

**EPA Screening Evaluation Report
Presentation and Discussion of Uncertainty and Variability in IRIS
Assessments**

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Summary

In support of the study that Congress has directed EPA to conduct (via HR-106-379), evaluating the extent of documentation of uncertainty and variability in IRIS assessments, EPA has carried out a screening of 67 of the 536 IRIS assessments on-line as of 1/31/2000. The purpose of this screening is to survey broadly the extent of this documentation in IRIS assessments, in order to facilitate an in-depth evaluation of a smaller, but representative set of IRIS assessments, to be carried out by a contractor. A simple random sample comprising 10% of the pre-Pilot IRIS assessments (52/522), plus all of the 15 Pilot and post-Pilot IRIS assessments were stratified into three categories, those with none/ minimal, some/ moderate, or extensive presentation and discussion of uncertainty and variability. This report summarizes this screening effort.

Introduction/Background

As pointed out in *Science and Judgment in Risk Assessment* (NRC, 1994) EPA has historically incorporated uncertainty in health risk assessments in a qualitative manner. There are no quantitative uncertainty analyses documented or referenced in IRIS. EPA formally stated its position in the *Policy for Use of Probabilistic Analysis in Risk Assessment* (1997):

For human health risk assessments, the application of Monte Carlo and other probabilistic techniques has been limited to exposure assessments in the majority of cases. The current policy, Conditions for Acceptance and associated guiding principles are not intended to apply to dose response evaluations for human health risk assessment until this application of probabilistic analysis has been studied further.

The information provided in IRIS concerning variability and uncertainty has gradually become more extensive as experience was gained in the IRIS program. At first, IRIS assessments mainly provided the results of the deliberations culminating in consensus health hazard conclusions. Gradually the assessments included more of the details of the data and of the considerations which led to the consensus conclusions.

Note that some general aspects of the extent of variability and uncertainty can be determined from the IRIS assessments. Concerning variability, upper bounds on response rates, when provided in the IRIS Summary. A few examples for RfDs and RfCs generated from NOAELS are provided in Table 1. For instance, for an RfC or RfD determined from a study with 6 animals per group, from which a NOAEL was identified, the 95% upper bound on the observed 0% response rate is approximately 50%. While this does not provide a confidence limit for the corresponding exposure level, it demonstrates that there is considerable variability (and uncertainty) in such a NOAEL. Also, the definition of RfDs and RfCs, accessible through the IRIS Web Site, points out that there is perhaps an order of magnitude of uncertainty associated with these determinations.

The goal of this study is to examine more closely the strengths and weaknesses of the documentation of the health hazard assessment conclusions available through IRIS, by examining specific, representative IRIS assessments. On the advice of the Executive Committee of the Science Advisory Board (11/29/99), the extent of documentation of variability and uncertainty in IRIS assessments was established in two steps. The first step was to classify a random sample of IRIS assessments into categories of documentation: none or minimal, some or moderate, or extensive. Then assessments randomly drawn from these categories or strata are to be examined in depth for their treatment of variability and uncertainty, given the state of the science and data available at the time of the assessment.

Stratified random sampling is an efficient method for characterizing a population. Through selection of strata which are reasonably internally homogeneous, we can expect that a small number of assessments randomly chosen from a stratum can represent that stratum. Due to the large number of pre-Pilot assessment, however, it is not possible to stratify the entire IRIS database. A smaller subset must be used to characterize the overall extent of documentation of uncertainty and variability in IRIS. The SAB recommended a 10% sample (52/522), which NCEA also believes can adequately characterize the entire set of pre-Pilot IRIS assessments for this evaluation. Thorough attention has been given during the entire IRIS program to generating consistent summaries of adverse health effects associated with the chemicals considered.

Methods

The goal of the screening was to classify a random sample of assessments according to the extent of the presentation and discussion of variability and uncertainty.

Selection of Screening Sample The total number of available IRIS assessments was fixed by focusing on the chemicals listed on the IRIS Website. All toxicity values that were addressed for each chemical - RfD, RfC, or cancer slope factors - were considered together. There were 522 pre-Pilot IRIS assessments available on-line as of 1/31/2000. These were numbered 1 through 522, in the order that the chemicals appear on-line, alphabetically. A table of random numbers (Daniel, 1978) was used to select 52 numbers between 1 and 522, inclusive. Computer-generated random numbers would have been appropriate, but this traditional method is more straightforward to document. All post-Pilot assessments were stratified, since there were relatively few post-Pilot assessments, and pre-Pilot and post-Pilot assessments are to be compared.

