF	IUR	WOE	UR
Carbaryl	63-25-2	N	C	--	--	O	7
Carbofuran	1563-66-2	C	--	--	--	O	15
Carbon disulfide	75-15-0	C	N	--	--	--	11
Carbonyl sulfide	463-58-1	-	C	--	--	--	9
Carbosulfan	55285-14-8	C	--	--	--	O	4
Carboxin	5234-68-4	C	--	--	--	O	2
Chlorimuron-ethyl	90982-32-4	C	--	--	--	--	7
Chlorine	7782-50-5	C	O	O	O	O	11
1-Chlorobutane	109-69-3	--	--	--	--	C	9
2-Chlorobutane	78-86-4	--	--	--	--	C	0
2-Chlorophenol	95-57-8	C	--	--	--	O	2
p-Chlorophenyl methyl sulfide	123-09-1	C	--	--	--	C	0
Coke oven emissions	8007-45-2	--	--	--	N	C	34
Cumene	98-82-8	C	C	--	--	C	6
Cyanazine	21725-46-2	N	--	O	--	O	3
Cyanogen	460-19-5	C	O	--	--	--	0
Cyclohexanone	108-94-1	C	O	--	--	O	18
Cyclohexylamine	108-91-8	C	--	--	--	O	8
Dalapon (sodium salt)	75-99-0	C	--	--	--	--	0
Danitol	39515-41-8	C	--	--	--	O	9
2,4-Diaminotoluene	95-80-7	--	C	--	--	O	20
Dibenzofuran	132-64-9	O	--	--	--	C	0
Dibromochloromethane	124-48-1	N	--	C	--	N	15
Dibromodichloromethane	594-18-3	--	--	--	--	C	2
p,p'-Dibromodiphenyl ether	2050-47-7	--	--	--	--	C	0
Dicamba	1918-00-9	N	--	--	--	O	20
p,p'-Dichlorodiphenyltrichloroethane	50-29-3	N		C	C	N	3
1,1-Dichloroethane	75-34-3	O	O	--	--	C	5
cis-1,2-Dichloroethylene	156-59-2	O	--	--	--	C	2
trans-1,2-Dichloroethylene	156-60-5	C	O	--	--	--	1
Dichloromethane	75-09-2	C	O	C	C	C	13
4-(2,4-Dichlorophenoxy)butyric acid	94-82-6	N	--	O	--	O	0
1,2-Dichloropropane	78-87-5	O	C	--	--	O	12
2,3-Dichloropropanol	616-23-9	C	--	--	--	--	3
Dicofol	115-32-2	O	--	C	C	C	1
Diethyl phthalate	84-66-2	N	--	--	--	C	9
Diethyl-p-nitrophenyl phosphate	311-45-5	--	--	--	--	C	3
Dimethipin	55290-64-7	C	--	--	--	C	7

Chemical	CAS Number	RfD	RfC	CSF	IUR	WOE	UR
N,N-Dimethylformamide	68-12-2	O	N	--	--	O	N/A
2,4-Dimethylphenol	105-67-9	N	--	--	--	--	0
3,4-Dimethylphenol	95-65-8	C	--	--	--	--	1
2,4-Dinitrotoluene	121-14-2	C	C	--	--	O	3
Diphenamid	957-51-7	C	--	--	--	--	2
1,2-Diphenylhydrazine	122-66-7	--	C	C	C	C	2
Disulfoton	298-04-4	N	O	--	--	--	N/A
Endosulfan	115-29-7	C	--	--	--	--	8
Endothall	145-73-3	N	--	--	--	--	9
Epichlorohydrin	106-89-8	N	N	C	N	N	78
1,2-Epoxybutane	106-88-7	--	C	--	--	O	13
Ethephon	16672-87-0	C	--	--	--	O	3
S-Ethyl dipropylthiocarbamate	759-94-4	C	--	--	--	O	0
Ethyl p-nitrophenyl phenylphosphorothioate	2104-64-5	C	--	--	--	--	7
Ethylene glycol monobutyl ether (EGBE)	111-76-2	C	C	--	--	C	22
Ethylphthalyl ethylglycolate	84-72-0	C	--	--	--	--	0
Fluridone	59756-60-4	C	--	--	--	--	5
Flurprimidol	56425-91-3	C	--	--	--	--	15
Fluvalinate	69409-94-5	C	--	--	--	--	10
Fomesafen	72178-02-0	--	--	C	--	N	2
Formic acid	64-18-6	C	O	--	--	O	5
Furmecyclox	60568-05-0	--	--	C	--	C	0
Glycidaldehyde	765-34-4	C	--	--	--	C	1
n-Heptane	142-82-5	--	--	--	--	C	14
alpha-Hexachlorocyclohexane	319-84-6	O	--	C	C	C	4
beta-Hexachlorocyclohexane	319-85-7	O	--	C	C	N	5
Hexachlorophene	70-30-4	N	--	--	O	O	8
1,6-Hexamethylene diisocyanate	822-06-0	--	C	--	--	O	23
Hexazinone	51235-04-2	N	--	--	--	O	N/A
Hydrazine/Hydrazine sulfate	302-01-2	--	O	N	N	C	N/A
Hydroquinone	123-31-9	O	C	O	O	O	43
Isobutyl alcohol	78-83-1	N	O	--	--	--	34
Lead and compounds (inorganic)	7439-92-1	N	--	--	--	C	N/A
d-Limonene	5989-27-5	--	C	--	--	O	6
Malathion	121-75-5	N	--	--	--	O	N/A
Maleic anhydride	108-31-6	N	O	--	--	--	13
Maleic hydrazide	123-33-1	N	--	--	--	O	N/A
Manganese	7439-96-5	C	N	--	--	C	6

