Appendix A - Comments from Reviewers

CHARACTERIZATION OF DATA UNCERTAINTY AND VARIABILITY IN IRIS ASSESSMENTS PRE-PILOT VS PILOT/POST-PILOT

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Table of Contents

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Review of Uncertainty and Variability Analysis In IRIS for Eight Substances

Prepared for VERSAR

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6-14-2000

Note: This report is intended to be read as an electronic document, using MS Word for Office 98 or later. The hyperlinks in the tables provide essential documentation and references

Substances reviewed. Please click on hyperlinks to browse reviews and source materials.

Substance	Summary (Q1)	Details (Q2-Q10)
Acetonitrile	**Acetonitrile summary**	**Acetonitrile details**
Benzene	**Benzene summary**	**Benzene details**
Beryllium	**Beryllium summary**	**Beryllium details**
Chlordane	**Chlordane summary**	**Chlordane details**
DBCP	**DBCP summary**	**DBCP details**
Hexachlorobenzene	**Hexachlorobenzene summary**	**Hexachlorobenzene details**
Manganese	**Manganese summary**	**Manganese details**
Prochloraz	**Prochloraz summary**	**Prochloraz details**

Overview of Results (Click on column heading for comments on each substance)

Name:		**Acetonitrile**	**Benzene**	**Beryllium**	**Chlordane**	**DBCP**	**Hexachlorobenzene**	**Manganese**	**Prochloraz**
Q1	Question: Did document appropriately address…								
A1	Uncertainty in data	Not fully	No	Partly	No	Not well	No	No	No
A2	Variability in data	Partly	No	No	No		No	No	No
	Model form uncertainty	No	No	No	No	NA	No	No	No
	Model parameter uncertainty	NA	No	No	No	NA		NA	NA
	Model validation	No	No	No	No	No	No	No	NA
C1	Strengths and weaknesses of available scientific evidence	Yes	No	Yes	No	Partly	Partly	Partly	Partly
C2	Sources of variability in the data used in the assessment	No	No	No	No	No	No	No	No
C3	Uncertainties in underlying data	Yes	No	No	No	No	No	No	No
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	Not really	No	No	No	No	No	No	Partly

Acetonitrile: Summary Tables

Name:	**Acetonitrile**		
Q1	Question: Did document appropriately address…	A:	Comments
A1	Uncertainty in data	Not fully	It does not point out that there are unexplained differences across data sets in mortality studies for rats (see Toxicology review of Acetonitrile, p. 11, paragraph 2) The **FEL of 400 ppm** is based on early death of one female mouse.
A2	Variability in data	Partly	Variability across data sets (e.g., contrast between Saillenfait and Mast studies in rats with respect to mortality patters) is not discussed.
	Model form uncertainty	No	Standard dose conversion calculations were used but not validated.
	Model parameter uncertainty	NA	NA
	Model validation	No	Not attempted. Using the approach to predict rat responses from mouse data, then comparing predicted to observed rat data might be an inexpensive way to get some partial validation. I found the **uncertainty summary** unclear about lack of a factor for extrapolating from high to low exposure concentrations.
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	Yes	The discussion of ambiguities (e.g., in causal interpretation of forestomach lesions is pretty good.)
C2	Sources of variability in the data used in the assessment	No	Variability across studies is not discussed much (e.g., that mice may be more sensitive than rats, as noted in the Toxicology Review.)
C3	Uncertainties in underlying data	Yes	
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	Not really	The qualitative discussion seems good. The choice of uncertainty factors seems ad hoc, in that I think it would be hard for anyone reading the discussion to confidently guess what uncertainty factors would the be applied.

Acetonitrile: Details

	Substance:	**Acetonitrile**		
Q2	Risk factor:	**q1*/Slope factor**	**Oral RfD**	**RfC**
	Value:	ACN is assigned carcinogen class D, not classifiable as to human carcinogenicity. There is an absence of human evidence and the animal evidence is equivocal.	**NA** (withdrawn)	6E-2 mg/m3
Q3	Data sources			
Q4	Omitted sources			
Q5	Basis:			Mouse inhalation studies (NTP 1996 study on B6C3F1 mice)
	Risk models used			
	Other models considered			
5a, c	Sex Strain Species Route Regimen			 B6C3F1 Mouse Inhalation Subchronic/chronic inhalation studies, e.g., 111 weeks inhalation exposure 6 hr./day, 5 days week, 0, 50, 100, 200 ppm
5b	Critical effect			**Mortality**
5d	Mechanism of action			Production of cyanide
5e, f	Sensitive sub-population or species			UF factor of 10. (Some people may metabolize CAN to cyanide more than others.)
	Relevant species?			Unknown.
Q9	Relevant exposure route?			Yes. (But whether inhalation is relevant for forestomach lesions is unclear.)
	Relevant regimen?			Uncertain.
	Relevant effect?			Relevance of mortality is uncertain. (Mortality is not evident at lower concentrations.)

	Relevant statistical model?			
Q6, **7**	UF			100
	Basis			3 for interspecies extrapolation 10 for sensitive human subpopulations 3 for database deficiencies
	Derivation			See above
	Inter-species variability			See above: Factor of 3
	Intra-species variability			Not included
	Inter-human variability			See above: Factor of 3
	Sub-chronic to chronic extrapolation			Not included. (Conversions applied deterministically.) Lack of mortality in longer-term studies is **discussed**, but not extrapolated.
	LOAEL to NOAEL extrapolation			Uncertainty discussed adequately (but not quantified in any rigorous way). **NOAEL** of 200 ppm because role of inhalation in forestomach lesions unclear.
	Data limitations, sufficiency			Factor of 3 to account for inadequate reproduction and hematological hazard data
Q8	**MF** = 10			MF = 10. **Basis**: Uncertain role of inhalation in causing forestomach lesions
Q10	**CF** = medium			Medium for study Medium for database Medium for RfC (It is not obvious to me why "medium" was chosen, given the stated uncertainties about relevance of observations, routes of exposure, etc.)

Benzene: Summary Table

Name:	**Benzene**		
Q1	Q: Did document appropriately address…	A:	Comments
A1 §	Uncertainty in data	No	Uncertainty in exposure estimates was not included in statistical models. Uncertainty in the oral absorption factor was ignored by assuming it was 0.5.
A2	Variability in data	No	A single low-dose slope parameter was assumed for all people
	Model form uncertainty	No	The model form was assumed to be low-dose linear. Better-fitting non-linear models (e.g., **Crump 96**) were not considered or used in the quantitative analysis.
	Model parameter uncertainty	No	Uncertainty in the oral absorption factor was ignored. Uncertainty about slope factors was not quantified in any rigorous way. (The word "uncertainty" is missing from the entire discussion in the document.)
	Model validation	No	
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	No	Relevant animal and epidemiological studies suggesting that the linear model is not appropriate for benzene were not discussed (e.g., **Farris, 97**, **Schnatter 96**, **Wong 95**, **Wong and Raabe 95**). Human, animal, and in vivo studies showing a non-linear mechanism (e.g., aneuploidy induced by spindle disruption) were ignored (**Zhang et al., 1998**, **Pfeiffer and Metzler, 1996**).
C2	Sources of variability in the data used in the assessment	No	Variability in the Pliofim data set based on exposure patterns across individuals (**Schnatter 96**) and plant locations was not addressed. The known inter-individual variability in benzene metabolism based on CYP2E1 was not addressed in the model.
C3	Uncertainties in underlying data	No	The fact that more years of follow-up data weakened the associations claimed by Rinsky is not discussed.
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	No	The assessment claims that the mechanism of action is unknown or very **uncertain**, and uses this to justify a linear model. On the other hand, it minimizes uncertainty about the reasonableness of a linear model by failing to cite or discuss the strong human, animal, and in vitro evidence of nonlinearity in the dose-response relation.

Summary: This document does not indicate that there is major uncertainty about whether benzene at concentrations less than 10 ppm can cause leukemia (i.e., q1* may be 0 at low concentrations). Substantial **epidemiological** and **mechanistic** evidence of a leukemic response threshold is not disussed. The quantitative analysis ignores uncertainties and variabilities (e.g., uncertainties about mechanism of action, model form, model parameters, inter-individual variability, exposure uncertainties, extrapolation uncertainties across routes and regimens). Thus, the assessment presents an artificially narrow uncertainty range that belies the true uncertainties. "Uncertainty" is not mentioned as a topic. "Variability" is discussed only in the context of obtaining an oral risk factor from the inhalation one.

Benzene: Details

	Substance:	**Benzene**		
Q2	Risk factor:	**q1*/Slope factor**	**RfD**	**RfC**
	Value:	A **range** of 2.2 × 10-6 to 7.8 × 10-6 is given as the increase in lifetime risk from 1 µg/m3 benzene in air. The range for water is derived from that in air.	Not available at this time.	Not available at this time.
Q3	Data sources	**Pliofilm cohort** (Rinsky)		
Q4	Omitted sources	Many, e.g., Petroleum Workers (Rushton, 1981, 1997; **Wong and Raabe, 1995**)		
Q5	Basis:	Human data		
	Risk models used	Low-dose linear with various exposure estimates		
	Other models considered	None. Non-linear models that fit the available data better (e.g., **Crump 96**) were rejected as not being **default** models.		
5a, c	Sex Strain Species Route Regimen	Several animal studies were reviewed. Relevance of animal tumor responses to humans is **unknown**.		
5b	Critical effect	AML and MDS in humans; various tumors in mice		
5d	Mechanism of action	The very likely mechanism of action is **aneuploidy** induced by binding of reactive metabolites (p-benzoquinone) to thiol/sulfhydryly groups on tubulin in CD34+ CFU-GM stem cells. This disrupts spindle formation and segregation of chromosomes during mitosis – an inherently non-linear mechanism. Dose-dependent aneuploidy has been found in benzene-exposed workers in vivo (**Zhang et al., 1998**). The above mechanism has been demonstrated in detail in vitro (**Pfeiffer and Metzler, 1996**). The IRIS document does not cite these or other relevant literature (including key papers by Irons and Stillman). It takes a linear model as a **default**, on the grounds that the non-linear aneuploidy mechanism just described "has not been shown **conclusively**". It also conjectures that **multiple mechanisms** may be involved, without citing specifics, and concludes that not enough is known to justify deviating from a low-dose linear model.		

5e, f	Sensitive sub-population or species	No (CYP2E1 variability is ignored.)		
	Relevant species?	No		
Q9	Relevant exposure route and regimen?	Yes. Inhalation route is relevant. But, previous exposures of hundreds of ppm may be irrelevant to responses at lower levels, such as 10 ppm or less.		
	Relevant effect?	Yes, AML is relevant. (The broader ANLL category, which includes AML, may be less relevant. MDS could also have been included.) Animal models may not be very relevant to humans, as recognized in the document.		
	Relevant statistical model?	No. Statistical models with quadratic terms or other non-linearities should be considered when the Paustenbach exposure estimates are used (**Crump, 1996**). Uncertainty about exposures was not modeled		
Q6, **7**	UF	A very narrow **range** of estimates is presented: 2.2 × 10-6 to 7.8 × 10-6 for the increase in lifetime risk from 1 µg/m3 benzene in air. The range for water is derived from that in air.		
	Basis	Range of estimates from fitting linear models to different exposure assumptions.		
	Derivation	Uncertainties about model form and exposure data were identified as **crucial** in the qualitative discussion, but ignored in the quantitative analysis.		
	Inter-species variability	Not needed.		
	Intra-species variability	Not needed.		
	Inter-human variability	Ignored.		

	Sub-chronic to chronic extrapolation	Ignored. This is a major source of uncertainty. For example, effects seen above 10 ppm are not seen below 10 ppm in mice (**Farris, 97**). Evidence of threshold effects in the Pliofilm (**Schnatter 96**, **Wong 95**) and other (**Wong and Raabe 95**) worker populations was not discussed.		
	LOAEL to NOAEL extrapolation	Apparent no-effects levels in epidemiological and animal studies were not discussed. Relevant studies were not cited. (**Farris, 97**, **Schnatter 96**, **Wong 95**, **Wong and Raabe 95**.)		
	Data limitations, sufficiency	The fact that the leukemias in the Pliofilm cohort occurred primarily at a plant for which no exposure data were available was not addressed.		
Q8	MF			
Q10	CF			

Beryllium: Summary Table

Name	**Beryllium**		
Q1	Q: Did document appropriately address…	A:	Comments
A1	Uncertainty in data	Partly	The qualitative discussion of uncertainties is good. But the mapping to factors of **3** (as opposed to, say, 1/3 or 30) to account for database uncertainties is not well motivated. For example, acounting for uncertainties in the following might change the risk estimates either upward or downward (by making a risk of zero more probable): · Exposure uncertainty. (This should be included in the model, not in the uncertainty factor; see **Greenland 96**.) · Residual confounding by smoking and other risk factors (**MacMahon 94**) · CBD disease misclassification These uncertainties do not seem to have been adequately captured by the risk factor of 3. (More generally, factors that can reduce risk estimates cannot be adequately expressed by choosing a factor of 3 or 10.)
A2	Variability in data	No	A mixture distribution model might be appropriate, given that only a small fraction of the exposed population exhibits a sensitization of CBD response.
	Model form uncertainty	No	Alternative model forms were not assessed. This can create overconfidence and too-narrow confidence ranges for risks (**Maldonado 96**)
	Model parameter uncertainty	No	Relative risk confidence limits were calculated without correcting for exposure estimation errors, omitted confounding variables, etc.
	Model validation	No	Not attempted
B	Pre-pilot vs.post-pilot		
C1	Strengths/weaknesses of the sci. evidence from available studies	Yes	Qualitative discussion is good.
C2	Sources of variability in the data used in the assessment	No	Variability due to confounders and exposure errors was not estimated. (See **Greenland 96** for methodology discussion.)
C3	Uncertainties in underlying data	No	Corrections for exposure estimation errors, omitted confounding variables, etc. were not made and their effects were left unquantified.
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	No	The range of uncertainties should probably be much wider than shown. See above.

Beryllium: Details

	Substance:	**Beryllium**		
Q2	Risk factor:	**q1* air unit risk estimate**	**RfD/BMD10**	**RfC**
	Value:	2.4E-3 per (µg/m3) fror concentrations below 4 µg/m3	BMD10 = **0.46 mg/kg-day**	2E-2 µg/m3
Q3	Data sources	Wagoner et al., 1980	**Morgareidge et al., 1976**	**Kreiss et al., 1996** Eisenbud et al., 1949
Q4	Omitted sources			
Q5	Basis:	Human	Animal (beagles)	Human: LOAEL from the **Kreiss et al.** study was used for **derivation** of RfC.
	Risk models used as basis	**Relative risk model**	Exponential polynomial model	**LOAEL**
	Other models considered	None	Not discussed	
5a, c	Sex Strain Species Route Regimen	NA Animal carcinogenicity was reviewed, but relevance to humans is unknown.	Male and female Beagle Dog Feed 0, 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate for 172 weeks. 500 ppm group terminated at 33 weeks due to overt toxicity	
5b	**Critical effect**	Lung cancer	Small intestinal lesions	Beryllium sensitization and progression to CBD
5d	Mechanism of action			Not elucidated. (See **Finch 98**.)