Criteria for Assigning Assessments to Strata Since the available assessments were generated over a period of approximately 14 years, it became clear that there was a continuum of relevant factors to consider. NCEA developed criteria (see Table 2) to describe the degree of the documentation and distinguish between qualitative and quantitative aspects of variability and uncertainty. The first category, None/Minimal, describes assessments which presented results and overall uncertainty and confidence conclusions, but no incidence rates or other quantitative effect

levels for the available studies, nor rationale for the conclusions. Assessments with Some or Moderate documentation contained quantitative effect levels and some discussion of variability of effects, including variability across dose groups and temporal variability. In addition, there was some discussion of the reasons for overall confidence in the assessment. Assessments with Extensive documentation contained quantitative variability information, some comparison of results across related studies, discussion of sources of uncertainty, comparison of uncertainties across available studies, and rationales for confidence in the available studies and conclusions drawn in the assessment.

In some cases, assessments contained somewhat more documentation of uncertainties relative to variability, or vice versa. This was apparent within some sections addressing a health hazard measure (RfC, RfD, or cancer unit risk), and between measures, especially when they were completed a few years apart. The overall rating for an assessment was determined by the characterization of the majority of the subsections. Appendix A provides a brief description of the rationale for classifying each assessment.

For the purposes of this study, the determination of the extent of the presentation and discussion of variability and uncertainty was restricted to what was explicitly provided in the on-line IRIS database for each assessment. Specifically, for the pre-Pilot assessments, only the IRIS Summary was examined. For the later IRIS assessments, the IRIS Summary and the Toxicological Review were examined. EPA source documents and literature cited in the assessments could not be consulted, due to the large volume of materials. Consequently, this stratification addressed only the overall quality or approach to providing this information in the on-line assessments, not the completeness of the summarized information nor the cited scientific literature available at the time of each assessment.

Independent Review of Assignments to Documentation Categories The Executive Committee of the SAB recommended that the assignment of the assessments in the screening sample to the broad documentation categories go through an independent verification, to evaluate the repeatability of the decision process. An EPA health scientist not routinely involved in IRIS assessments applied the criteria developed above to the pre-screening sample of 67 assessments. The report of this independent review is in Attachment A.

Results and Discussion

The results of applying the criteria in Table 2 to the pre-Pilot and the later IRIS assessments are given in Tables 3 and 4, respectively. Of the 52 pre-Pilot IRIS assessments screened (Table 3), 3/52 had extensive, 16/52 some or moderate, and 33/52 none or minimal presentation or discussion of variability and uncertainty. In sharp contrast, assessments carried out during or after the Pilot nearly unanimously (14/15) showed extensive treatment of variability and uncertainty (see Table 4).

As noted earlier, this evaluation was carried out to facilitate choosing assessments for in-depth reviews. These in-depth evaluations were to cover a range of IRIS entry dates, types of chemicals, scientific complexities, and toxic endpoints of concern. To that end, the sampled assessments are listed in Tables 3 and 4 in chronological order within each of the three categories of documentation, with broad categories of chemicals and critical health endpoints noted.

Note that a few pre-Pilot assessments referred to data which were not summarized in the assessment, or otherwise included conclusions which were not supported by the available summary. In these cases, assessments which otherwise fit the Extensive or Some/Moderate criteria, but clearly omitted available data, were downgraded one category. These choices seemed justified, since it seemed likely that if these assessments happened to be selected for the in-depth phase of the evaluation, these deficiencies would be immediately apparent and remarked on. These instances are noted in Appendix A.

Recall that 8 Pilot and 8 Pilot/post-Pilot assessments were to be randomly selected from those screened, with 4 each from the Some/Moderate and Extensive categories within each of the pre-Pilot and post-Pilot sets. As noted above, however, there were fewer than 4 assessments in 2 of the targeted subgroups. Specifically, only three assessments fell in the Extensive subset of the pre-Pilot assessments sampled, so an additional Some/Moderate assessment must be evaluated among the pre-Pilot assessments, resulting in a total of 5 Some/Moderate and 3 Extensive pre-Pilot assessments. Similarly, among the post-Pilot assessments, only one assessment fell in the Some/Moderate category, so 7 Extensive assessments must be evaluated to complete the in-depth sample of post-Pilot assessments.