Chemical	CAS Number	RfD	RfC	CSF	IUR	WOE	UR
Mepiquat chloride	24307-26-4	N	--	--	--	O	N/A
Mercuric chloride	7487-94-7	C	--	C	--	C	11
Mercury, elemental	7439-97-6	--	N	--	--	C	33
Merphos oxide	78-48-8	N	C	--	--	O	1
Methamidophos	10265-92-6	N	--	--	--	O	N/A
Methyl isocyanate	624-83-9	--	C	--	--	O	27
Methyl methacrylate	80-62-6	C	C	--	--	C	10
2-Methyl-4-chlorophenoxyacetic acid	94-74-6	N	--	--	--	O	5
2-(2-Methyl-4-chlorophenoxy) propionic acid	93-65-2	C	--	--	--	--	9
Methylmercury	22967-92-6	C	--	--	--	C	17
3-Methylphenol	108-39-4	N	C	--	--	C	5
4-Methylphenol	106-44-5	N	C	--	--	C	9
Metribuzin	21087-64-9	N	--	--	--	C	0
Nitrate	14797-55-8	N	--	O	--	O	44
Nitrite	14797-65-0	C	--	O	--	O	22
N-Nitrosodimethylamine	62-75-9	O	--	N	C	N	20
N-Nitrosodi-N-propylamine	621-64-7	O	--	C	O	C	19
N-Nitrosodiphenylamine	86-30-6	O	--	C	--	C	3
Oxyfluorfen	42874-03-3	N	--	--	--	O	N/A
Pentabromodiphenyl ether	32534-81-9	C	--	--	--	C	37
Pentachlorocyclopentadiene	25329-35-5	--	--	--	--	C	0
Pentafluoroethane	354-33-6	--	N	--	--	O	5
m-Phenylenediamine	108-45-2	N	--	--	--	O	71
Phenylmercuric acetate	62-38-4	C	--	--	--	O	11
Phosmet	732-11-6	N	--	O	--	O	N/A
Phthalic anhydride	85-44-9	C	--	--	--	O	10
Picloram	1918-02-1	N	--	--	--	O	2
Pirimiphos-methyl	29232-93-7	N	--	--	--	--	N/A
Potassium silver cyanide	506-61-6	N	--	--	--	--	0
Prometon	1610-18-0	N	--	--	--	O	0
Pronamide	23950-58-5	N	--	--	--	O	N/A
Propanil	709-98-8	N	--	--	--	O	13
Propargyl alcohol	107-19-7	C	--	--	--	O	4
Propham	122-42-9	C	--	--	--	O	1
Propylene glycol monomethyl ether	107-98-2	--	N	--	--		32
Propylene glycol	57-55-6	--	N	--	--		29
Propyleneimine	75-55-8	--	C	--	--	O	1