5e, f	Sensitive sub-population or species			**UF = 1** for sensitive subpopulation, based on assumption that only sensitives respond
	Relevant species?	Yes		NA
Q9	Relevant route and regimen?	Yes		
	Relevant effect?	Uncertain. It is not clear whether beryllium is a human carcinogen.	Probably not. CBD and sensitization are the effects of interest in human. They have distinct etiologies from intestinal lesions.	Yes
	Relevant statistical model?	No. (Relative risk model is simplistic, especially for a non-genotoxic carcinogen.)		
Q6, **7**	UF		**300**	**10**
	Basis			
	Derivation		10 for extrapolation for interspecies differences, 10 for consideration of intraspecies variation, and 3 for database deficiencies.	3 from LOAEL for Beryllium sensitization endpoint, 3 for database uncertainty. See below.
	Inter-species variability		**10**, Only one chronic study in dogs showed adverse effect levels; other chronic studies in rodents demonstrated NOAELs at the highest doses tested	NA
	Intra-species variability		**10**	NA

	Inter-human variability		Not addressed in UF	**1** (Assumes only sensitive people respond. Dos not allow for different sensitivities among responders.)
	Sub-chronic to chronic extrapolation			**1** (Assumes duration does not affect CBD response)
	LOAEL to NOAEL extrapolation			**3** "The RfC was derived from the LOAEL (Kreiss et al., 1996) with an uncertainty factor of 3 to account for the sensitive nature of the subclinical endpoint (beryllium sensitization)."
	Data limitations, sufficiency	**Residual confounding** by smoking and exposure to other potential lung carcinogens are not completely resolvable with the data currently available.	Small sample sizes (5/sex/dose), early mortality at high dose level. Randomization or control for litter effects not clear, no measure of immune response.	**3** "A database uncertainty factor of 3 was used to account for the poor quality of exposure monitoring in the co-principal studies and other epidemiology studies that assessed the incidence of beryllium sensitization and CBD among exposed workers and community residents."
Q8	MF		1	1
Q10	CF	**Limited**	**Low to medium**	**Limited**

Chlordane: Summary Table

Name:	**Chlordane**		
Q1	Q: Did document appropriately address…	A:	Comments
A1	Uncertainty in data	No	Relevant data for hematotoxic effects (human endpoint) were not obtained. This uncertainty was mentioned but ignored in the quantitative assessment.
A2	Variability in data	No	**Inter-species variability** in available data was not addressed.
	Model form uncertainty	No	LMS model used. Models for **non-genotoxic** and known **tumor promoter** effects not used.
	Model parameter uncertainty	No	Cancer: Evidence of **sub-linearity** at low doses was mentioned but ignored in quantitative analysis on the grounds that linearity "could not be ruled out in theory". (For a non-genotoxic hepatocarcinogen like this, however, theory does allow sub-linearity.) Possibility of zero slope at the origin was not separately evaluated. RfC: Interspecies dose conversion uncertainties for RfC were not addressed using available **monkey** data.
	Model validation	No	Not addressed. For example, monkey data were not used to help validate interspecies dose conversion assumptions.
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	No	Significance of **non-genotoxic**, **tumor promoting** mechanism was not discussed. That the principal study was interpreted by its authors as showing **absence** of a cancer effect was not discussed.
C2	Sources of variability	No	Not addressed
C3	Uncertainties in underlying data	No	Uncertainty about relevance of endpoint to humans was **mentioned** but not addressed.
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	No	The key uncertainties due to (a) available **mechanistic** knowledge, (b) evidence of **sublinear** dose-response, and (c) evidence that rodent endpoints (liver responses) are not **relevant** for humans, were not addressed.

Comments:

1. Key scientific uncertainties (item C4 above) were recognized in qualitative discussions, but they were ignored in the quantitative assessment and uncertainty factor calculations.
2. The following seemed to me to be a non sequitur: "Although the evidence for chlordane exposure leading to cancer in humans is tentative at best, it indicates that the target is the hematopoietic system rather than the liver. Therefore, it is prudent to regard mice liver cancer as an indicator of human hazard."

3. **Monkey data** suggest that monkeys may be 10 to 100 times less susceptible to inhhaled chlordane than in rats. The assessment uses a UF of 3 to adjust for inter-species variability (from rats to humans) in the RfC. Shouldn't there be a way to reflect evidence that inter-species variability may favor a smaller risk for humans than for rats? (Choosing between a factor of 3 and a factor of 10 does not allow such evidence to be expressed.)

Chlordane: Details

	Substance:	**Chlordane**		
Q2	Risk factor:	**q1*/Slope factor**	**RfD**	**RfC**
	Value:	**Oral Slope Factor** = 3.5E-1 per mg/(kg-day) **Air slope factor = 1E-4 per (ug/cu.m)**	5E-4 mg/kg-day	7E-4 mg/cu m
Q3	Data sources	Mouse/CD-1 (IRDC) Mouse/B6C3F1 (NCI) **Mouse/ICR (Khasawinah and Grutsch, 1989)**	**Khasawinah and Grutsch, 1989**	**Khasawinah, Hardy, Clark,1989** rat data
Q4	Omitted sources			**Khasawinah, Hardy, Clark,1989** monkey data (not used in RfC)
Q5	Basis:	Animal (mouse)	**Animal (mouse) 104-week oral study**	Animal: Rat subchronic inhalation study
	Risk models used	**Linearized multistage procedure, extra risk**		
	Other models considered	None/Not addressed		
5a, §	Sex Strain Species Route Regimen	Both CD-1, B6C3F1, ICR Mouse Diet See **description**.	Both (80/ sex/group) ICR mice diet 0, 1, 5, or 12.5 ppm chlordane in diet for 104 weeks.	(35 47/sex/group) Wistar rats inhalation 0, 0.1, 1.0, or 10 mg/cu.m technical chlordane, 8 hours/day, 5 days/week, for 13 weeks, followed by a 13-week recovery period.
5 b	Critical effect	**Hepatocellular carcinoma**	**Hepatic Necrosis**	**Hepatic effects**

5d	Mechanism of action	Chlordane is a liver tumor promoter in mice (**Williams 84**). The assessment says it has been classified as a **non-genotoxic murine hapatocarcinogen**, with some similarities to chloroform.		
5e, f	Sensitive sub-population or species	Not addressed		
	Relevant species?	No. Mouse liver tumors do not appear to be relevant to **human effects**.		
Q9	Relevant exposure route and regimen?	Yes, ingestion route is relevant. Regimen may not be.		
	Relevant effect?	No. Mouse liver tumors do not appear to be relevant to **human effects**. Relevant (**hematopoietic**) effects were not addressed in the quantitative assessment.		
	Relevant statistical model?	No. Chlordane is a **non-genotoxic carcinogen** and a known promoter of hepatocarcinogenesis in mice (**Williams 84**). Thus, an MVK model or other model of promotion would be relevant.		
Q6, 7	UF		**300**	**1000**
	Basis/Derivation	Discussion could be clearer. (Example: **Khasawinah and Grutsch, 1989** interpreted their data as showing **absence** of a tumor effect, but the assessment cites this study as **supporting** a carcinogenic effect.)	10 for intraspecies variation 10 for interspecies extrapolation 3 for lack of reproductive studies	10 for subchronic to chronic extrapolation; 10 for intraspecies variation. 10 for interspecies extrapolation (addressed partially by HEC) and database deficiencies (lack of any reproductive studies).

	Inter-species variability		10	3
	Intra-species variability		10	10
	Inter-human variability		Not addressed	Not addressed
	Sub-chronic to chronic extrapolation	High- to low-dose extrapolation uncertainty is not addressed.		10
	LOAEL to NOAEL extrapolation			NA
	Data limitations, sufficiency	Mouse liver tumors do not appear to be **relevant** to humans.		3
Q8	MF		1	**1**
Q10	**CF**	Confidence is **high** that chlordane is a mouse liver carcinogen at dietary concentrations above 10 ppm.	**Study -- Medium Data Base – Medium RfC -- Medium**	**Study -- Medium Data Base – Low RfC -- Low**

DBCP: Summary Table

Name:	**DBCP**		
Q1	Did document appropriately address…	Answer	Comments
A1	Uncertainty in data	Not well	Uncertainty about the extent to which rabbit data can be extrapolated was not addressed except by use of a UF. The conceptual basis for the UF in this context is not clear (see below.)
A2	Variability in data		Not addressed (except in UF calculation; see below)
	Model form uncertainty	NA	
	Model parameter uncertainty	NA	
	Model validation	No	Quantitative validation of rabbit-based predictions in human populations using available epidemiological data (e.g., **Goldsmith 80**) was not attempted.
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	Partly	Discussion of inter-species differences and epidemiology (rather than just applying default uncertainty factors) might be useful for this chemical, given the studies that were available.
C2	Sources of variability in the data used in the assessment	No	Not addressed (except via a factor in the UF calculation)
C3	Uncertainties in underlying data	No	See above
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	No	It appears that rabbits are more **sensitive** than rats to the critical effect, and rats are more sensitive than humans (**Bjorge 96**). Putting a factor of 3 in the UF does not seem to account for the possibility that humans are less sensitive than rabbits. (More generally, the UF methodology does not seem able to express factors that tend to reduce risk estimates for humans, even for non-cancer endpoints.)

DBCP: Details

	Substance:	**DBCP**		
Q2	Risk factor:	**q1***	**RfD**	**RfC**
	Value:	Not now avail-able	Not now available	2E-4 mg/cu.m
Q3	Data sources			**Rao et al., 1982**
Q4	Omitted sources			Some epidemiological studies (e.g., **Goldsmith, 1980**. See **Goldsmith, 1997** for update.) Various worker studes were discussed, and confounding was noted as a limitation.
Q5	Basis:			Animal
	Risk models used			NA
	Other models considered			NA
5a, c	Sex Strain Species Route Regimen			male New Zealand white rabbits inhalation Rabbits exposed to 0, 0.1, 1 or 10 ppm (0, 0.94, 9.4 or 94 mg/cu.m) DBCP vapors , 6 hours/day, 5 days/week for 14 weeks. Those receiving 10-ppm were exposed for only 8 weeks due to high mortality (apparently from pneumonia).
5b	Critical effect			Testicular effects
5d	Mechanism of action			Not addressed. (See **Bjorge 96** for information.)
5e, f	Sensitive sub-pop./species			Assessment notes that rabbit is **most sensitive species**.
	Relevant species?			Uncertain. Known differences in responses across species (**Bjorge 96**) were not modeled.
Q9	Relevant exposure route and regimen?			Yes
	Relevant effect?			Yes. Assessment notes that some other effects (e.g., on imhalation) might also occur, but data are not available.
	Relevant statistical model?			NA
Q6, **7**	UF			**1000**

	Basis/Derivation			10 for sensitive human subpopulations. 3 for interspecies extrapolation 10 for subchronic study to reflect marginal NOAEL 3 for data base deficiency (lack of a multigenerational reproductive study, and inhalation development toxicity studies)
	Inter-species variability			3
	Intra-species variability			Not addressed
	Inter-human variability			10 for sensitive human subpopulations, no othervariability (e.g., in PBPK) addressed
	Sub-chronic to chronic extrapolation			10
	LOAEL to NOAEL extrapolation			See factor of 10 above for sub-chronic to chronic
	Data limitations, sufficiency			Lack of a multigenerational reproductive study and of inhalation development toxicity studies were cited as limitations.
Q8	MF			**None**
Q10	CF			**Study -- Medium** **Data Base -- Medium** **RfC -- Medium**

Hexachlorobenzene: Summary Table

Name:	**Hexachlorobenzene**		
Q1	Q: Did document appropriately address…	A:	Comments
A1	Uncertainty in data	No	Not addressed. The word "uncertainty" does not appear in the discussion, except when a UF of 100 for the RfD is given. Uncertainty for carcinogenicity in humans is not discussed.
A2	Variability in data	No	Not addressed. The word "variability" does not appear in the discussion, except as part of the UF of 100 for the RfD. This was not data-based.
	Model form uncertainty	No	Model for promotion (e.g., MVK model) should be considered for this chemical. Uncertainty about extrapolation of unit risks from rats to humans was not discussed.
	Model parameter uncertainty		Not discussed (but implicit in statistical risk models for cancer unit risk)
	Model validation	No	Not addressed. For example, predictions of tumor rates in one species (e.g., mice) from rates in other species (e.g., rats) could be used to validate the extrapolation procedure.
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	Partly	The classification of **carcinogenicity** is reasonable. The main omissions are discussion of (a) the mode of action and known role of hexachlorobenzene as a liver tumor promoter in rats and mice (e.g., **Shirai 78**); (b) Enzyme induction and interspecies differences.
C2	Sources of variability in the data used in the assessment	No	See above
C3	Uncertainties in underlying data	No	See above
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	No	The qualitative discussion on evidence for carcinogenicity is useful, though mode of action is not adequately addressed. The quantitative judgments are not adequately supported. Specifically, the probability that hexachlorobenzene is (or is not) not a human carcinogen is not assessed or considered in the quantitative assessment.

Hexachlorobenzene: Details

	Substance:	**Hexachlorobenzene**		
Q2	Risk factor:	**q1*/Slope factor**	**RfD**	**RfC**
	Value:	Oral Slope Factor -- 1.6 per (mg/kg)/day for concentrations less than 2E+2 ug/L,	8E-4 mg/kg/day	None available
Q3	Data sources	Erturk et al., 1986	Arnold et al., 1985	
Q4	Omitted sources	Mechanistic studies (e.g., **Stewart 89**).	Epidemiological studies (e.g**., Currier 80**, **Sala 99**)	
Q5	Basis:	Animal (94 rats of each sex)	Rat Chronic Feeding Study	
	Risk models used	Linearized multistage, extra risk		
	Other models considered	None. Models that allow promotion (e.g., MVK) would be appropriate for this chemical.		
5a, c	Sex Strain Species Route Regimen	Female Sprague-Dawley Rat Diet Groups of 94 Sprague-Dawley rats/sex/dose were fed 0, 75, or 150 ppm hexachlorobenzene in the diet for up to 2 years	Male and female Sprague-Dawley Rat Diet F0 generation fed 0, 0.32, 1.6, 8.0, or 40 ppm of hexachlorobenzene for 90 days prior to mating and until 21 days after parturition (at weaning). The number of offspring (F1 generation) from these matings was reduced to 50 males and 50 females per dose group at 28 days of age and fed their respective parents' diets.	
5b	Critical effect	hepatocellular carcinoma	Liver effects	

5d	Mechanism of action	Not discussed. There is evidence that hexachlorobenzene is a liver tumor promoter (e.g., **Stewart 89**, **Gustafson, 2000**).		
5e, f	Sensitive sub-population or species	Females more sensitive to liver effects.	Not addressed	
	Relevant species?	Not discussed	Not addressed	
Q9	Relevant exposure route and regimen?	Not discussed		
	Relevant effect?	Yes		
	Relevant statistical model?	No. Since hexachlorobenzene promotes hepatocarcinogenesis, **Stewart 89**, **Gustafson, 2000**) an MVK model or other model of promotion would be relevant.		
Q6, **7**	UF		**100**	
	Basis / derivation		10 for interspecies and 10 for intraspecies variability.	
	Inter-species variability	Not addressed	10	
	Intra-species variability	Not addressed	10	
	Inter-human variability	Not addressed	Not addressed	
	Sub-chronic to chronic extrapolation	Low-dose extrapolation issues not addressed	Low-dose extrapolation issues not addressed	
	LOAEL to NOAEL extrapolation			
	Data limitations, sufficiency		**Porphyria endpoint not evaluated.**	**Not adequate**
Q8	MF		None	
Q10	CF		**Study -- Medium Data Base -- High RfD -- Medium**	