Due to time constraints, the independent verification of the classifications was carried out after the in-depth assessments needed to be chosen. Overall, agreement was good (see Table 5), with a Spearman rank correlation coefficient of 0.82 (Lehmann, 1975). Differences in assignments for individual assessments were primarily due to the second reviewer classifying 11 'borderline' assessments in the next lower category than the first reviewer had. Also, there were 4 assessments which the first reviewer downgraded for omitting information referenced elsewhere in the assessment; by the standards of the time the assessments were incomplete. The second reviewer did not downgrade these assessments, emphasizing the quality of the approach to presenting variability and uncertainty.

The second reviewer reached equally valid conclusions. Recognizing the subjectiveness involved in drawing clear distinctions among characterizations which must consider a number of heterogeneous issues, it is therefore constructive to consider the results of the two rankings simultaneously. Among pre-Pilot assessments, approximately three-fourths (63-79%, from Table 5) contained none to minimal documentation of variability and uncertainty information. Note that the vast majority of these assessments were completed before 1990 (see Table 3). Assessments containing some to moderate documentation represented about 15-31% (Table 5) of the sample. These were completed uniformly throughout the pre-Pilot period, at least among the assessments in the screening sample.

The distribution of assessments with extensive documentation of variability and uncertainty clearly increased with time. Virtually all of the Pilot/post-Pilot (starting in 1995) assessments demonstrated extensive treatment of variability and uncertainty information (93-100%, Table 5). The earliest “Extensive” assessment in the screening sample was either 1,2-dibromo-3-chloropropane (1991), according to the first reviewer, or manganese or 2,4-/2,6-toluene diisocyanate mixture (1995), which both reviewers agreed upon.

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Table 1: Upper 95% bounds on 0% responses for selected toxicity study group sizes	
Animals/sex/group	Upper 95% bound on observed 0% response
4	60%
6	46%
20	17%
50	7%

Table 2: Criteria for classifying extent of presentation and discussion of variability and uncertainty		
Category	Variability	Uncertainty
None/ Minimal	Any studies relevant to the conclusions are listed, only qualitative dose-responses indicated; no discussion.	Uncertainty factors listed, and overall confidence stated; no discussion.
Some/ Moderate	Conditions for Minimal met, plus adverse effect levels provided for principal study; some discussion.	Uncertainty factors listed; some discussion of uncertainty and confidence in the assessment.
Extensive	Conditions for Some/ Moderate met, plus measures of variability or discussion of variability of the results.	Discussion of the strengths and weaknesses of the available studies, some assessment of the level of confidence in the body of evidence.

Table 3: Extent of documentation of variability and uncertainty in a 10% random sample of pre-Pilot IRIS Assessments.

Chemical	Overall Documentation	Last Significant Revision	Chemical Type	Key Health Endpoints ^a
Dibromo-3-chloropropane, 1,2-	Extensive	10/01/1991	Pesticide	RfC: testicular effects
Toluene diisocyanate mixture, 2,4-/2,6-	Extensive	09/01/1995	Other	RfC: chronic lung-function decline
Manganese	Extensive	11/01/1995	Metal	RfD: CNS effects RfC: impaired neurobehavioral function Cancer: D, no human data, animal data inadeq.
Fluorine (soluble fluoride)	Some/Moderate	01/31/1987	Element	RfD: dental fluorosis
Ethylene glycol	Some/Moderate	09/30/1987	Other	RfD: kidney toxicity
Hexachlorodibenzo-p-dioxin, mixture	Some/Moderate	03/01/1988	Other	Cancer: B2, liver tumors
Dichlorodiphenyltrichloroethane, p,p'-	Some/Moderate	08/02/1988	Pesticide	RfD: liver lesions Cancer: B2, liver tumors, benign and malignant
Fomesafen	Some/Moderate	08/22/1988	Pesticide	Cancer: C, hepatadenomas, -carcinomas
Furmecyclox	Some/Moderate	09/07/1988	Other	Cancer: B2, liver carcinomas, neoplastic nodules
Prochloraz	Some/Moderate	01/01/1989	Pesticide	RfD: Increased SAP and liver wt, liver histopath Cancer: C, liver tumors
Propargite	Some/Moderate	05/01/1990	Pesticide	RfD: None (at any dose tested)
Methylphenol, 4-	Some/Moderate	09/01/1990	Other	Cancer: C, skin papillomas
Dimethylformamide, N,N-	Some/Moderate	10/01/1990	Other	RfC: digestive disturbances
Vinyl acetate	Some/Moderate	10/01/1990	Other	RfC: Nasal epithelial lesions
Hexachlorobenzene	Some/Moderate	03/01/1991	Pesticide	RfD: liver effects Cancer: B2, liver, thyroid, kidney tumors
Pentachlorophenol	Some/Moderate	03/01/1991	Other	RfD: liver, kidney pathology Cancer: B2, hepatic, adrenal tumors; hemang.
Aldicarb sulfone	Some/Moderate	11/01/1993	Pesticide	RfD: brain ChE inhibition
Danitol	Some/Moderate	10/01/1994	Pesticide	RfD: tremors
Arsenic, inorganic	Some/Moderate	06/01/1995	Metal	RfD: hyperpigmentation, keratosis Cancer: A, lung cancer
Chlorsulfuron	None/Minimal	01/31/1987	Pesticide	RfD: decreased BW
Metalaxyl	None/Minimal	01/31/1987	Pesticide	RfD: increased SAP; increased liver-to-brain wt ratio RfC: inadequate data
Phosmet	None/Minimal	01/31/1987	Other	RfD: reduced. BW; liver cell vacuolation; ChE inhibition
Pronamide	None/Minimal	01/31/1987	Pesticide	RfD: None (at any dose tested)
Dibromobenzene, 1,4-	None/Minimal	03/31/1987	Other	RfD: relative liver wt; hepatic microsomal enzyme induction