Chemical	CAS Number	RfD	RfC	CSF	IUR	WOE	UR
Pyridine	110-86-1	C	--	--	--	O	11
Quinalphos	13593-03-8	N	--	--	--	O	4
Quinoline	91-22-5	C	C	C	--	C	2
Quinone	106-51-4	--	C	--	--	O	23
Radium 226,228	7440-14-4	--	--	C	C	C	5
Radon 222	14859-67-7	--	--	C	C	C	0
Resmethrin	10453-86-8	C	--	--	--	O	17
Savey	78587-05-0	C	--	--	--	--	4
Selenious acid	7783-00-8	C	--	--	--	C	0
Selenium sulfide	7446-34-6	O	--	--	--	C	0
Selenium and Compounds	7782-49-2	N	--	--	--	C	6
Selenourea	630-10-4	C	--	--	--	--	4
Silver cyanide	506-64-9	C	--	--	--	--	0
Simazine	122-34-9	N	--	O	--	O	19
Sodium diethyldithiocarbamate	148-18-5	C	--	O	--	O	4
Strychnine	57-24-9	C	--	--	--	--	13
Systhane	88671-89-0	C	--	--	--	--	5
Tebuthiuron	34014-18-1	C	--	--	--	O	0
Terbutryn	886-50-0	N	--	--	--	O	2
Tetrabromodiphenyl ether	40088-47-9	--	--	--	--	C	1
1,2,4,5-Tetrachlorobenzene	95-94-3	N	--	--	--	O	N/A
Tetrachlorocyclopentadiene	695-77-2	--	--	--	--	C	0
1,1,1,2-Tetrachloroethane	630-20-6	C	--	C	C	C	15
1,1,2,2-Tetrachloroethane	79-34-5	O	--	C	C	C	6
2,3,4,6-Tetrachlorophenol	58-90-2	C	--	--	--	O	6
Tetraethyl lead	78-00-2	N	O	--	O	O	21
Thallic oxide	1314-32-5	C	--	--	--	C	1
Thallium carbonate	6533-73-9	N	--	--	--	C	0
Thallium nitrate	10102-45-1	C	--	--	--	C	0
Thallium sulfate	7446-18-6	C	--	--	--	C	1
Thiobencarb	28249-77-6	C	--	--	--	O	0
Thiophanate-methyl	23564-05-8	N	--	O	--	O	N/A
Toxaphene	8001-35-2	O	--	N	C	C	1
1,2,4-Tribromobenzene	615-54-3	C	--	--	--	--	3
Tributyltin oxide	56-35-9	N	C	--	--	C	0
Trichloroacetic acid	76-03-9	O	--	O	--	C	4
Trichlorocyclopentadiene	77323-84-3	--	--	--	--	C	0
Trichlorofluoromethane	75-69-4	C	--	--	--	O	8

Chemical	CAS Number	RfD	RfC	CSF	IUR	WOE	UR
2,4,5-Trichlorophenol	95-95-4	C	C	--	O	O	1
2,4,6-Trichlorophenol	88-06-2	O	C	C	C	C	1
2 (2,4,5-Trichlorophenoxy) propionic acid	93-72-1	C	--	--	--	N	3
1,2,3-Trichloropropane	96-18-4	N	O	O	--	O	N/A
1,1,2-Trichloropropane	598-77-6	C	--	--	--	--	1
1,1,2-Trichloro-1,2,2-trifluoroethane	76-13-1	C	O	--	O	O	31
Tridiphane	58138-08-2	N	--	O	--	--	1
Triethylene glycol monobutyl ether	143-22-6	--	C	--	--	--	4
Triethylene glycol monoethyl ether	112-50-5	--	C	--	--	--	5
Trifluralin	1582-09-8	N	--	C	--	C	3
Uranium, soluble salts	N.A.	N	O	--	--	--	N/A
Vanadium pentoxide	1314-62-1	N	O	--	--	O	8
Vinclozolin	50471-44-8	N	--	O	--	O	N/A

Summary of Assessments:

Available in the existing IRIS summary	**141**	**40**	**30**	**21**	**80**
Not available in the existing IRIS summary	**59**	**160**	**170**	**179**	**120**
No literature likely to produce a significant change in the IRIS summary was identified	**80**	**31**	**24**	**15**	**69**
New literature was identified that could potentially produce a significant change in the IRIS summary[1]	**61**	**9**	**6**	**6**	**11**
Not available in IRIS, but potentially relevant information was identified	**23**	**20**	**18**	**9**	**75**

Notes:

[1] The screening-level review of the IRIS summaries for 79 chemicals (40%) identified new health effects information that, if evaluated in detail, could possibly result in a change to at least one existing value.

-- No value is available in the existing IRIS file
C The literature published since the IRIS consensus review does not appear to contain study data that could potentially produce a change in the IRIS summary. The existing IRIS summary is considered current.
N New health effects information that could potentially affect the IRIS summary was identified.
O No value is available in the existing IRIS file. Potentially relevant information was identified during evaluation of the literature compilations or literature search results. This information may or may not support the derivation of an IRIS toxicity value or WOE designation. The narratives for individual chemicals provide further discussions about the nature of this information

CAS	chemical abstracts registry service
CSF	oral cancer slope factor
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
N/A	not applicable, no literature search was deemed necessary
RfD	oral reference dose
RfC	inhalation reference concentration
UR	unknown relevance, number of studies identified as being of unknown relevance during literature sorting
WOE	cancer weight-of-evidence