Manganese: Summary Table

Name:	**Manganese**		
Q1	Did document appropriately address…	A:	Comments
A1	Uncertainty in data	No	Uncertainties due to multiple testing (**Ludbrook 98**) and to residual confounding of age with cumulative exposure were not well characterized, but may be **present**.
A2	Variability in data	No	Test-re-test variability was not characterized. **Crump 99** shows that some of the originally reported effects were not found upon later examination.
A3	Model form uncertainty, variable selection uncertainty, variable coding uncertainty	No	Uncertainty due to variable selection and data coding biases (**Greenland 96**, **Greenland 89**) were not assessed, but could have been **present**. Uncertainties due to effects of unmeasured confounders, residual confounding with age and **education**, etc. were not assessed quantitatively (**Greenland 96**)
	Model parameter uncertainty	NA	
	Model validation	No	
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	Partly	Consistent findings that could reflect consistent biases due to residual confounding (e.g., of exposure and effects with age), **multiple testing bias**, etc. are **interpreted** without clear rationale as evidence for a true effect.
C2	Sources of variability in the data used in the assessment	No	See A2 above
C3	Uncertainties in underlying data	No	See C1 above
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	No	See A3 and C1 above

Manganese: Details

	Substance:	**Manganese**		
Q2	Risk factor:	**q1* not assessed**	**RfD**	**RfC**
	Value:	**Classification** -- D; not classifiable as to human carcinogenicity	1.4E-1 mg/kg-day	5E-5 mg/cu.m
Q3	Data sources		NRC, 1989; Freeland-Graves et al., 1987; WHO, 1973;	**Roels et al., 1992**
Q4	Omitted sources			**Crump 99**
Q5	Basis:	Existing studies are inadequate to assess the carcinogenicity of manganese.	**Review of Manganese in standard diets**	**Neurobehavioral testing,** self-completed **surveys**
	Risk models used		None	None
	Other models considered			
5a, c	Sex Strain Species Route Regimen			
5b	Critical effect		None specified	Neurological-behavioral impairments
5d	Mechanism of action			
5e, f	Sensitive sub-population or species			**Neonates**
	Relevant species?			
Q9	Relevant exposure route and regimen?		Yes	
	Relevant effect?			
	Relevant statistical model?			
Q6, 7	UF		1	**1000**

	Basis/derivation		**homeostasis**	10 for sensitive individuals, 10 for LOAEL, 10 for data-base limitations -- less-than-chronic exposure, lack of developmental data, unquantified differences in toxicity of different Mn forms.
	Inter-species variability			
	Intra-species variability			
	Inter-human variability			10
	Sub-chronic to chronic extrapolation			10
	LOAEL to NOAEL extrapolation			10
	Data limitations, sufficiency			Data inconclusive (**Crump 99**) and limitedl see CF.
Q8	MF		**1 for food, 3 for soil and water**	**1**
Q10	CF		**Study -- Medium Data Base -- Medium RfD -- Medium**	**Study -- Medium Data Base -- Medium RfC -- Medium**

Prochloraz: Summary Table

Name:	**Prochloraz**		
Q1	Did document appropriately address…	Answer	**Comments**
A1	Uncertainty in data	No	Not addressed. The word "uncertainty" does not appear in the discussion, except when a UF of 100 for the RfD is given (without discussion).
A2	Variability in data	No	Not addressed
	Model form uncertainty	No	Statistical risk models for genotoxic carcinogens were used, but Prochloraz may be a promoter (**Kato 98**). MVK or other models were not considered. Model uncertainty was not addressed.
	Model parameter uncertainty	NA	Not discussed (but implicit in statistical risk models for cancer unit risk)
	Model validation	NA	Not addressed
B	Pre-pilot vs.post-pilot		
C1	Strengths and weaknesses of the scientific evidence from available studies	Partly	The classification of carcinogenicity as **possible** for humans and **limited** for animals seems reasonable, and the **discussion** for animals is useful. The main omission is discussion of mode of action and role of Prochloraz as a promoter.
C2	Sources of variability in the data used in the assessment	No	
C3	Uncertainties in underlying data	No	
C4	Uncertainties in qualitative and quantitative judgments given in the assessment	Partly	The discussion of evidence for carcinogenity in animals is useful.
Summary: The main uncertainties are (a) Whether Prochloraz acts purely as a non-genotoxic promoter, in which case an MVK type model might be appropriate for the cancer part; (b) Whether it causes liver damage in humans at low doses. Neither uncertainty is discussed in the current assessment.			

Prochloraz: Details

	Substance:	**Prochloraz**		
Q2	Risk factor:	**q1*/Slope factor**	**RfD**	**RfC**
	Value:	Oral Slope Factor -- **1.5E-1 per (mg/kg)/day** Drinking Water Unit Risk -- 4.3E-6 per (ug/L)/day Air unit risk: **Not available**	9E-3 mg/kg/day	None
Q3	Data sources	Nor-Am Chemical Co., 1983	**FBC Limited, 1981**	
Q4	Omitted sources			
Q5	Basis:	**CD-1 mouse liver tumors**	2-Year Dog Feeding study (4.07 mg/kg/day)	
	Risk models used	Male mice: time-to-tumor linearized multistage in dose, Weibull in time. Female mice: linearized multistage Extrapolation to humans: Based on mg/kg-day	None	
	Other models considered	Not discussed		
5a, c	Sex Strain Species Route Regimen	Both sexes CD-1 Mouse Diet 0, 78, 325, 1300 ppm per day	**Both sexes** **Beagle** **dogs** **Diet** 0, 30, 135, 600 ppm for 104 weeks. (600 increased to 1000 ppm after 56 weeks)	
5b	Critical effect	liver adenoma/carcinoma combined	Increase in SAP and liver weights, liver histopathology	
5d	Mechanism of action	Unclear. Prochloraz is Ames negative and not genotoxic in most assays. There is evidence that it may be a promoter rather than an initiator (**Kato 98**).		
5e, f	Sensitive sub-population or species	Not addressed	Not addressed	

	Relevant species?	Unclear. (Mechanism of action not identified.)	Relevance of dogs to humans is not addressed.	
Q9	Relevant exposure route and regimen?	Ingestion route is relevant.	Ingestion route is relevant.	
	Relevant effect?	Unclear. (Mechanism of action not identified.)		
	Relevant statistical model?	Perhaps not. The models used are for genotoxic carcinogens.		
Q6, 7	UF		**100**	
	Basis		UF of 100 was used to account for inter- and intraspecies differences.	
	Derivation		Not discussed	
	Inter-species variability	Not addressed	10	
	Intra-species variability	Not addressed	10	
	Inter-human variability	Not addressed	Not addressed	
	Sub-chronic to chronic extrapolation	Not addressed	High-concentration to low-concentration extrapolation not addressed	
	LOAEL to NOAEL extrapolation			
	Data limitations, sufficiency	Data considered adequate		
Q8	MF		None	
Q10	CF	**Study -- Medium** **Data Base -- High** **RfD -- High**		

Brent L. Finley, Ph.D., DABT

TRIVALENT CHROMIUM

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

The summary really only discusses one study in any detail (Ivankovic and Preussman, 1975), which is the critical study. The summary notes that there are several other studies which also show no effects but that these studies used much lower doses. This is true. Still, I think it would raise the comfort level of the reader, and impart a better understanding of the variability and uncertainty in the data set, if these "other" studies were at least briefly summarized with respect to species used, duration of dosing, and doses involved. And did all of these studies use chromic oxide, as Ivankovic and Preussman did, or did they use salts with different solubilities?

Also, there is no mention at all of human data. Such studies do exist, as described in the accompanying documentation. Although these studies are highly uncertain in their own rights (usually due to multiple chemical exposure and lack of exposure information), they should at least be acknowledged and their uncertainties mentioned.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

As noted above, relative strengths and weaknesses of the different studies, and the variability within the overall data set, are barely addressed. The strengths/weaknesses of the critical study are adequately addressed

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

Per my comment below, the text underlying the quantitative uncertainties (the UFs) should be expanded upon. Also, it is unclear exactly what "insoluble salts" refers to and how one should use the accompanying tox criteria. Do these tox criteria only apply to chromium salts with a particular solubility product? Or only salts that are less soluble than chromic oxide? This is an uncertainty that needs to be addressed.

D. Are there other relevant observations or comments that you would like to raise?

No

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

RfD

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The EPA 1998 toxicological review of Chromium.

Were all necessary documents reviewed? If not, what was missing?
Yes

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RfD=animal NOAEL

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

Animal data. 120 per group

B. Critical effect.
None

C. Route of exposure that yielded the critical effect.
Oral

D. Mechanism of action for the critical effect observed, if known.
Not known

E. For human data: was a sensitive sub-population included?
Not applicable

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

Standard strains were used

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

This section needs some expansion. The subchronic to chronic and LOAEL to NOAEL values are not mentioned but are presumed to be 1. This should be identified. Also, there is no justification for the 10-fold factors applied to interspecies and intrahuman variability. Why would these values apply and not something less, like a factor of 3? Also it is unclear why the “database deficiency” is addressed as a modifying factor and not a UF.

7. Was the UF data derived?

No.

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

Yes…it just needs more justification

8. Identify the MF (modifying factor) used, if any, and its basis.

A modifying factor of 10 was used to account for data base deficiencies

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Yes

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?

RfD=low

I concur

4-METHYLPHENOL

General comments:

1) The IRIS summary is confusing in one respect: the summary is purportedly for 4-methylphenol, yet virtually all of the toxicity data are discussed in terms of cresol isomers. There needs to be some explanation of the fact that 4-methlyphenol is a "cresol", more specifically that it is p-cresol
2) Related to the above comment: there needs to be some distinction regarding the toxic effects of the different cresol isomers…are we to assume that the toxic effects of the o- and m-cresol isomers are relevant? And to what degree? The toxic effects of the 3 cresol isomers, and their species-specific metabolism, are in fact quite different. I would recommend that this be discussed and the p-cresol data be given greater emphasis in instances in which tox data for one or more isomers is being presented.

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

This is somewhat of a moot point because there is very little data and no tox critieria were developed. Still, I don't believe this summary gives an adequate discussion of the uncertainties of the data that do exist. See detailed response in Section 1C below.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

In general, the summary does not give a sufficiently balanced review of the strengths and weaknesses of the available data, as described below.

Regarding Section II.A.1: this section simply notes that the three cresol isomers produced positive results in genetic toxicity studies both alone and in combination, as support for the weight-of-evidence classification of "C", possible human carcinogen. This does not accurately reflect the weight of evidence related to gene-tox studies. As noted in Section 6.3 of the ECAO document, and as summarized in Section II.A.4 of the IRIS summary, 4-methylphenol (4-MTHP) has NOT been found to be mutagenic in at least 6 different reverse mutation assays. Several different SCE assays and cell transformation assays were all negative. The ONLY instances in which 4-MTHP was found to be positive were in unpublished studies. This section should clearly state that all published genetic toxicity data (that have undergone external peer review) are negative, only unpublished data show positive results. The IRIS summary for methyl macrylate takes care to note when citing data from unpublished studies.

In addition, this section states that increased skin papillomas were observed in a mouse skin-painting study. While this is true, it would be more balanced to note (as noted in Section II.A.3) that this study only evaluated the PROMOTING activity of 4-MTHP…and no carcinomas were observed at any dose.

Regarding Section II.A.2: the only data cited here are case reports. If IRIS were to list case reports in the summaries for other chemicals, e.g., benzene, the summary would run for over 20 pages. I would suggest that case reports involving single individuals exposed to multiple chemicals do not warrant mention in any IRIS summary.

Regarding Section II.A.3.: this section begins by saying that "four skin application studies had positive results". This suggests to the reader that there may have been numerous negative studies, and should be rephrased to say "X skin application studies have been performed, and Y reported positive results".

I think this section loses focus with the references to o- and m-cresol toxicity data. If the summary is intended to be for 4-MTHP, then the summary should discuss the tox data for that chemical only.

There is some subjective language in this section that should be improved upon. For example: "Many of the cresol-treated mice died, presumably of cresol toxicity". "Many" doesn't help the reader…the summary should give the number of mortalities and indicate whether it was statistically significantly increased over controls. Also, it is probably not appropriate to make "presumptions" about the tox data without accompanying scientific support.

The IRIS summary notes that the last 2 studies are "of limited value" but then devotes more discussion to these studies than any others in the entire summary. I would suggest that the weaknesses of these studies are so significant (multiple chemicals present in tea and distillate extracts) that they should not be considered at all or only briefly mentioned.

It is unclear why an acute dermal toxicity study is included in this section. It should be removed.

Regarding Section II.A.4: as noted above, discussions of other cresol isomers or mixtures of isomers don't seem appropriate here. Also, as noted above, this section should clearly state that all published genetic toxicity data (that have undergone external peer review) are negative, only unpublished data show positive results.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

No, per my discussions above.

D. Are there other relevant observations or comments that you would like to raise?

See above. Also, I think it would be useful to explain WHY a chemical has been withdrawn, as this one has (for the RfD). Is it because new data have become available? Flaws found in the previous analysis?

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

None were established

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

Not applicable

Were all necessary documents reviewed? If not, what was missing?

Yes.

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

Not applicable

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

Not applicable

B. Critical effect.

C. Route of exposure that yielded the critical effect.

D. Mechanism of action for the critical effect observed, if known.

E. For human data: was a sensitive sub-population included?

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

Not applicable

7. Was the UF data derived?

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

Not applicable

8. Identify the MF (modifying factor) used, if any, and its basis.

Not applicable

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Not applicable

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?
Not applicable

DANITOL

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

Partially. The results of several animal studies are presented and described, and the NOEL doses for each are identified. However, there is no narrative text or interpretation that describes the variability across the aggregated data set. Some discussion as to how the variability and uncertainty of the individual studies compare to one another would be helpful. Also, no justification is provided as to why the 1-year dog-feeding study is superior to the 2-year mouse and rat feeding studies. As the summary points out, a major source of uncertainty in the dog-feeding study is the animals were fed ad libitum so the actual doses are unknown. Were the rat and mouse feeding studies ad libitum also, and if not, why aren't these studies (which are lifetime dosing studies) considered to have less uncertainty than the dog-feeding study?

Also, the summary makes no mention of human data. If no data exist, the summary should say so and indicate that this is a source of uncertainty.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

Per my comment above, the relative strengths and weaknesses of the animal studies were NOT addressed and need to be

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

Per my comment below, the quantitative adjustments (the UF) are not given adequate justification. The only qualitative uncertainty offered in the summary is the ad libitum dosing issue. Other sources of uncertainty are the lack of human data and the fact that the dog-feeding study was not a lifetime study.

D. Are there other relevant observations or comments that you would like to raise?

No

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

RfD

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The animal exposure studies conducted by Valent and Sumitomo

Were all necessary documents reviewed? If not, what was missing?
Yes

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RfD=animal NOAEL

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

Animal data. 8 per group

B. Critical effect.
Tremors

C. Route of exposure that yielded the critical effect.
Oral

D. Mechanism of action for the critical effect observed, if known.
Not known

E. For human data: was a sensitive sub-population included?
Not applicable

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

Standard strains were used

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

This section needs some expansion. Factors for some of these components are given without justification, and others aren't discussed at all. Specifically, a factor of 10 is suggested for inter-species and inter-human variability, but there is no discussion as to why these values are appropriate. I assume the LOAEL to NOAEL adjustment is given a value of 1 since a NOAEL was used, but this component is not mentioned. Similarly, the database insufficiency component is not discussed, though it was apparently assigned a value of 1.

7. Was the UF data derived?
No.

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

Yes…it just needs more justification

8. Identify the MF (modifying factor) used, if any, and its basis.

There was no modifying factor…but no basis was given as to why not.

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?
Yes

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?

RfC=high

I would think that a medium to high rating is more appropriate. There do not appear to be any human data. Given that this is a pesticide, it is reasonable to expect that some residues will end up in the diet, and that human exposure will occur. Although the animal data are robust and there is little variability in the results, I just think a rating of "high" is inappropriate without some human data to support.