Table 3: Extent of documentation of variability and uncertainty in a 10% random sample of pre-Pilot IRIS Assessments.

Chemical	Overall Documentation	Last Significant Revision	Chemical Type	Key Health Endpoints ^a
Pydrin	None/Minimal	03/31/1987	Pesticide	RfD: neurological dysfunction
Sodium azide	None/Minimal	03/31/1987	Other	RfD: decreased BW; hunched posture
Tetrachlorovinphos	None/Minimal	03/31/1987	Pesticide	RfD: reduced BW gain; increased liver and kidney wt; RBC ChE inhibition
Cyromazine	None/Minimal	09/30/1987	Pesticide	RfD: hematologic effects
Diphenamid	None/Minimal	09/30/1987	Other	RfD: liver toxicity
Hexazinone	None/Minimal	09/30/1987	Other	RfD: decreased BW
Methamidophos	None/Minimal	09/30/1987	Pesticide	RfD: ChE inhibition
Butylphthalyl butylglycolate	None/Minimal	03/01/1988	Other	RfD: None (at any dose tested)
N-Nitroso-N-methylethylamine	None/Minimal	03/01/1988	Other	Cancer: B2, hepatic tumors
Carboxin	None/Minimal	06/30/1988	Other	RfD: reduced BW gain, organ wt changes, death
Vanadium pentoxide	None/Minimal	06/30/1988	Other	RfD: decreased hair cystine
Hexachlorophene	None/Minimal	08/22/1988	Other	RfD: swollen salivary glands; status spongiosis in brain and optic nerve
Dieldrin	None/Minimal	09/07/1988	Pesticide	RfD: liver lesions Cancer: B2, hepatocarcinoma
Dimethyl phthalate	None/Minimal	09/07/1988	Other	Cancer: D, no data found
Maneb	None/Minimal	09/07/1988	Pesticide	RfD: increased thyroid wt
Trichloroethane, 1,1,1-	None/Minimal	09/07/1988	Other	Cancer: D, no human data, animal data inadeq.
Bis(chloromethyl)ether	None/Minimal	09/26/1988	Other	RfC: inadequate data Cancer: A, respiratory tract tumors
Benomyl	None/Minimal	03/01/1989	Pesticide	RfD: decreased pup BW
Cypermethrin	None/Minimal	03/01/1989	Pesticide	RfD: GI tract disturbances
Pursuit	None/Minimal	01/01/1990	Pesticide	RfD: decreased cell vol, HGB, erythrocytes
Chlorocyclopentadiene	None/Minimal	03/01/1990	Other	Cancer: D, no data found
Octabromodiphenyl ether	None/Minimal	08/01/1990	Other	RfD: induction of hepatic enzymes; liver histopath Cancer: D, no data found
beta-Chloronaphthalene	None/Minimal	11/01/1990	Other	RfD: dyspnea; abnormal appear.; enlarged liver
Brominated dibenzofurans	None/Minimal	12/01/1990	Other	Cancer: D, no data found
Dibromodichloromethane	None/Minimal	03/01/1991	Other	Cancer: D, no data found
Apollo	None/Minimal	06/01/1991	Pesticide	RfD: liver effects; organ wt. changes Cancer: C, thyroid gland follicular cell tumors
Dinitrobenzene, o-	None/Minimal	09/01/1992	Other	Cancer: D, no human or animal data found
Triethylene glycol monobutyl ether	None/Minimal	09/01/1994	Other	RfC: inadequate data

^a Note that RfDs or RfCs followed by 'None' indicate that no adverse health effects were seen; RfDs or RfCs were determined from the particular exposure levels used in the cited experiments or studies.