DDT

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

I would have to say no, but most of this could be rectified with just a bit more text. The animal studies are briefly described, but there is no objective discussion or interpretation as to the merit or validity of the studies. For example, given that the key study that underlies the RfD is almost 50 years old, it would seem appropriate to be a little more critical of the study design and interpretation. Would this study meet current criteria for proper conduct of a long-term animal feeding study? In the methyl macrylate IRIS summary, it is noted that a study conducted in 1964 did not appear to adhere to Good Laboratory Practice….could this also be true for a DDT study conducted in 1950?. Also, there is no discussion at all in the RfD section as to the human data. Have the liver effects in male rats been observed in occupational exposures? This needs to be addressed.

The RfD section does do a good job of pointing out that alternative animal data sets yield the same RfD. Similarly, the discussion of the variability in the cancer bioassays is thorough. Several oral slope factors from numerous animal studies are presented and it is made clear that there is little variability in the potency data, even though the studies include several different species and strains. This is something that should be done more often in the IRIS summaries.

There is one significant variability/uncertainty issue that is mentioned but not sufficiently addressed. The summary notes that one multi-generational repro study showed increased offspring mortality at all doses, but that three other studies at much higher doses showed no increased mortality. No observations or possible interpretations of these highly conflicting datasets are offered. The summary goes on to state that there is clear lack of a repro NOEL because of these data, and suggests that this results in a "medium to low" confidence in the RfD. It would be appropriate to devote some text to why these data conflict.

Finally, there is no mention of developmental effects in animals or humans. If no such data exist, this is an uncertainty that needs to be addressed.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

See my comment above. Although the variability in the animal data is addressed, there is insufficient discussion of noncancer human effects in the RfD section.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

Per my comment above, more discussion needs to be given to uncertainties in the RfD critical study.

Also, the discussion of the UFs and their basis should be given more consideration. Preferably, each component of the aggregate UF would be discussed, even if the individual factor is being assigned a value of 1. For example, the database sufficiency UF is not even mentioned in the RfD section. If it is assigned a value of 1, explain why.

Also, there is no discussion of the uncertainty associated with 1) selection of the geometric mean of the slope factors, or 2) use of the LMS model to estimate potency. Both of these are critical decisions and they both carry some degree of uncertainty that needs to at least be qualitatively discussed.

Finally, there is one glaring omission: there is no discussion of the uncertainty associated with using oral exposure data to develop an inhalation slope factor. The text simply says that the oral data were used. There is no discussion of HOW the oral data were used, much less any discussion of the obviously significant uncertainties associated with extrapolating these studies to an inhalation SF. I would suggest that the uncertainty is probably so great that in fact the oral data CANNOT be used to set an inhalation SF. This omission needs to be seriously considered.

D. Are there other relevant observations or comments that you would like to raise?

No

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

RfD and oral and inhalation slope factor

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The EPA Jan. 1985 CAG evaluation

Were all necessary documents reviewed? If not, what was missing?
Yes

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RFD=animal LOAEL
Oral and inhalation slope factor=animal bioassays

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

RfD=animal data; 25 subjects per group
Oral and inhalation slope factors=this was the geometric mean of several different animal bioassays.

B. Critical effect.
Liver lesions (RfD)
Liver tumors (slope factors)

C. Route of exposure that yielded the critical effect.
Oral

D. Mechanism of action for the critical effect observed, if known.
DDT metabolism to DDE and DDD, which interact with cellular consituents

E. For human data: was a sensitive sub-population included?

Not applicable

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

No, standard strains were used.

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

As noted above, not all of the above factors were considered. For the RfD, a UF of 10 for interspecies sensitivity was used, and another UF of 10 was used for sensitive humans. A value of 1 was used for subchronic to chronic because of corroborative evidence. The UFs for LOAEL to NOAEL extrapolation and database insufficiencies are presumed to be 1, but no mention of these UFs is made.

7. Was the UF data derived?

No.

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

There was adequate information to make a quantitative assessment of uncertainty for both the RfD.

8. Identify the MF (modifying factor) used, if any, and its basis.

An MF of 1 was used for the RfD. No basis was given.

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

The critical noncancer effect (liver damage) is relevant. It is not clear whether the critical cancer effect (liver cancer) is relevant, and this issue has been the subject of a lot of debate. It is probably prudent to assume DDT can induce cancer in humans at high doses.

The route of exposure for the RfD and oral slope factor is relevant. As noted above, the route of exposure for the inhalation slope factor is IRRELEVANT and contains a significant degree of uncertainty.

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?

RfD=medium
Oral and inhalation slope factors: none given

It is strange to note that the text of the RfD confidence section consistently concludes medium to low confidence in various aspects of the data, yet “medium” confidence is ultimately assigned to the RfD. I believe the confidence should be assigned medium to low for the reasons discussed by the author.

EGBE

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

The uncertainties and variabilities in the animal data supporting the reference doses and concentrations were well-described, particularly with respect to interspecies (rat vs. mouse) and intergender sensitivities and possible effects of age. I don't think any additional text is required regarding the animal data.

However, there are a couple of areas related to variability and uncertainty in human exposure/toxicity where I believe more characterization is required. First, there is no discussion as to whether the most sensitive endpoint in animals, hemolytic effects, even occurs in humans. Indeed, the only human data discussed are case reports in which NO hemolytic effects were observed. Since the EPA's analysis is based on the assumption that hemolytic effects will occur in humans at sufficient doses of EGBE, this uncertainty needs to be discussed. Similarly, the summary does not discuss whether BAA formation in the blood, which is used as the target metric for the PBPK model, is thought to be a precursor to or even related to toxic effects in humans. Again, this is a critical underpinning of EPA's analysis, and the uncertainties associated with this assumption are not mentioned.

In addition, the uncertainties and variabilities in the Corley PBPK model, and in the human data underlying the model, should be addressed in more detail. Use of this model probably introduces the greatest degree of uncertainty and variability into the analysis, and it warrants some discussion. In particular, it would be useful to have some text which describes the variability/uncertainty regarding the human kinetic data. This doesn't need to be too lengthy, but some of the basics should be addressed. Is it mostly in vivo data? in vitro? Were the EGBE doses and concentrations relevant? Was there a dose-response curve? The summary notes that adult women may be a sensitive subpopulation….were any of the kinetic data taken from women? It would also be helpful to know if the model has been validated.

Finally, simply as a "reality check" it would be useful to describe an RfD and RfC that would be obtained using the standard and customary methods (single dose from single study divided by UF).

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

The strengths and weaknesses were thoroughly discussed, as were the sources of variability, in the ANIMAL data. As discussed above, such a discussion is lacking regarding the Corley PBPK model and the relevance of the BAA formation endpoint in humans.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

Per my comments above, the uncertainties associated with the PBPK model need to be addressed in more detail. Also, the uncertainties associated with the benchmark dose model need some discussion. Use of benchmark dose modeling is a refinement to EPA's historical approach to setting tox criteria and there are obviously some uncertainties that are governed by the choice of model, goodness of fit, slope of dose response curves, etc. These

should be briefly addressed. At the very least, the goodness of fit of the model should be identified. Ideally, the results obtained with other models would be addressed as well. The methyl methacrylate IRIS summary is a good example.

D. Are there other relevant observations or comments that you would like to raise?

I think it would be helpful to eventually develop QUANTITATIVE estimates of uncertainty and variability, through the use of probabilistic and sensitivity analyses, for those chemicals where adequate data exist. EGBE is probably one of those chemicals.

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

RfD and RfC

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The October 99 EPA toxicological review

Were all necessary documents reviewed? If not, what was missing?
Yes

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RFD=animal LOAEL with BMD
RFC=animal LOAEL with BMD

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

Animal data with a PBPK analysis. 10 animals per dose.

B. Critical effect.
Increase in mean corpuscular volume (RfD)
Decrease in RBC count (RfC)

C. Route of exposure that yielded the critical effect.
Oral for RfD; inhalation for RfC

D. Mechanism of action for the critical effect observed, if known.

Thought to be metabolism of EGBE to 2-butoxyacetic acid, which causes hematological effects.

E. For human data: was a sensitive sub-population included?

This is a source of uncertainty…a PBPK model was used to normalize animal doses to human doses, and human kinetic data were used to construct the model. It is thought that adult females may be more sensitive, but it is unclear whether human female data were used in the construct of the model.

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

No, standard strains were used.

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

All of the above factors were considered. For the RfD, a UF of 10 for intrahuman sensitivity was used; all other UFs were given a value of 1. For the RfC, a UF of 30 was used: 10 for intrahuman sensitivity and 3 for extrapolation from an adverse effect level…all other UFs were given a value of 1.

7. Was the UF data derived?

No.

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

There was adequate information to make a quantitative assessment of uncertainty for both the RfD and RfC.

8. Identify the MF (modifying factor) used, if any, and its basis.

MFs of 1 were used for the RfD and RfC. No basis was given.

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

The routes of exposure were relevant for both the RfD and RfC. It is unclear whether the critical effect (hemolysis) is relevant. Numerous studies discussed in the IRIS summary and supporting documentation do not appear to show any consistent evidence that hemolysis occurs in humans exposed to EGBE. Hence, I would have to conclude that the critical effect MAY NOT be relevant to humans.

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?

RfD=medium to high
RfC=medium to high

I would concur.

METHYL METHACRYLATE

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?
This summary was very thorough and I believe it captured the main uncertainties and variabilities in the underlying data. The relative strengths and weaknesses of the animal data are discussed, and the uncertainty in the key study is addressed. Repro and developmental effects are addressed. The acknowledged differences in MM metabolism and how these influence the selection of the interspecies UF is sufficiently addressed.

I have a couple of recommendations, however. First, it is difficult to understand the variability in the animal data sets when the doses are not normalized to mg/kg-day. For example, the summary cites a year-long dog-feeding study, but the doses are given in ppm administered in the diet. This makes it impossible to compare the dog doses to the rat doses from the critical study, which are reported in terms of mg/kg-day. All doses should be normalized to mg/kg-day if possible to assist the reader in understanding the variability of the underlying data.

Similarly, it would be of use to understand the RANGE of RfDs that might be derived from different studies. This gives the reader another mechanism for assessing variability in the underlying data. For MM, there are several animal-feeding studies with exposure durations of 8 months or longer. Each of these studies has its shortcomings, and I believe the EPA chose the proper study as the critical study. Still, it would be helpful to know the RfD values that would be derived from the other, less desirable studies after the appropriate UFs have been incorporated. Along the same lines, it would be helpful to know the RfC that would be generated using standard methods (critical study with UFs) instead of a BMD analysis.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

Per my comment above, yes.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

For the most part, yes. However, the summary notes that the critical study, which was conducted in 1964, may not meet current GLP criteria. This deserves more discussion: what aspects of the study would fail to meet GLP and how does this influence the conclusions regarding the uncertainty of the study and the RfD overall?

D. Are there other relevant observations or comments that you would like to raise?

No

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

RfD and RfC.

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The EPA Jan. 1998 Toxicological Review of Methyl Macrylate

Were all necessary documents reviewed? If not, what was missing?
Yes

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RFD=animal NOAEL
RFC=animal LOAEL with BMD

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

RfD=animal data; 50 subjects per group
RfC=animal data; several studies

B. Critical effect.
None (RfD)
Degeneration of olfactory epithelium (RfC)

C. Route of exposure that yielded the critical effect.
Oral for RfD…inhalation for RfC

D. Mechanism of action for the critical effect observed, if known.
Metabolism to methacrylic acid, which destroys nasal tissues

E. For human data: was a sensitive sub-population included?

Not applicable

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

No, standard strains were used.

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL

Data-base insufficiencies (e.g., too few studies, limited types of studies).

For the Rfd, the UFs for interspecies, inter-human, and database insufficiencies are adequately discussed. The UFs for subchronic to chronic and LOAEL to NOAEL are not discussed. Even though these factors are appropriately given a value of 1, they should be mentioned for completeness sake. The same is true of the subchronic to chronic and LOAEL to NOAEL factors for the RfC.

7. Was the UF data derived?

No.

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

There was adequate information to make a quantitative assessment of uncertainty for both the RfD and the RfC.

8. Identify the MF (modifying factor) used, if any, and its basis.

An MF of 1 was used for the RfD. No basis was given.

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

The critical effect is known to be relevant in humans. The routes of exposure were relevant.

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?

RfD=low to medium
RfC=medium to high

I concur, though I feel the oral exposure data might support a slightly higher confidence level.

NAPTHALENE

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

The uncertainties and variabilities in the data are generally addressed in a thorough manner. In particular, the variability in the oral exposure data sets and the rationale for choosing the critical study was concise and clear. In addition, I appreciated the comparison of the RfDs as calculated by the LOAEL/NOAEL vs. BMD methods. This is a comparison that I think would be useful for other chemicals where the data are sufficient to support such an analysis.

However, as described below, I don't believe the UFs for the RfD/RfC evaluations are given adequate characterization.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

Yes, in general. For both the RfD and RfC derivation, each of the most relevant animal studies was discussed in great detail, and the rationale for selecting the key study was clear and supported by the information given in the summary. As noted above, I felt the variability issue for the RfD was well-addressed with the LOAEL/NOAEL vs BMD comparison.

However, there was virtually no mention of human data in the RfD and RfC discussions. It seems reasonable to expect that there have been epidemiological studies of noncancer effects workers exposed to naphthalene. And if there haven't, the IRIS summary should clearly say so.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?
For the most part, yes. I think some additional text on the uncertainties associated with calculating the HEC for the RfC would be appropriate. In particular, the uncertainty in the assumption regarding the mouse:human blood/gas partition coefficients should be addressed. Because these coefficients are "not available", a default ratio of 1 was used. It is unclear to the reader whether any level of confidence should be assigned to this value. It would be useful to understand the impact on the analysis if different but reasonable ratios were used. This is part of my general comment on all of the summaries: a sensitivity analysis should be performed whenever a "default" assumption is made in the total absence of data.

In addition, as described below, I don't feel the UFs for the RfC/RfD evaluations are given adequate justification.

D. Are there other relevant observations or comments that you would like to raise?
NO

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.
RfD and RfC

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The EPA August 1998 Tox Review

Were all necessary documents reviewed? If not, what was missing?
Yes.

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RfD=animal NOAEL
RfC=animal LOAEL

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?
Animal data
RfD=20
RfC=150

B. Critical effect.
RfD=decreased mean terminal body weight in males
RfC=nasal effects

C. Route of exposure that yielded the critical effect.
RfD= oral
RfC= inhalation

D. Mechanism of action for the critical effect observed, if known.
For inahalation effects: metabolism to reactive metabolites

E. For human data: was a sensitive sub-population included?
Not applicable

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

No…standard strains were used

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

Yes, each of these were addressed.

However, the UFs for the RfD and RfC are both 3,000. These are very high values and therefore further justification for each factor is needed. As it reads now, the text just states which value was used, with little to no supporting discussion.

For example, for the RfD a 10-fold factor is used for interspecies variability, intrahuman variability, and subchronic to chronic extrapolation. Yet there is no text explaining why humans might be more sensitive to oral effects than rodents. Given that no effects were even seen in the rodent studies, a factor of 10 might be challenged as too high by some. There is no justification for assuming that there may be sensitive subpopulations…again given that no effects were observed in the animals studies, there doesn't seem to be an age-specific or genetic basis for this factor. The same applies to the RfC, where factors of 10 were used for interspecies extrapolation, sensitive subpopulations, and LOAEL to NOAEL. Given that the critical effects are nasal effects, what is the justification for assuming humans could be much more sensitive than rodents, and that there might be sensitive subpopulations? I am not disagreeing with the values per se, but because there is no accompanying text it is difficult to assess their validity.

7. Was the UF data derived?
No

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

As noted above, I believe that sufficient information exists, but that the summary currently does not use that information to justify the choices made in deriving the RfD and RfC.

8. Identify the MF (modifying factor) used, if any, and its basis.

Values of 1 were used for both the RfC and RfC; but no basis was offered

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

The routes of exposure and critical effect (inhalation) are relevant.

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?
RfD=low
RfC=medium

I concur

TOLUENE DIISOCYANATE

1. EPA would like to have your comments on the following questions:

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

Very thoroughly. There are several epidemiological studies of worker exposure to TDI and the summary does a good job of sorting through them and identifying the uncertainties and variabilities in the overall data set. Particularly with respect to co-exposure to other chemicals and smoking effects. The choice of the critical study (Diem) is justified based on the information presented. Perhaps the only "variability" issue that is not addressed in detail is how atopy influences the results, if at all. There were atopics in the study but I couldn't discern whether the dose-response curve for them was the same as for non-atopics.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?

I believe so. Per my comment above.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

The uncertainties in the entire data set, and in the critical study (Diem) are very well described. The lack of breathing-zone measurements in the first years of plant operation is appropriately identified and discussed. As described below, the quantitative UFs need a little more textual discussion.

D. Are there other relevant observations or comments that you would like to raise?

No

2. Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

RfC

3. List what relevant background date for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

The November 1992 EPA Health and Environmental Effects document.

Were all necessary documents reviewed? If not, what was missing?
Yes

4. Identify the basis for each risk factor: (e.g., NOAEL, NOEL, LOAEL, LOEL, BMD, etc.)

RFC=human NOAEL

5. Identify:

A. Was the risk factor based on human data (describe) or an animal data? How many subjects in the critical stud(ies)?

The risk factor was based on an epidemiological study of 277 male workers.

B. Critical effect.
Chronic lung function decline

C. Route of exposure that yielded the critical effect.
Inhalation

D. Mechanism of action for the critical effect observed, if known.
Irritation and sensitization

E. For human data: was a sensitive sub-population included?

Yes….atopics were included in the population. They would be the most likely to demonstrate enhanced sensitivity to the sensitization properties of TDI

F. For animal data: was the species/strain know to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

Not applicable

6. Identify:

A. Uncertainty factor & basis, breaking down the UF into its component parts, as necessary. Were the following considered?

- Inter-species and intra-species variability
- Inter-human variability
- Extrapolation from less-than-chronic to chronic toxicity
- Extrapolation from LOAEL to NOAEL
- Data-base insufficiencies (e.g., too few studies, limited types of studies).

This is the only part of the summary I would suggest needs improvement. The text is simply too sparse. A UF of 3 is proposed for subchronic to chronic extrapolation but no justification is offered. A UF of 3 is suggested, presumably for database insufficiencies, because of the lack of developmental data. Why not the standard factor of 10? And what about repro effects? And the fact that all the workers were male? The factor of 10 for intrahuman variability: is this appropriate for a sensitizer? Since we're dealing with human data here, it might be possible to use a lower UF. I'm not quibbling with the actual UF values themselves….but they certainly need more justification.

7. Was the UF data derived?

No.

Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?

Yes…it just needs more justification

8. Identify the MF (modifying factor) used, if any, and its basis.

There was no modifying factor…but no basis was given as to why not.

9. In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?
Definitely

10. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC? Do you concur?

RfC=medium

I would concur.

Russell E. Keenan, Ph.D.

ACETONITRILE
Pilot Assessment

RfC: Uncertainty associated with the underlying data for the RfC is briefly outlined in the Confidence section and in the section that discusses uncertainty factors. Specific uncertainties that are discussed include uncertainty in the data regarding reproductive toxicity, and uncertainty associated with whether the RfC is protective of hematological effects. Uncertainty is also associated with how inhalation may be involved with the development of forestomach lesions in the test animals. EPA has applied a modifying factor of 10 to account for this uncertainty. As stated in the general comments, this Pilot assessment represents a marked improvement over pre-Pilot assessments. As a pilot chemical, EPA did a better job in characterizing the uncertainty and variability in the data used to develop the RfC. However, as discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: n/a

RfD: n/a

RfC: 6E-2 mg/m^3

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

EPA. 1999. Toxicological Review of Acetonitrile. In Support of Summary Information on the Integrated Risk Information System (IRIS).

CSF: Human carcinogenicity data: none available
Animal carcinogenicity data: NTP, 1996. Animal evidence is equivocal

RfD: Not applicable

RfC: NTP, 1996

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: n/a

RfD: n/a

RfC: NOAEL: 336 mg/m^3 (200 ppm)
NOAEL (human equivalent concentration, HEC): 60 mg/m^3

Identify:

Risk Factor: *RfC*

Date of study: 1996

Type of study: Toxicology and carcinogenesis inhalation studies

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
10/sex/group

D. Number of doses in the dose range?
6 doses in the dose range: 0, 100, 200, 400, 800, or 1600 ppm (0; 168; 336; 672; 1,343; or 2,686 mg/m^3)

E. Critical effect?
Mortality

Route of exposure that yielded the critical effect?
Inhalation

Mechanism of action for the critical effect observed, if known?
Not stated

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain:
B6C3F1 mice

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?

UF = 100

inter-species and intra-species variability
3:inter-species

inter-human variability
10

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
3 to account for limited data on reproductive endpoints involving exposure of mice before and during mating and the lack of hematological measurements in either mouse study.

Identify the MF (modifying factor) used, if any, and its basis.

A modifying factor of 10 was applied because of the uncertain role that inhalation may have played in the development of the concentration related increase in the incidence of forestomach lesions in both male and female mice.

In your judgment, is the critical effect identified relevant to humans?
Based on the lack of human data, it can not be adequately determined if the critical effect is relevant to humans. Other than one case-referent study, there are no epidemiological studies of the effects of acetonitrile exposure to humans. Effects seen in the one available study included nausea, shallow and/or irregular respiration and impaired motor activity.

Is the route of exposure relevant to humans?
Based on the lack of human data, it can not be adequately determined if the route of exposure is relevant to humans.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Medium. Hematology was not measured in mice and only at the 15-month interim evaluation in rats.

References

EPA. 1999. Toxicological Review of Acetonitrile. In Support of Summary Information on the Integrated Risk Information System (IRIS). U. S. Environmental Protection Agency. Washington, D.C. January.

National Toxicology Program (NTP). 1996. Toxicology and carcinogenesis studies of acetonitrile (CAS No. 75-05-8) in F3444/N rats and B6C3F1 mice (inhalation studies). NTP TR 447.

BENZENE
Pilot Assessment

CSF: Uncertainty regarding the carcinogenic potential of benzene is discussed under the Confidence section. The slope factor is extrapolated from the linear no-threshold dose-response curve. No relevant human data exist in the literature for the oral absorption of benzene, but it is known that complete gastrointestional absorption occurs in rat and mice studies. Therefore, estimates of the relative absorption efficiencies across pulmonary and gastrointestional barriers are used as the basis of route-to-route extrapolation, an oral slope factor was derived from the inhalation slope factor. Numerous studies of pulmonary absorption in humans show that absorption of benzene via the inhalation route is incomplete and that an absorption factor of 50% should be used. While the human data support that approximately one-half of inhaled benzene is absorbed into the bloodstream, interindividual variability, and differences in the disposition of benzene after it crosses the pulmonary or gastrointestional barrier exist. Therefore, as discussed in our general comments, use of an upper-bound estimate from a linear model precludes a proper evaluation of uncertainty.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: 1.5E-2 to 5.5E-2 $(mg/kg\text{-}day)^{-1}$

RfD: not available at this time

RfC: not available at this time

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.
EPA. 1998. Carcinogenic Effects of Benzene: An Update.
EPA. 1999. Extrapolation of the Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure.

CSF:
Human Studies:
Aksoy et al. 1974, 1980; Infante et al., 1977; Ott et al., 1978; Rinsky et al., 1981, 1987; IARC, 1982; Wong, 1983, 1987; Bond et al., 1986; Yin et al., 1987, 1989, 1994, 1996; Dosemeci et al., 1994; Hayes et al., 1996, 1997; ATSDR, 1997; EPA, 1998

Animal Studies: EPA, 1979, 1985, 1998; Snyder et al., 1980, 1982, 1984, 1988; Goldstein et al., 1982; Maltoni et al., 1982, 1983, 1985, 1988, 1989; Cronkite al., 1984, 1985, 1989; NTP, 1986; Parmley, 1988; Huff et al., 1989; Low et al., 1989, 1995; Farris et al., 1993

RfD: n/a

RfC: n/a

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: Category A; known human carcinogen

RfD: n/a

RfC: n/a

Identify:

Risk Factor: *CSF*

Date of study: See dates under #4.

Type of study: Human occupational epidemiological studies. Benzene-exposed workers in the chemical industry, shoemaking and oil refineries.

Was the risk factor based on human data (describe) or on animal data?
Human: Pliofilm workers of Rinsky et al. (1981, 1987) still represent the best data for evaluating human cancer risks. Continued use of the low-dose linearity model. Inhalation unit risk estimate was extrapolated to the oral route. 50% absorption is assumed for inhalation; 100% absorption is assumed for oral route.

How many subjects in the critical stud(ies)?

Human:

Aksoy et al., 1974: 28,500 Turkish workers employed in shoe industry.
Infante et al., 1977 and Rinsky et al., 1981: 748: White male Pliofilm rubber workers employed in the manufacture of rubber products.
Rinsky et al., 1987: 1165 Pliofilm rubber workers.
Ott et al., 1978 and Bond et al., 1986: 594 Pliofilm rubber workers.
Wong 1983 and 1987: 4602 male chemical workers exposed to benzene from 7 chemical plants.
Dosemeci et al., 1994, Hayes et al., 1996, 1997, Yin et al., 1987, 1989, 1994, and 1996: epidemiology study of 74,828 benzene-exposed workers employed from 1972 to 1987 in 672 factories in 12 cities in China.

D. Number of doses in the dose range?
Not stated

Critical effect?
Tumor type: leukemia, chiefly acute myelogenous leukemia

Route of exposure that yielded the critical effect?
Inhalation exposure

Mechanism of action for the critical effect observed, if known?
Benzene is metabolized in the liver by cytochrome P4502E1 (CYP2E1) to its major metabolites: phenol, hydorquinone and catechol. Toxicity likely results from a synergistic combination of phenol with the other metabolites.

For human data:

Was a sensitive sub-population included?
Yes; Turkish workers employed in shoe industry, white male Pliofilm rubber workers employed in the manufacture of rubber products, male chemical workers exposed to benzene from 7 chemical plants, and

benzene exposed workers employed from 1972 to 1987 in 672 factories in 12 cities in China.

For animal data:

Note species/strain.
Studies on the carcinogenicity of benzene in rodents include inhalation exposures to Sprague-Dawley rats, C57BL/6 mice, AKR mice, CD-1 mice, and CBA mice; and gavage treatment of Sprague-Dawley rats, Wistar rats, F344 rats, RF/J mice, Swiss mice, and B6C3F1 mice.

Was the species/strain known to be genetically sensitive?
n/a

To have any genetic peculiarity with regard to the toxicity of the compound?
n/a

J. Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?
While the human data indicate that approximately 1/2 of inhaled benzene is absorbed into the bloodstream at exposure concentrations between 1 and 100 ppm, a great deal of interindividual variability was observed in all studies which reported on multiple subjects. Characterization of the extent of variability is limited.

In your judgment, is the critical effect identified relevant to humans?
Based on occupational epidemiological studies, the critical effect appears to be relevant to humans. According to these studies, exposure to benzene is related to significantly increased risks of leukemia, mainly acute myelogenous leukemia (AML).

Is the route of exposure relevant to humans?
The route of exposure appears to be relevant to humans. Inhalation of benzene has been reported in the chemical industry, shoemaking, and oil refineries.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
This benzene update reaffirms within an order of magnitude the benzene interim unit risk estimate derived in 1985. This update affirms that Rinksy et al. (1981, 1987) still provide the best data and the update supports the continued use of the low-dose linearity model.

References

Aksoy, M., S. Erden, and G. Dincol. 1974. Leukemia in show-workers exposed chronically to benzene. *Blood* 44:837-841.

Aksoy, 1980: cited in IRIS, but reference not found in either IRIS or support documents

ATSDR. 1997. Agency for Toxic Substances and Disease Registry; Toxicological profile for benzene. Update. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA.

Bond, G.G., E.A. McLaren, C.L. Baldwin, et al. 1986. An update of mortality among chemical workers exposed to benzene. *Br. J. Ind. Med.* 43:685-691.

Cronkite et al., 1984: cited in IRIS, but reference not found in either IRIS or support documents

Cronkite et al., 1985: cited in IRIS, but reference not found in either IRIS or support documents

Cronkite, E.P., R.T. Drew, T., Inoue, et al. 1989. Hematotoxicity and carcinogenicity of inhaled benzene. *Environ. Health Perspect.* 82:97-108.

Dosemeci, M., G.L. Li, R.B. Hayes et al. 1994. Cohort study among workers exposed to benzene in China: II. Exposure assessment. *Am. J. Ind. Med.* 26:401-411.

EPA. 1979. *Final report on population risk to ambient benzene exposures*. Prepared by United States Environmental Protection Agency, Carcinogen Assessment Group, Research Triangle Park, NC. EPA/450/5-80-004.

EPA. 1985. *Interim quantitative cancer unit risk estimates due to inhalation of benzene*. Prepared by United States Environmental Protection Agency, Carcinogen Assessment Group, Office of Research and Development, Washington, DC. EPA/600/X-85-022.

EPA. 1998. *Carcinogenic effects of benzene: An update*. National Center for Environmental Assessment – Washington Office. Office of Research and Development. U.S. Environmental Protection Agency. Washington, D.C. EPA/600/P-97/001F. April

EPA. 1999. *Extrapolation of the benzene inhalation unit risk estimate to the oral route of exposure*. U.S. Environmental Protection Agency. Washington, D.C. NCEA-W-0517. November.

Farris, G.M., J.I. Everitt, R.D. Irons, et al. 1993. Carcinogenicity of inhaled benzene in CBA mice. *Fundam. Appl. Toxicol.* 20(4):503-507.

Goldstein, B.D., C.A. Snyder, S. Laskin, et al. 1982. Myelogenous leukemia in rodents inhaling benzene. *Toxicol. Lett.* 13:169-173.

Hayes, R.B., S.N. Yin, M. Dosemeci, et al. 1996. Mortality among benzene-exposed workers in China. *Environ. Health Perspect.* 104(suppl 6):1349-1352.

Hayes, R.B., S.N. Yin, M.S. Dosemeci, et al. 1997. Benzene and the dose-related incidence of hematologic neoplasms in China. *J. Nat. Cancer Inst.* 89:1065-1071.

Huff, J.E., J.K. Haseman, D.M. DeMarini, et al. 1989. Multiple-site carcinogenicity of benzene in Fischer 344 rats and $B6CsF_1$ mice. *Environ. Health Perspect.* 82:125-163.

IARC. 1982. IARC monographs on the evaluation of carcinogenic risks of chemicals to humans: Some industrial chemicals and dyestuffs. Vol. 29, Lyon, France: International Agency for Research on Cancer, pp. 93-148.

Infante, P.F., R.A. Rinsky, J.K. Wagoner, et al. 1977. Leukemia in benzene workers. *Lancet* 2:76-78.

Low, L.K., J. Meeks, K.J. Norris, et al. 1989. Pharmacokinetics and metabolism of benzene in Zymbal gland and other key target tissues after oral administration in rats. *Environ. Health Perspect.* 82:215-222.

Low, L.K., C. Lambert, J. Meeks, et al. 1995. Tissue-specific metabolism of benzene in Zymbal gland and other solid tumor target tissues in rats. *J. Am. Coll. Toxicol.* 14:40-60.