Descriptions of cancer endpoints include cancer classifications from 1986 Cancer Guidelines (US EPA, 1986).

Table 4: Extent of documentation and variability in post-Pilot IRIS Assessments

Chemical	Overall Documentation	Last Significant Revision	Chemical Type	Key Health Endpoints ^a
Cumene	Extensive	08/01/1997	Petroleum constituent	RfD: increased kidney wt RfC: increased kidney, adrenal weights Cancer: D/CBD, (see description)
Tributyltin oxide	Extensive	09/01/1997	Pesticide	RfD: immunosuppression RfC: inadequate data Cancer: D/CBD, benign pituitary, parathyroid tumors
Trinitrobenzene, 1,3,5- Chlordane	Extensive Extensive	10/01/1997 02/07/1998	Other Pesticide	RfD: methemoglobinemia; spleen-erythroid cell hyperplasia RfD: hepatic necrosis RfC: hepatic effects Cancer: B2/L, hepatocarcinomas
Methylene diphenyl diisocyanate	Extensive	02/07/1998	Other	RfC: olfactory epithelium hyperplasia Cancer: D/CBD, data inadequate
Bentazon	Extensive	03/02/1998	Pesticide	RfD: blood loss into GI tract Cancer: E/NL, (see description)
Methyl methacrylate	Extensive	03/02/1998	Other	RfD: None (at any dose tested) RfC: olfactory epithelium degeneration Cancer: E/NL,
Beryllium and compounds	Extensive	04/03/1998	Metal	RfD: small intestinal lesions RfC: Beryllium sensitivity, progression to CBD Cancer: B1/L, lung cancer
Chromium VI	Extensive	09/03/1998	Metal	RfD: none (at any dose tested) RfC: nasal septum atrophy, lower respiratory effects Cancer: A/K, lung cancer
Naphthalene	Extensive	09/17/1998	Pesticide	RfD: decreased BW RfC: respiratory lesions Cancer: C/CBD, respiratory tract tumors
Barium and compounds	Extensive	01/21/1999	Metal	RfD: none (at any dose tested) RfC: unverifiable Cancer: D/NL, (see description)
Acetonitrile	Extensive	03/03/1999	Other	RfC: mortality Cancer: D/CBD, (see description)
Ethylene glycol monobutyl ether	Extensive	12/30/1999	Other	RfD: MCV changes RfC: red blood cell count changes Cancer: C/CBD, pheochromocytoma

Table 4: Extent of documentation and variability in post-Pilot IRIS Assessments

Chemical	Overall Documentation	Last Significant Revision	Chemical Type	Key Health Endpoints ^a
Benzene	Extensive	01/19/2000	Solvent	Cancer: A/K, leukemia
Chromium III, insoluble salts	Some/Moderate	09/03/1998	Metal	RfD: none (at any dose tested) RfC: inadequate data Cancer: D/CBD, (see description)

^a Note that RfDs or RfCs followed by ‘None’ indicate that no adverse health effects were seen; RfDs or RfCs were determined from the particular exposure levels used in the cited experiments or studies.

Descriptions of cancer endpoints include cancer classifications from 1986 Cancer Guidelines (USEPA, 1986), and abbreviations of the descriptors in the proposed 1996 Cancer guidelines (USEPA, 1996):

CBD = Cannot be determined

NL = Not likely

L = Likely

K = Known

Table 5: Correspondence between two independent assignments of IRIS assessments to categories of extent of documentation of variability and uncertainty.

			Reviewer Classifications, count (and %)			Totals
			Minimal	Moderate	Extensive	
Pre-Pilot	Initial Classifications	Minimal	31	2	-	33 (63%)
		Moderate	10	5	1	16 (31%)
		Extensive	-	1	2	3 (6%)
	Totals		41 (79%)	8 (15%)	3 (6%)	52
Pilot/post-Pilot	Initial Classifications	Minimal	-	-	-	-
		Moderate	-	-	1	1 (7%)
		Extensive	-	-	14	14 (93%)
	Totals		-	-	15 (100%)	15

Appendix A - Summary of classifications for screening sample of IRIS assessments

A=pre-Pilot B=later	Chemical	Overall Documentation	Comments
B	Acetonitrile	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Aldicarb sulfone	Some/Moderate	Relative effect levels reported, some discussion of effects across dose levels. Some discussion of rationale for level of confidence reported.
A	Apollo	None/Minimal	Conclusions primarily; some discussion of variability for cancer assessment
A	Arsenic, inorganic	Some/Moderate	Portions have extensive discussion of variability and uncertainty, but important sections (human inhalation cancer studies) are missing; downgraded one category.
B	Barium and compounds	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Benomyl	None/Minimal	Conclusions only
B	Bentazon	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
B	Benzene	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
B	Beryllium and compounds	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	beta-Chloronaphthalene	None/Minimal	Limited discussion of consistency of results within principal study; some discussion of consistency of results between studies.
A	Bis(chloromethyl)ether	None/Minimal	Limited presentation of variability in results and discussion of uncertainty; unclear uncertainty conclusions, downgraded one category
A	Brominated dibenzofurans	None/Minimal	No chemical-specific data available; some discussion of relevance of structure-activity information
A	Butylphthalyl butylglycolate	None/Minimal	Only one study available, with no adverse effects observed; no discussion of medium confidence
A	Carboxin	None/Minimal	Conclusions only
B	Chlordane	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Chlorocyclopentadiene	None/Minimal	Conclusions only
A	Chlorsulfuron	None/Minimal	Conclusions only
B	Chromium III, insoluble salts	Some/Moderate	Incomplete reporting of subchronic studies cited, otherwise extensive discussion of variability and uncertainty; downgraded one category
B	Chromium VI	Extensive	Detailed findings presented, relative significance of results discussed;

Appendix A - Summary of classifications for screening sample of IRIS assessments

A=pre-Pilot B=later	Chemical	Overall Documentation	Comments
B	Cumene	Extensive	rationales provided for uncertainty factors, confidence levels Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Cypermethrin	None/Minimal	Conclusions only
A	Cyromazine	None/Minimal	Conclusions; minimal discussion for not using several uncertainty factors
A	Danitol	Some/Moderate	Extended discussion of variability for principal and supporting studies, but incomplete; no discussion of uncertainty factors, some discussion of overall confidence
A	Dibromo-3-chloropropane, 1,2-	Extensive	Extensive discussion of adverse effects, including temporal variability; some discussion of uncertainty factors and overall confidence
A	Dibromobenzene, 1,4-	None/Minimal	Conclusions mainly, with minimal discussion of confidence
A	Dibromodichloromethane	None/Minimal	No chemical-specific data available
A	Dichlorodiphenyltrichloroethane, p,p'-	Some/Moderate	Some discussion of variability among cancer studies; some discussion of uncertainty and confidence
A	Dieldrin	None/Minimal	Mostly qualitative effect levels, except for SMRs; 13 slope factors with no incidence data; minimal discussion of confidence or uncertainty
A	N,N-Dimethylformamide	Some/Moderate	Thorough presentation of average effect magnitudes; some discussion of confidence in data base
A	Dimethyl phthalate	None/Minimal	No human or animal studies available; some discussion of supporting data.
A	o-Dinitrobenzene	None/Minimal	No human or animal studies available; some discussion of supporting data.
A	Diphenamid	None/Minimal	Conclusions only
A	Ethylene glycol	Some/Moderate	Some discussion of variability between studies, and adverse effect magnitudes; some discussion of confidence.
B	Ethylene glycol monobutyl ether	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Fluorine (soluble fluoride)	Some/Moderate	Some discussion of variability; assessment alludes to a 'large number of studies' which were not summarized
A	Fomesafen	Some/Moderate	Some discussion of variability among studies; some discussion of uncertainty and confidence
A	Furmecycloz	Some/Moderate	Some discussion of variability among studies; some discussion of uncertainty and confidence
A	Hexachlorobenzene	Some/Moderate	Some discussion of variability across studies, confidence in assessment