Maltoni et al., 1982: cited in IRIS, but reference not found in either IRIS or support documents

Maltoni, C., B. Conti, and G. Cotti. 1983. Benzene: A multipotential carcinogen. Results of the long-term bioassays performed at the Bologna Institute of Oncology. *Am. J. Ind. Med.* 4:589-630.

Maltoni et al., 1985: cited in IRIS, but reference not found in either IRIS or support documents

Maltoni, C., B. Conti, G. Perino, et al. 1988. Further evidence of benzene carcinogenicity. Results on Wistar rats and Swiss mice treated by ingestion. *Ann. NY Acad. Sci.* 534:412-426.

Maltoni et al., 1989: cited in IRIS, but reference not found in either IRIS or support documents

NTP. 1986. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F333/N Rats and B6C3F$_1$ Mice (Gavage Studies). National Toxicity Program, Public Health Service, U.S. Department of Health and Human Services, National Institutes of Health, Research Triangle Park, NC. NTP TR 289.

Ott, M.A., J.C. Townsend, W.A. Fishbeck, et al. 1978. Mortality among individuals occupationally exposed to benzene. *Arch. Environ. Health* 33:3-10.

Parmley, R. 1988. Mammals. In: Vertebrate blood cells. Rowley, A.F. and N.A. Ratcliffe, eds. Cambridge: Cambridge University Press, pp. 337-424.

Rinsky, R.A., R.J. Young, and A.B. Smith. 1981. Leukemia in benzene workers. *Am. J. Ind. Med.* 2:217-245.

Rinsky, R.A., A.B. Smith, R. Horning, et al. 1987. Benzene and leukemia: An epidemiologic risk assessment. *N. Engl. J Med.* 316:1044-1050.

Snyder, C.A., B.D. Goldstein, A.R. Sellakumar, et al. 1980. The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in AKR/J and C57BL/6J mice. *Toxicol. Appl. Pharmacol.* 54:323-331.

Snyder, C.A., B.D. Goldstein, A. Sellakumar, et al. 1982. Toxicity of chronic benzene inhalation: CD-1 mice exposed to 300 ppm. *Bull. Environ. Contam. Toxicol.* 29:385-391.

Snyder, C.A., B.D. Goldstein, A.R. Sellakumar, et al. 1984. Evidence for hematotoxicity and tumorigenesis in rats exposed to 100 ppm benzene. *Am. J. Ind. Med.* 5:429-434.

Snyder et al., 1988: cited in IRIS, but reference not found in either IRIS or support documents

Wong, O., R.W. Morgan, and M.D. Whorton. 1983 . An industry-wide mortality study of chemical workers occupationally exposed to benzene. Technical report submitted to Chemical Manufacturers Association by Environmental Health Associates, Berkely, CA. December.

Wong, O. 1987. An industry-wide study of chemical workers occupationally exposed to benzene. *Br. J. Ind. Med.* 44:382-395.

Yin, S.N., G.L. Li, F.D. Tain, et al. 1987. Leukemia in benzene workers: A retrospective cohort study. *Br. J. Ind. Med.* 44:124-128.

Yin, S.N., G.L. Li, F.D. Tain, et al. 1989. A retrospective cohort study of leukemia and other cancers in benzene workers. *Environ. Health Perspect.* 82:207-213.

Yin, S.N., M.S. Linet, R.B. Haynes, et al. 1994. Cohort study among workers exposed to benzene in China: I. General methods and resources. *Amer. J. Ind. Med.* 26:383-400.

Yin, S.N., R.B. Hayes, M.S. Linet, et al. 1996. A cohort study of cancer among benzene-exposed workers in China: Overall results. *Am. J. Ind. Med.* 29:227-235.

BERYLLIUM
Pilot Assessment

RfD: A brief summary of the uncertainties associated with the underlying data for the RfD is given in the Confidence section. Specific areas of uncertainty that are discussed include whether the RfD is protective of the young (lack of reproductive toxicity data), whether the RfD is protective of immunological effects, and how the critical effect relates to human toxicity. As stated in the general comments, this Pilot assessment represents a marked improvement over pre-Pilot assessments. As a pilot chemical, EPA did a better job in characterizing the uncertainty and variability in the data used to develop the RfD. However, as discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty.

RfC: Overall, this is a good assessment. Minimal uncertainty exists for the RfC. RfC is based on data from a sensitive human subpopulation. The most significant uncertainty lies in the poor quality of the exposure monitoring in the principal study.

CSF: Uncertainty regarding the carcinogenic potential of beryllium is discussed under the Confidence section. While the CSF is based on human data, the principal study is limited due to confounding variables. Definitive exposure data are lacking in this study and in other epidemiological studies. It is possible that a better quantitative cancer estimate will be developed when exposure data from a recent NIOSH case-control study become available.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: Air Unit Risk: 2.4E-3 $(\mu g/m^3)^{-1}$

RfD: 2E-3 mg/kg-day

RfC: 2E-2 $\mu g/m^3$

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

EPA. 1998. Toxicological Review of Beryllium Compounds. CAS No. 7440-41-7.

CSF: Human: Mancuso, 1979, 1980; Infante et al., 1980; Wagoner et al., 1980; Steenland and Ward, 1991; Ward et al., 1992

Animal: Vorwald and Reeves, 1959; Reeves et al., 1967; Vorwald, 1968; Reeves and Deitch, 1969; Wagner, 1969; Morgareidge et al., 1975, 1977; Schroeder and Mitchner, 1975; Nickell-Brady et al., 1994

RfD: Morgareidge et al., 1976

RfC: Eisenbud et al., 1949; Kreiss et al., 1996

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: B1; probable human carcinogen

RfD: BMD_{10}: 0.46 mg/kg-d

RfC: LOAEL: 0.55 µg/m^3
LOAEL (human equivalent concentration, HEC): 0.20 µg/m^3

Identify:

Risk Factor: *CSF*

Date of study: Wagoner et al., 1980

Type of study: Cohort mortality study of 3,055 white males employed at a beryllium extraction, processing, and fabrication facility in Reading, Pennsylvania.

Was the risk factor based on human data (describe) or on animal data?
Human data

How many subjects in the critical stud(ies)?
3,055 white males

D. Number of doses in the dose range?
2 doses in the dose range; 100 µg/m^3 and 1,000 µg/m^3

Critical effect?
Tumor type: lung cancer

Route of exposure that yielded the critical effect?
Inhalation, occupational exposure

Mechanism of action for the critical effect observed, if known?
Not stated

For human data:

Was a sensitive sub-population included?
Yes; 3,055 white males employed at a beryllium extraction, processing, and fabrication facility in Reading, Pennsylvania.

For animal data:

Note species/strain.
Morgareidge et al., 1975, 1977: Wistar albino rats
Schroeder and Mitchner, 1975: Long-Evans rats and swiss mice
Reeves et al., 1967: Sprague-Dawley rats
Vorwald and Reeves, 1959: Sherman rats
Reeves and Reitch, 1969: Charles River CD rats
Wagner et al., 1969: Squirrel monkeys, male CR-CD rats, male Greenacres Controlled Flora (GA) rats and male Golden Syrian hamsters
Vorwald, 1968: Rhesus monkeys

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

In your judgment, is the critical effect identified relevant to humans?
The critical effect may be relevant to humans as a number of human epidemiological studies suggest a casual relationship between beryllium exposure and an increase in lung cancer. However, the studies appear to be limited due to confounding factors; e.g., smoking and exposure to other lung carcinogens.

Is the route of exposure relevant to humans?
Exposure to beryllium via inhalation appears to be the primary route of uptake for occupationally exposed individuals in a number of human studies.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Human - limited. Wagoner et al. (1980) study and others are limited due to confounding factors, e.g. smoking and exposure to other lung carcinogens.
Animal - sufficient, although epidemiological data are considered better for quantitating risk.

Risk Factor: *RfD*

Date of study: Morgareidge et al., 1976

Type of study: Chronic feeding study

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
5 male and 5 female beagle dogs

D. Number of doses in the dose range?
4 doses in the dose range: 0, 5, 50, or 500 ppm

E. Critical effect?
Small intestinal lesions

Route of exposure that yielded the critical effect?
Diet/oral

Mechanism of action for the critical effect observed, if known?
Not stated

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain.
Beagle dogs

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

Uncertainty Factor & Basis, breaking down the UF into its component
parts, as necessary. Were the following considered?

UF= 300

inter-species and intra-species variability
100:10 interspecies, 10 intraspecies

inter-human variability
n/a

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
3 to account for lack of oral human toxicity data and adequate reproductive/developmental and immunotoxicologic endpoint assessments in animals.

Identify the MF (modifying factor) used, if any, and its basis.
1

In your judgment, is the critical effect identified relevant to humans?
No human information is available describing the oral toxicity of beryllium.
Therefore, it could not be determined whether the critical effect observed in the Morgareidge et al., 1976 dog dietary study is relevant to humans.

Is the route of exposure relevant to humans?
It does not appear that the route of exposure is relevant to humans because oral absorption has been shown to contribute to only very small amounts of the total body burden of beryllium in exposed individuals. However, no human information is available describing the oral toxicity of this chemical making it difficult to determine with certainty whether the route of exposure is relevant to humans.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?

Low to Medium. Lack of chronic oral studies establishing LOAELs, lack of a chronic oral study examining immunologic endpoints, lack of critical effect in humans by the inhalation route, lack of sensitive indicators for rickets, lack of reproductive and developmental studies (including multigenerational studies or male reproductive toxicity), and lack of human toxicity information.

Risk Factor: *RfC*

Date of study: Eisenbud et al., 1949 and Kreiss et al., 1996

Type of study: Eisenbud et al., 1949: Community exposure study
Kreiss et al., 1996: Occupational study

Was the risk factor based on human data (describe) or on animal data?
Both studies: human data

How many subjects in the critical stud(ies)?
Eisenbud et al., 1949: 11 community cases of Chronic Beryllium Disease (CBD).
Kreiss et al., 1996: 136 beryllium workers in a plant that made beryllia ceramics from beryllium oxide powder.

D. Number of doses in the dose range?
Not stated

E. Critical effect?
Beryllium sensitization and progression to CBD

Route of exposure that yielded the critical effect?
Inhalation

Mechanism of action for the critical effect observed, if known?
Not stated

For human data:

Was a sensitive sub-population included?
Yes, Kreiss et al., 1996: 136 beryllium workers in a plant that made beryllia ceramics from beryllium oxide powder and Eisenbud et al., 1949: 11 community cases of CBD.

For animal data: n/a

Note species/strain.
n/a

Was the species/strain known to be genetically sensitive?
n/a

To have any genetic peculiarity with regard to the toxicity of the compound?
n/a

Uncertainty Factor & Basis, breaking down the UF into its component

parts, as necessary. Were the following considered?

UF= 10

Sensitive nature of subclinical endpoint
3

inter-species and intra-species variability
n/a

inter-human variability
1

extrapolation from less-than-chronic to chronic toxicity
1

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
3 to account for the poor quality of exposure monitoring in the co-principal studies.

Identify the MF (modifying factor) used, if any, and its basis.
1

In your judgment, is the critical effect identified relevant to humans?
The critical effect does appear to be relevant to humans as it has been observed in various human studies including both occupational studies as well as studies of individuals who live a short distance from beryllium production plants.

Is the route of exposure relevant to humans?
The route of exposure appears to be relevant to humans. As stated above, exposure to beryllium via inhalation is reported in both occupational studies as well as studies of individuals who live a short distance from beryllium production plants.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Medium. Poor quality of exposure monitoring in the co-principal studies.

References

Eisenbud, M., R.C. Wanta, C. Dustan, et al. 1949. Non-occupational berylliosis. *J. Ind. Hyg Toxicol.* 31:282-294.

Infante, P.F., J.K. Wagoner, and N.L. Sprince. 1980 . Mortality patterns from lung cancer and nonneoplastic respiratory disease among white males in the beryllium case registry. *Environ. Res.* 21(1):35-43.

Kreiss, K., M.M. Mroz, L.S. Newman, et al. 1996. Machining risk of beryllium disease and sensitization with median exposures below 2 MU-G/M(3). *Am. J. Ind. Med.* 30(1):16-25.

Mancuso, T.F. 1979 . Occupational lung cancer among beryllium workers. In: Conference on Occupational Exposures to Fibrous and Particle Dust and Their Extension into the Environment, Lemen, R.; Dement, J., eds. Society for Occupational and Environmental Health, Washington, DC. Pp. 463-482.

Mancuso, T.F. 1980. Mortality study of beryllium industry workers' occupational lung cancer. *Environ. Res.* 21:48-55.

Morgareidge, K., G.E. Cox, and D.E. Bailey. 1975. Chronic feeding studies with beryllium sulfate in rats: Evaluation of carcinogenic potential. Submitted to Alcan Research and Development, Ltd. By Food and Drug Research Laboratories, Inc.

Morgareidge,K; G.E.Cox; M.A. Gallo. 1976. Chronic feeding studies with beryllium in dogs. Food and Drug Research Labs, Inc. Submitted to the Aluminum Company of America, Alcan Research and Development, Ltd., Kawecki, Berylco Industries, Inc., and Brush-Wellman, Inc.

Morgareidge, K., G.E. Cox, D.E. Bailey, et al. 1977. Chronic oral toxicity of beryllium in the rat. *Toxicol. Appl. Pharmacol.* 41(1):204-205.

Nickell-Brady, C., F.F. Hahn, G.L. Finch, et al. 1994. Analysis of K-ras, p53 and c-raf-1 mutations in beryllium-induced rat lung tumors. *Carcinogenesis* 15:257-262.

Reeves, A.L. and D. Deitch. 1969. Influence of age on the carcinogenic response to beryllium inhalation. In: Proceedings of the 16th International Congress on Occupational Health, Harishima, S., ed. Japan Industrial Safety Association, Tokyo, Japan. Pp.651-652.

Reeves, A.L., D. Deitch, and A.J. Vorwald. 1967. Beryllium carcinogenesis. I. Inhalation exposure of rats to beryllium sulfate aerosol. *Cancer Res.* 27:439-445.

Schroeder, H.A. and M. Mitchner. 1975. Life-term studies in rats: Effects of aluminum, barium, beryllium, and tungsten. *J. Nutr*. 105:421-427.

Steenland, K. and E. Ward. 1991. Lung cancer incidence among patients with beryllium disease: A cohort mortality study. *J. Am. Cancer Inst.* 83(19):1380-1385.

Vorwald, A.J. 1968. Biologic manifestations of toxic inhalants in monkeys. In: Use of nonhuman primates in drug evaluation, Vagtborg, H., ed. Austin, TX: University of Texas Press, pp. 222-228.

Vorwald, A.J. and A.L. Reeves. 1959. Pathologic changes induced by beryllium compounds: Experimental studies. *Arch. Ind. Health* 19:190-199.

Wagner, W.D., D.H. Groth, J.L. Holtz, et al. 1969. Comparative chronic inhalation toxicity of beryllium ores, bertrandite and beryl, with production of pulmonary tumors by beryllium. *Toxicol. Appl. Pharmacol.* 15:10-129.

Wagoner, J.K., P.F. Infante, and D.L. Bayliss. 1980. Beryllium: An etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease, and heart disease among industrially exposed workers. *Environ. Res.* 21:15-35.

Ward, E., A. Okun, A. Ruder, et al. 1992. A mortality study of workers at seven beryllium processing plants. *Am. J. Ind. Med.* 22:885-904.

CHLORDANE
Pilot Assessment

1. RfD: The uncertainty relative to the concern that appropriate toxicity endpoints have not been studied is summarized in the Confidence section. In contrast to other Pilot chemicals, very little discussion on uncertainty relative to database insufficiencies is provided in the section on Uncertainty and Modifying Factors. Specific uncertainties that are discussed in the Confidence section include uncertainty associated with whether the RfD is protective o neurotoxicity effects, an endpoint that has been reported in humans exposed to chlordane, but not examined in chronic animal studies; and uncertainty associated with whether the RfD is protective of reproductive toxicity (uncertainty relative to the toxicological significance of endocrine mimicry effects of chlordane).

As stated in the general comments, this Pilot assessment represents a marked improvement over pre-Pilot assessments. As a pilot chemical, EPA did a better job in characterizing the uncertainty and variability in the data used to develop the RfD. However, as discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty.

RfC: Similar concerns regarding the underlying data for the RfD are raised for the RfC. The uncertainty relative to the concern that appropriate toxicity endpoints have not been studied is summarized in the Confidence section. In contrast to other Pilot chemicals, very little discussion on uncertainty relative to database insufficiencies is provided in the section on Uncertainty and Modifying Factors. Specific uncertainties that are discussed in the Confidence section include uncertainty associated with whether the RfC is protective of neurotoxicity effects, an endpoint that has been reported in humans exposed to chlordane, but not examined in chronic animal studies; and uncertainty associated with whether the RfC is protective of reproductive toxicity (uncertainty relative to the toxicological significance of endocrine mimicry effects of chlordane). It is unclear why the database for the RfC received a low confidence rating, while the database for the RfD received a medium confidence rating. The uncertainty discussion relative to the respective databases was the same for both risk factors.

As stated in the general comments, this Pilot assessment represents a marked improvement over pre-Pilot assessments. As a pilot chemical, EPA did a better job in characterizing the uncertainty and variability in the data used to develop the RfC. However, as discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty.

CSF: Uncertainty regarding the carcinogenic potential of chlordane is discussed under the Confidence section. While underlying data for chlordane indicate that the dose-response curve may be sublinear in the low dose region, EPA cannot rule out linearity at low doses. Thus, the slope factor is extrapolated from the linear no-threshold dose-response curve. As discussed in our general comments, use of an upper-bound estimate from a linear model precludes a proper evaluation of uncertainty.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: 3.5E-1 $(mg/kg\text{-}day)^{-1}$

RfD: 5E-4 mg/kg-d

RfC: 7E-4 mg/m^3

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

EPA. 1997. Toxicological Review of Chlordane (Technical). In Support of Summary Information on the Integrated Risk Information System (IRIS).

CSF: Human carcinogenicity data:
Case-control studies of non-Hodgkin's lymphoma among farmers
Cantor et al., 1992; Brown et al., 1990, 1993; Woods et al., 1987; Pesatori et al., 1994
Occupational cohort studies in manufacturing plant and pesticide applicators
Wang and MacMahon, 1979; Brown, 1992; Shindell and Ulrich, 1996
Case reports of disease in people exposed to chlordane in non-occupational settings
Epstein and Ozonoff, 1987; Infante et al., 1978; Caldwell et al., 1981, Teufel et al., 1990; Falck et al., 1992

Animal carcinogenicity data:
IRDC, 1973; Khasawinah and Grutsch, 1989a,b; Barrass et al., 1993; Malarkey et al., 1995; NCI, 1977

RfD: Principal study:

Velsicol Chemical Corp., 1983; Khasawinah and Grutsch, 1989a

RfC: Principal study(s):

Khasawinah et al., 1989a,b

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: Classified as a B2: probable human carcinogen, using *1986 Guidelines for CarcinogenicRisk Assessment*. Sufficient evidence in animals; inadequate evidence in humans. Classified as a likely carcinogen in humans using 1996 *Proposed Guidelines for Carcinogen Risk Assessment.*

RfD: NOAEL: 0.15 mg/kg-day

RfC: NOAEL: 1.0 mg/m^3
NOAEL (human equivalent concentration, HEC): 0.65 mg/m^3

Identify:

Risk Factor: *RfD*

Dates of studies: Khasawinah and Grutsch, 1989a Velsicol Corp., 1983

Type of studies: Chronic toxicity and tumorigenicity test in mice

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
80/sex/group (mice)

D. Number of doses in the dose range?

4 doses in the dose range: 0, 1, 5 or 12.5 ppm

E. Critical effect?
Hepatic necrosis

Route of exposure that yielded the critical effect?
Oral intake

Mechanism of action for the critical effect observed, if known?
Not stated

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain.
ICR mice

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?

UF = 300

inter-species and intra-species variability
100: 10 intra-species, 10 inter-species

inter-human variability
n/a

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
3 to account for lack of reproductive studies.

Identify the MF (modifying factor) used, if any, and its basis.
1

In your judgment, is the critical effect identified relevant to humans?
Based on available occupational studies, although limited, the critical effect does not appear to be relevant to humans. These studies give no indication that the liver is the target organ as a result of chronic exposure to low levels of chlordane. Rather, recent epidemiological findings indicate that neurotoxicity may be a relevant endpoint in humans exposed to chlordane.

Is the route of exposure relevant to humans?
Chlordane, a pesticide, is commonly used by farmers and in manufacturing plants. Humans are likely to be exposed to chlordane via inhalation of vapors or via ingestion of crops. Therefore, the route of exposure is considered relevant to humans.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Medium. Neurotoxicity was not looked at as an endpoint in the chronic animal studies.

Risk Factor: *RfC*

Dates of studies: Khasawinah et al., 1989a,b

Type of studies: Inhalation toxicity

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
Khasawinah et al., 1989a: (35 to 47/sex/group)
Khasawinah et al., 1989b: (10/sex/group)

D. Number of doses in the dose range?
Khasawinah et al., 1989a: 4 doses in the dose range: 0, 0.1, 1.0 or 10 mg/m^3
Khasawinah et al., 1989b: 5 doses in the dose range: 0, 5.8, 28.2, 154 or 416 mg/m^3

E. Critical effect?
Hepatic effects

Route of exposure that yielded the critical effect?
Inhalation

Mechanism of action for the critical effect observed, if known?
Not stated

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain.

Wistar rats (in both studies)

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

Uncertainty Factor & Basis, breaking down the UF into its component
parts, as necessary. Were the following considered?

UF= 1000

inter-species and intra-species variability
3 10

inter-human variability
n/a

extrapolation from less-than-chronic to chronic toxicity
10

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
3 to account for lack of reproductive studies.

Identify the MF (modifying factor) used, if any, and its basis.
1

In your judgment, is the critical effect identified relevant to humans?
The critical effect does not appear to be relevant to humans because the human data (albeit limited) give no indication that the liver is a target organ of chronic exposure to low levels of chlordane. According to recent epidemiological findings, neurotoxicity may be a more relevant endpoint in humans.

Is the route of exposure relevant to humans?
The route of exposure is considered relevant to humans. For example, farmers, pesticide workers or employees at organochlorine pesticide manufacturing plants may be exposed to chlordane via inhalation.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Low. No chronic animal studies examined neurotoxicity, no multigenerational reproductive studies exist and studies on pre- and postnatal animals indicate chlordane mimicry of sex steroids which raises reproductive concerns.

Risk Factor: *CSF*

Dates of principal studies:
IRDC, 1973
NCI, 1977

Khasawinah and Grutsch, 1989b

Type of studies:
Tumorgenicity studies in mice

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
IRDC, 1973: 100 male and 100 female mice
NCI, 1977: 50 male and 50 female mice
Khasawinah and Grutsch, 1989b: 80/sex/group (mice)

D. Number of doses in the dose range?
IRDC, 1973: 4 doses in the dose range: 0,5,25, or 50 ppm
NCI, 1977: 4 doses in the dose range: Male: 0, 29.9, or 56.2 ppm. Female: 0, 30.1, or 63.8 ppm
Khasawinah and Grutsch, 1989b: 4 doses in the dose range: 0, 1, 5, 12.5 ppm

E. Critical effect?
Hepatocellular carcinoma - All studies

Route of exposure that yielded the critical effect?
Oral intake

Mechanism of action for the critical effect observed, if known?
Animal studies: Several toxicological properties have been described which may play roles in the expression of chlordane carcinogenicity in rodents, including chlordane induction of hair follicle nuclear aberrations in CD-1 mice, irreversible binding of chlordane metabolite to intracellular macromolecules, including DNA and RNA, chlordane inhibition of intercellular communication, chlordane stimulation of protein kinase C activity, chlordane induction of *in vitro* hepatic lipid peroxidation and DNA single-strand breaks, and chlordane suppression of *in vitro* immune responses.

For human data:

Was a sensitive sub-population included?
Not stated

For animal data:

Note species/strain.
Khasawunah and Grutsch, 1989b: ICR mice
IRDC, 1973: CD-1 mice
NCI, 1977: B6C3F1 mice

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

In your judgment, is the critical effect identified relevant to humans?
It does not appear that the critical effect is relevant to humans based on the available data. Human epidemiology studies of chlordane show very different effects than the critical effect (hepatocellular carcinoma). These effects in humans include non-Hodgkin's lymphoma in farmers and cases of aplastic anemia associated with home use of chlordane.

Is the route of exposure relevant to humans?
Incidental ingestion of chlordane is a relevant route of exposure in humans.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Animal studies: High
Human studies: Tentative at best

References

Barrass, N., M. Stewart, S. Warbuton, J. Aitchison, D. Jackson, P. Wadsworth, A. Marsden, and T. Orton. 1993. Cell proliferation in the liver and thyroid of C57B1/10J mice after dietary administration of chlordane. *Environ. Health Perspect*. 101(suppl.5): 219-224.

Brown, D.P. 1992. Mortality of workers employed at organochlorine pesticide manufacturing plants – an update. *Scand. J. Work Environ. Health*. 18:155-161.

Brown, L.M., A. Blaair, R. Gibson, G.D. Everett, K.P. Cantor, M. Schuman, L.F. Burmeister, S. F. Van Lier and F. Dick. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res*. 50:6,585-6,591.

Brown, L.M., L. F. Burmeister, G.D. Eeverett, and A. Blair. 1993. Pesticide exposures and multiple myeloma in Iowa men. *Cancer Causes Control*. 4:153-156.

Caldwell, G.G., S. B. Cannon, C.B. Pratt, and R. D. Arthur. 1981. Serum pesticide levels in patients with childhood colorectal carcinoma. *Cancer*. 48:774-778.

Cantor, K.P., A. Blair, G. Everett, R. Gibson, L.F. Burmeister, L.M. Brown, L. Schuman, and F.R. Dick. 1992. Pesticides and other agricultural risk factors for Non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res*. 52:2,447-2,455.

EPA. 1997. Toxicological Review of Chlordane (Technical). In Support of Summary Information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency. Washington, D.C. December.

Epstein, S. S., and D. Ozonoff. 1987. Leukemias and blood dyscrasias following exposure to chlordane and heptachlor. *Teratog. Carcinogen. Mutagen*. 7(6):527-540.

Falck, F., A. Ricci, M. S. Wolff, J. Godbold, and P. Deckers. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch. Environ. Health*. 47:143-146.

Infante, P., S. S. Epstein, and W. A. Newton, Jr. 1978. Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. *Scand. J. Work Environ. Health* 4:137-150.

IRDC (International Research and Development Corporation). 1973. Eighteen-month oral carcinogenic study of chlordane in mice. Unpublished report to Velsicol Chemical Corporation. MRID No.00067568. Available from U.S. Environmental Protection Agency.

Khasawinah, A.M. and J.F. Grutsch. 1989a. Chlordane: 24-month tumorigenicity and chronic toxicity test in mice. *Regul. Toxicol. Pharmacol*. 10:244-254.

Khasawinah, A.M. and J.F. Grutsch. 1989b. Chlordane: thirty-month tumorigenicity and chronic toxicity test in mice. *Regul. Toxicol. Pharmacol*. 10(2):95-109.

Khasawinah, A., C.Hardy, and G. Clark. 1989a. Comparative inhalation toxicity of technical chlordane in rats and monkeys. *J. Toxicol. Environ. Health* 28(3):327-347. (The 90-day rat study).

Khasawinah, A., C. Hardy and G. Clark. 1989b. Comparative inhalation toxicity of technical chlordane in rats and monkeys. *J. Toxicol. Environ. Health* 28(3):327-347. (The 28-day rat study).

Malarkey, D.E., T. R. Devereux, G.E. Dinse, P. C. Mann, and R. R. Maronpot. 1995. Hepatocarcinogenicity of chlordane in B6C3F1 and B6D2F1 male mice: evidence for regression in B6C3F1 mice and carcinogenesis independent of ras proto-oncogene activation. *Carcinogenesis* 16:2,617-2,625.

NCI (National Cancer Institute). 1977. Bioassay of chlordane for possible carcinogenicity. Technical Report Series No. 8. U. S. Department of Health, Education and Welfare; National Institutes of Health. PB271/977.

Pesatori, A.C., J. M. Sonntag, J. H. Lubin, d. Consonni, and A. Blair. 1994. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). *Cancer Causes Control*. 5:310-318.

Shindell, S. and S. Ulrich. 1986. Mortality of workers employed in the manufacture of chlordane: an update. *J. Occup. Med*. 28:497-501.

Teufel, M., K. H. Niessen, J. Sartoris, W. Brands, H. Lochbuhler, K. Waag, P. Schweizer, and G. V. Oelsnitz. 1990. Chlorinated hydrocarbons in fat tissue: Analyses of residues in healthy children, tumor patients and malformed children. *Arch. Environ. Contam. Toxicol*. 19:646-652.

Velsicol Chemical Corporation. 1983. Twenty-four month chronic toxicity and tumorigenicity test in mice by chlordane technical. Unpublished study by Research Institute for Animal Science in Biochemistry and Toxicology, Japan. MRID No. 00144312, 00132566. Available from U.S. EPA.

Wang, H. H. and B. MacMahon. 1979. Mortality of pesticide applicators. *J. Occup. Med*. 21:741-744.

Woods, J.S., L. Polissar, R. K. Severson, L. S. Heuser, and B. G. Kulander. 1987. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J. Natl. Cancer Inst*. 78(5):899-910.

CHROMIUM III, INSOLUBLE SALTS
Pilot Assessment

1. RfD: Unlike other Pilot chemicals, very little detail is presented on the principal study and there are no supporting studies. Little discussion is provided of the uncertainties, although it is quite evident that a great deal of uncertainty exists with the underlying data. EPA has attempted to characterize this uncertainty by applying a modifying factor of 10. The modifying factor accounts for the lack of studies, for the uncertainty regarding potential reproductive effects of Chromium III, and for the uncertainties regarding the NOAEL derived from the principal study. In the Confidence section, EPA acknowledges that the RfD may be overprotective due to the uncertainty. In our general comments, we recommend a probabilistic approach to characterize the uncertainty associated with noncarcinogenic toxicity criteria. We demonstrate this approach with Chromium III. The results clearly show the conservative nature of the RfD as derived by EPA's assessment.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: Group D - not classified as to its human carcinogenicity.

RfD: 1.5E+0 mg/kg-day

RfC: Not available

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

CSF: Akatsuka and Fairhall, 1934; Baetjer et al., 1959; Hueper and Payne, 1962; Schroader et al., 1965; Venitt and Levy, 1974; Ivankovic and Preussman, 1975; Levy and Venitt, 1975; Petrilli and DeFlora, 1977, 1978 a,b; Nakamuro et al., 1978; Levy and Martin, 1983; EPA, 1984, 1986, 1996, 1998; IARC, 1990; Lees et al., 1995

RfD: Ivankovic and Preussman, 1975; Zahid et al., 1980; EPA, 1984, 1988; NCR, 1989; Anderson, 1993, 1995; Finley et al., 1993; DHHS and FDA, 1995; NTP, 1996 a,b,1997; Elbetieha and Al-Hamood, 1997

RfC: Akatsuka and Fairhall, 1934; Baetjer et al., 1959; Hueper and Payne, 1962; Levy and Venitt, 1975; Johansson et al., 1980; Levy and Martin, 1983; EPA, 1989, 1994, 1998

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: n/a

RfD: NOAEL (ADJ): 1,468 mg/kg-day

RfC: n/a

Identify:

Risk Factor: *RfD*

Date of study: Ivankovic and Preussman, 1975

Type of study: Chronic feeding study

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
Part 1 - groups of 60 male and female rats
Part 2 - 12-19 rats/group

D. Number of doses in the dose range?
Part 1 - 4 doses: 0, 1%, 2%, or 5% (360, 720 or 1,800 g/kg BW)
Part 2 - 3 doses: 0, 2%, or 5% (5% equivalent to 1,400 mg/kg-day)

Critical effect?
No effects observed

Route of exposure that yielded the critical effect?
Oral

Mechanism of action for the critical effect observed, if known?
n/a

For human data:

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain.
Rats

Was the species/strain known to be genetically sensitive?
n/a

To have any genetic peculiarity with regard to the toxicity of the compound?
n/a

J. Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?