Appendix A - Summary of classifications for screening sample of IRIS assessments

A=pre-Pilot B=later	Chemical	Overall Documentation	Comments
A	Hexachlorodibenzo-p-dioxin, mixture	Some/Moderate	Some discussion of confidence in assessment
A	Hexachlorophene	None/Minimal	Conclusions only
A	Hexazinone	None/Minimal	Conclusions only
A	Maneb	None/Minimal	Conclusions only
A	Manganese	Extensive	Discussion of variability of results and of uncertainties and confidence in the assessment
A	Metalaxyl	None/Minimal	Conclusions only
A	Methamidophos	None/Minimal	Conclusions only
B	Methyl methacrylate	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
B	Methylene diphenyl diisocyanate	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Methylphenol, 4-	Some/Moderate	Incidence rates reported; some discussion of variability
B	Naphthalene	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	N-Nitroso-N-methylethylamine	None/Minimal	Incidence rates reported; incomplete rationale for model defaults; minimal discussion of uncertainty; downgraded one category
A	Octabromodiphenyl ether	None/Minimal	Conclusions only
A	Pentachlorophenol	Some/Moderate	Some discussion of variability
A	Phosmet	None/Minimal	Conclusions only
A	Prochloraz	Some/Moderate	Some discussion of variability
A	Pronamide	None/Minimal	Conclusions only
A	Propargite	Some/Moderate	Some discussion of variability
A	Pursuit	None/Minimal	Conclusions only
A	Pydrin	None/Minimal	Conclusions mainly; limited discussion of uncertainty
A	Sodium azide	None/Minimal	Conclusions only
A	Tetrachlorovinphos	None/Minimal	Conclusions only
A	Toluene diisocyanate mixture, 2,4-/2,6-	Extensive	Discussion of variability and confidence in assessment
B	Tributyltin oxide	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Trichloroethane, 1,1,1-	None/Minimal	Limited discussion of supporting data

Appendix A - Summary of classifications for screening sample of IRIS assessments

A=pre-Pilot B=later	Chemical	Overall Documentation	Comments
A	Triethylene glycol monobutyl ether	None/Minimal	No RFC, RfD or unit risk; some discussion of variability and uncertainty
B	Trinitrobenzene, 1,3,5-	Extensive	Detailed findings presented, relative significance of results discussed; rationales provided for uncertainty factors, confidence levels
A	Vanadium pentoxide	None/Minimal	No quantitative response levels; no discussion of uncertainty
A	Vinyl acetate	Some/Moderate	Some discussion of confidence in assessment

Appendix B - Independent Review of Assignments to Documentation Categories

July 14, 2000

Reviewer: Hugh Tilson

<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
Acetonitrile		
Overall Rating-Extensive based on variability and uncertainty narrative in the Toxicological Review		
Aldicarb sulfone		
RfD	Moderate	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Apollo		
RfD	Minimal	Minimal
RfC-Not listed	Not Scored	Not scored
Cancer	Moderate	Minimal
Overall Rating-Minimal		
Arsenic, inorganic		
RfD	Extensive	Moderate
RfC-Not listed	Not Scored	Not scored
Cancer	Extensive	Extensive
Overall Rating-Extensive		
Barium and compounds		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Benomyl		
RfD	Minimal	Minimal
RfC-Not listed	Not Scored	Not Scored
Cancer-Not listed	Not Scored	Not Scored
Overall Rating-Minimal		
Bentazon		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Benzene		
Overall Rating-Extensive for both variability and uncertainty based on Support Documents on IRIS		
Beryllium and compounds		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
beta-Chloronaphthalene		
RfD	Minimal	Minimal
RfC-Not listed	Not Scored	Not Scored
Cancer-Not listed	Not Scored	Not Scored
Overall Rating-Minimal		
Bis(chloromethyl)ether		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Moderate	Minimal
Overall Rating-Moderate		
Butylphthalyl butylglycolate		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		

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<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
Carboxin		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Chlordane		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Chlorocyclopentadiene		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Chlorsulfuron		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Chromium III, insoluble salts		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Chromium VI		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Cumene		
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Cypermethrin		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Cyromazine		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Danitrol		
RfD	Moderate	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Moderate		
Dibromo-3-chloropropane, 1,2-		
RfD-Not listed	Not scored	Not scored
RfC	Moderate	Minimal
Cancer-Not listed	Not scored	Not scored
Overall Rating-Moderate		
Dibromobenzene, 1,4-		
RfD	Minimal	Minimal

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<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Dibromodichloromethane		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal (on the basis that a classification was made without presenting data)		
Dichlorodiphenyltrichloroethane, p,p'-		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Dieldrin		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Dimethyl phthalate		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Dimethylformamide, N,N-		
RfD-Not listed	Not scored	Not scored
RfC	Moderate	Minimal
Cancer-Not listed	Not scored	Not scored
Overall Rating-Moderate		
Dinitrobenzene, o-		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal (classified as non carcinogenic, supporting data are largely mechanistic and not described in detail)		
Diphenamid		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Ethylene glycol		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Ethylene glycol monobutyl ether		

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<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
Overall Rating-Extensive for both variability and uncertainty based on Toxicological Review		
Fluorine (soluble fluoride)		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Fomesafen		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Furmecyclox		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Moderate		
Hexachlorobenzene		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Hexachlorodibenzo-p-dioxin, mixture		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Minimal	Minimal
Overall Rating-Minimal		
Hexachlorophene		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Hexazinone		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Maneb		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Manganese		
RfD	Moderate	Extensive
RfC	Extensive	Extensive
Cancer	Not scored (moderate narrative)	Not scored (not carcinogenic)

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<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
Overall Rating-Extensive		
Metalaxyl		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Methamidophos		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Methyl methacrylate		
Overall Rating- Extensive for both variability and uncertainty based on Toxicological Review		
Methylene diphenyl diisocyanate		
Overall Rating- Extensive for both variability and uncertainty based on Toxicological Review		
Methylphenol, 4-		
RfD-Withdrawn	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Moderate	Minimal
Overall Rating- Moderate		
Naphthalene		
Overall Rating-Extensive based on both variability and uncertainty in Toxicological Review		
N-Nitroso-N-methylethylamine		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer	Moderate	Minimal
Overall Rating- Moderate		
Octabromodiphenyl ether		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not carc.	Not scored	Not scored
Overall Rating-Minimal		
Pentachlorophenol		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer	Moderate	Minimal
Overall Rating-Minimal		
Phosmet		
RfD	Minimal	Minimal
RfC	Not scored	Not scored
Cancer	Not scored	Not scored
Overall Rating-Minimal		
Prochloraz		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored

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<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
Cancer	Moderate	Minimal
Overall Rating-Minimal		
Pronamide		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Propargite		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer	Not scored	Not scored
Overall Rating-Minimal		
Pursuit		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Pydrin		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Sodium azide		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Tetrachlorovinphos		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Toluene diisocyanate mixture, 2,4-/2,6-		
RfD-Not listed	Not scored	Not scored
RfC-	Extensive	Moderate
Cancer-Not listed	Not scored	Not scored
Overall Rating-Extensive		
Tributyltin oxide		
Overall Rating-Extensive based on variability and uncertainty in Toxicological Review		
Trichloroethane, 1,1,1-		
RfD-Not listed	Not scored	Not scored
RfC-Not listed	Not scored	Not scored
Cancer-	Minimal	Minimal
Overall Rating-Minimal		
Triethylene glycol monobutyl ether		

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<u>Chemical</u>	<u>Variability</u>	<u>Uncertainty</u>
RfD-Not listed	Not scored	Not scored
RfC-Not verifiable	Minimal	Minimal
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Trinitrobenzene, 1,3,5-		
Overall Rating-Extensive on the basis of narrative for variability and uncertainty in the Support Document		
Vanadium pentoxide		
RfD	Minimal	Minimal
RfC-Not listed	Not scored	Not scored
Cancer-Not listed	Not scored	Not scored
Overall Rating-Minimal		
Vinyl acetate		
RfD-Not listed	Not scored	Not scored
RfC	Moderate	Minimal
Cancer-Not listed	Not scored	Not scored
Overall Rating-Moderate		

Criteria for Classification:

	<u>Variability</u>	<u>Uncertainty</u>
Minimal	No incidence generally provided for RfD/RfC	Relatively terse description of what the uncertainty factors were with little or no discussion about their rationale; no discussion about strengths or weaknesses
Moderate	Incidence, magnitude, onset or duration mentioned with some discussion, little discussion about variability within or across studies	Rationale developed for the selection of the uncertainty factors, strengths or weaknesses mentioned
Extensive	Incidence, magnitude, onset and duration mentioned repeatedly; considerable discussion about sources of variability across and within studies	Considerable rationale for confidence in studies and support provided for conclusions, strengths or weaknesses discussed

In some cases, assessments contained somewhat more documentation of uncertainties relative to variability, and vice versa. If only one area qualified as Extensive, then the entire assessment was categorized as Extensive. At the other end of the scale, if one part of an assessment contained Moderate documentation, the entire assessment was categorized as Moderate. Several assessments were based on Supporting Documents or Toxicological Reviews located on IRIS. All of these were categorized as Extensive.