UF = 100

inter-species and intra-species variability
10

inter-human variability
10

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
n/a

K. Identify the MF (modifying factor) used, if any, and its basis.
A 10-fold modifying factor was applied to reflect database deficiencies including the lack of a study in a nonrodent mammal, lack of unequivocal data evaluating reproductive impacts, and the concern regarding potential reproductive effects raised by the study of Elbetieha and Al-Hamood (1997).

L. In your judgment, is the critical effect identified relevant to humans?
No effects were observed.

Is the route of exposure relevant to humans?
Trivalent chromium is an essential element that potentiates insulin action in
peripheral tissue and is essential in the metabolism of lipids, proteins and fats. Therefore, oral ingestion of chromium III is a relevant route of exposure for humans.

M. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Low confidence due to lack of detail in the Ivankovic and Preussman (1975) study protocol and results. Furthermore data on reproductive and developmental effects of Cr (III) were lacking. The RfD should be considered conservative, since the MF addresses only those factors that might lower the RfD.

References

Akatsuka, K.; J. Fairhall. 1934. The toxicology of chromium. *J Ind Hyg* 16:1-24 (cited in EPA, 1983).

Anderson, RA. 1993. Recent advances in the clinical and biochemical effects of chromium deficiency. *Prog. Clin. Biol. Res.* 380:221-234.

Anderson, RA. 1995. Chromium and parental nutrition. *Nutr* 11(1 suppl.):83-86.

Baetjer, AM; Lowney, JF; Steffe, H.; et al. 1959. Effect of chromium on incidence of lung tumors in mice and rats. *Arch Ind Health* 20:124-135 (cited in EPA, 1983).

Elbetieha, A., Al-Hamood, M.H. 1997. Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: effect on fertility. *Toxicology* 116:19-47.

Finley, BL; Johnson, EM; Holson, JF. 1993. Comment on "Comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse." *Toxicol Env Chem.* 39:133-137.

Hueper, WC.; Payne, WW. 1962. Experimental studies in metal carcinogenesis--chromium, nickel, iron, arsenic. *Arch Environ Health* 5:445-462 (cited in EPA, 1983).

International Agency for Research on Cancer (IARC). 1990. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: some metals and metallic compounds. Lyon, France: World Health Organization, IARC.

Ivankovic, S., Preussman, R. 1975. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. *Food Cosmet Toxicol.* 13(3):347-351.

Johansson, A.; Lundborg, M.; Hellstrom, P. et al. 1980. Effect of iron, cobalt, and chromium dust on rabbit alveolar macrophages: a comparison with the effects of nickel dust. *Environ Res.* 21:165-176.

Lees, PSJ; Gibb, HJ; Rooney, BC. 1995. Derivation of exposure-response relationship for chromium from historic exposure data. 11th International Symposium of Epidemiology in Occupational Health, the Netherlands, September 1995.

Levy, LS.; Martin, PA. 1983. The effects of a range of chromium-containing materials on rat lung. Dye Color Manufacturers Association.

Levy, LS.; Venitt, S. 1975. Carcinogenic and mutagenic activity of chromium-containing materials. *BR J Cancer* 32:254-255 (cited in EPA, 1983).

Levy, LS; Martin, PA. 1983. The effects of a range of chromium-containing materials on rat lung. Dye Color Manufacturers Association.

Nakamuro, K.; Yoshikawa, K., Sayato, Y. et al. 1978. Comparative studies of chromosomal aberration and mutagenicity of trivalent and hexavalent chromium. *Mutat Res* 58:175-181.

National Research Council (NCR). 1989. Recommended dietary allowances. 10th ed. Washington, DC: National Academy of Sciences, 241-243.

National Toxicology Program (NTP). 1996a. Final Report. Potassium dichromate (hexavalent): The effects of potassium dichromate on Sprague-Dawley rats when administered in the diet. December 13, 1996.

NTP. 1996b. Final Report. Potassium dichromate (hexavalent): the effects of potassium dichromate in BALB/c mice when administered in the diet. November 27, 1996.

NTP. 1997. Final Report. Potassium dichromate (hexavalent): reproductive assessment by continuous breeding when administered to BALB/c mice in the diet. February 18, 1997.

Petrilli, FL; DeFlora, S. 1977. Toxicity and mutagenicity of hexavalent chromium on Salmonella typhinurium. *Appl Environ Microbiol.* 33:805-809.

Petrilli, FL; DeFlora, S. 1978a. Oxidation of inactive trivalent chromium to the mutagenic hexavalent form. *Mutat Res.* 58:167-178.

Petrilli, FL., DeFlora, S. 1978b. Metabolic deactivation of hexavalent chromium mutagenicity. *Mutat Res.* 54:139-147.

Schroeder, HA; Balassa, JJ; Vinton, WH, Jr. 1965. Chromium, cadmium and lead in rats: effects on lifespan, tumors, and tissue levels. *J Nutr.* 86:51-66.

EPA. 1983. Health assessment document for chromium. Prepared by the Environmental Criteria and Assessment Office, Research Triangle Park, NC. External review draft. EPA/600/8-83-014A. NTIS PB 83-252205.

EPA. 1984. Health effects assessment for trivalent chromium. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA, for the Office of Solid Waste and Emergency Response, Washington, DC.

EPA. 1986. Guidelines for carcinogen risk assessment. *Federal Register* 51(185):33992-34003. September 24.

EPA. 1988. Toxicological review of trivalent chromium. Available online at http://www.epa.gov/iris.

EPA. 1989. Interim methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-90/066F.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-90/066F.

EPA. 1996. Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960-18011. April 23.

EPA. 1998. Toxicological review of trivalent chromium. Available online at../index.html.

U.S. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA). 1995. Food labeling: reference daily intakes, final rule. 21 CFR Part 101. *Federal Register* 60(249):67164-67175.

Venitt, S; Levy, LS. 1974. Mutagenicity of chromates in bacteria and its relevance to chromate carcinogenesis. *Nature* 250:493-495.

Zahid, ZR; Al-Hakkak, ZS; Kadhim, AHH; et al. 1980. Comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse. *Toxicol Environ Chem.* 25:131-136.

1,2-DIBROMO-3-CHLOROPROPANE (DBCP)
Pre-Pilot Assessment

RfC: Although DBCP is a pre-Pilot chemical, more data are provided than for other pre-Pilots that we reviewed. Uncertainty accounts for inter and intraspecies differences, for subchronic to chronic and for database insufficiencies. More discussion regarding the uncertainty associated with the lack of developmental toxicity studies would be useful. As discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty associated with the underlying data.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: Not available at this time

RfD: Not available at this time

RfC: 2E-4 mg/m^3

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

CSF: n/a

RfD: n/a

RfC: Rao et al. (1982)

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: n/a

RfD: n/a

RfC: NOAEL: 0.94 mg/m^3
NOAEL: (human equivalent concentration, HEC): 0.17 mg/m^3

Identify:

Risk Factor: *RfC*

Date of study: 1982

Type of study: Subchronic inhalation study

Was the risk factor based on human data (describe) or on animal data?
Animal data - 6 month old male New Zealand white rabbits

How many subjects in the critical stud(ies)?
10/dose group

D. Number of doses in the dose range?
4 doses in the dose range: 0, 0.1, 1 or 10 ppm (0, 0.94, 9.4, or 94 mg/m^3)
Duration - adjusted doses: 0, 0.17, 1.7 and 17 mg/m^3

E. Critical effect?
Testicular effects

Route of exposure that yielded the critical effect?
Inhalation

Mechanism of action for the critical effect observed, if known?
Follicle stimulating hormone (FSH)

For human data: n/a

Was a sensitive sub-population included?
n/a
For animal data:

Note species/strain
6 month old male New Zealand white rabbits

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
n/a

Uncertainty Factor & Basis, breaking down the UF into its component
parts, as necessary. Were the following considered?

UF = 1000

inter-species and intra-species variability
3

inter-human variability
10

extrapolation from less-than-chronic to chronic toxicity and extrapolation from LOAEL to NOAEL
10

data-base insufficiencies (e.g. too few studies, limited types of studies)
3 to account for lack of a multigenerational reproductive study and inhalation development toxicity studies.

Identify the MF (modifying factor) used, if any, and its basis.
None

In your judgment, is the critical effect identified relevant to humans?

The critical effect appears to be relevant in humans as it has been seen in a number of occupational studies. Testicular effects (i.e., azoospermic or oligospermic) have been reported in male workers at DBCP production facilities.

Is the route of exposure relevant to humans?
The route of exposure appears to be relevant to humans although none of the occupational studies to date have evaluated the possible respiratory tract effects of DBCP exposure.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Confidence in the inhalation RfC -- medium

References

Rao, K.S., J.D. Burek, F.Murray, et al. 1982. Toxicologic and reproductive effects of inhaled 1,2-dibromo-3-chloropropane in male rabbits. *Fund. Appl. Toxicol* 2 (5): 241-251.

HEXACHLOROBENZENE
Pre-Pilot Assessment

RfD: As a pre-Pilot chemical, limited data are provided in the IRIS assessment. Uncertainty accounts for inter and intraspecies differences. No evaluation is made of database insufficiencies and limited information is provided regarding the confidence in the RfD. Uncertainty in whether the RfD is protective for the sensitive endpoint of porphyria is discussed, but not adequately characterized. An evaluation like those done for the Pilot chemicals would more adequately characterize uncertainty and variability. However, as discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty.

CSF: In comparison to Pilot chemicals, EPA did not characterize uncertainty to an appropriate extent. The slope factor is extrapolated from the linear no-threshold dose-response curve. As discussed in our general comments, use of an upper-bound estimate from a linear model precludes a proper evaluation of uncertainty.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: 1.6 $(mg/kg\text{-}day)^{-1}$

RfD: 8E-4 mg/kg-day

RfC: Not able to be derived

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

CSF: Human: Cripps et al., 1984.

Animal: Cabral et al., 1977,1979; Shirai et al., 1978; Smith and Cabral, 1980; Arnold et al., 1985; Erturk et al., 1986.

RfD: Arnold et al., 1985.

RfC: n/a

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: B2; probable human carcinogen

RfD: NOAEL: 0.08 mg/kg-day (1.6 ppm - diet)

RfC: n/a

Identify:

Risk Factor: *CSF*
Date of study: Erturk et al., 1986

Type of study: Feeding study

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
94 Sprague-Dawley rats/sex/dose

D. Number of doses in the dose range?
3 doses in the dose range: 0, 75, or 150 ppm

E. Critical effect?
Hepatocellular carcinoma

Route of exposure that yielded the critical effect?
Diet/oral

Mechanism of action for the critical effect observed, if known?
Not stated

For human data:

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain.
Sprague-Dawley rats

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?

Significant increases in malignant tumors were observed among an adequate number of animals observed for their lifetime. Slope factors have been calculated from 14 different data sets encompassing 3 species, 4 studies and various endpoints. Those fell within the range of approximately 1 order of magnitude.

inter-species and intra-species variability
n/a

inter-human variability
n/a

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
n/a

Identify the MF (modifying factor) used, if any, and its basis.
None

In your judgment, is the critical effect identified relevant to humans?
It does not appear that the critical effect is relevant to humans based on available data. Although human studies of hexachlorobenzene are considered inadequate and limited, the primary effects caused by ingestion include death, porphyria and enlarged thyroids with no mention of hepatocellular carcinoma, the critical effect.

Is the route of exposure relevant to humans?
Based on the limited and inadequate human studies, it does not appear that the route of exposure is relevant to humans.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Inadequate human data
Sufficient animal data

Risk Factor: *RfD*

Date of study: Arnold et al., 1985

Type of study: Feeding study

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
50 Sprague-Dawley males and 50 females per dose group

D. Number of doses in the dose range?
5 doses in the dose range: 0, 0.32, 1.6, 8.0, or 40 ppm

E. Critical effect?
8.0 ppm group - hepatic centrilobular basophilic chromogenesis
40 ppm group - mortality, hepatic centrilobular basophilic chromogenesis, and severe chronic nephrosis (males only).

Route of exposure that yielded the critical effect?
Diet/oral

Mechanism of action for the critical effect observed, if known?
Not stated

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain.
Sprague-Dawley rats

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

J. Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?

UF= 100

inter-species and intra-species variability
100: 10 interspecies, 10 intraspecies

inter-human variability
n/a

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
n/a

K. Identify the MF (modifying factor) used, if any, and its basis.
None

In your judgment, is the critical effect identified relevant to humans?
The critical effect does not appear to be relevant to humans because the available human data do not show liver effects, specifically centrilobular basophilic chromogenesis. The primary effects seen in humans include skin lesions, pink sore disease, hypertrichosis and hyperpigmentation.

Is the route of exposure relevant to humans?
The route of exposure does appear to be relevant to humans based on the available studies.

What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Medium. Exposure to hexachlorobenzene is linked to porphyria cutanea tarda (PCT) in humans, but these data cannot be used to quantitative risk because accurate exposure data are lacking. Medium rating is due to the fact that PCT was not evaluated in the principal animal study.

References

Arnold, D. L., C.A. Moodie, S.M. Charbonneau et al. 1985. Long term toxicology of hexachlorobenzene in the rat and the effect of dietary vitamin A. *Fd. Chem. Toxicol.* 23(9):779-793.

Cabral, J.R.P., C.A. Moodie, S.M. Charbonneau, et al. 1977. Carcinogenic activity of hexachlorobenzene in hamsters. *Nature* 269:510-511.

Cabral, J.R.P., T. Mollner, F. Raitano and P. Shubik. 1979. Carcinogenesis of hexachlorobenzene in mice. *Int. J. Cancer* 23(1):47-51.

Cripps, D.J., H.A. Peters, A. Gocmen and I. Dogramaci. 1984. Porphyria turcica due to hexachlorobenzene: A 20- to 30-year follow-up study on 204 patients. *Br. J. Dermatol* 111:413-422.

Erturk, E., R.W. Lambrecht, H.A. Peters, D.J. Cripps, A. Gocmen, C.R. Morris and G.T. Bryan. 1986. Oncogenicity of hexachlorobenzene. In: Hexachlorobenzene: Proc. Int. Symp., C.R. Morris and J.R.P. Cabral, Ed. IAR Scientific Publ. No. 77, Oxford University Press, Oxford. P. 417-423.

Smith, A.G. and J.R. Cabral. 1980. Liver-cell tumors in rats fed hexachlorobenzene. *Cancer Lett.* 11(2):169-172.

PROCHLORAZ
Pre-Pilot Assessment

RfD: As a pre-Pilot chemical, limited data are provided in the IRIS assessment. Uncertainty accounts only for inter and intraspecies differences. No evaluation is made of database insufficiencies and very little information is provided regarding the confidence in the underlying data for the RfD. Uncertainty is not well characterized. An evaluation similar to those done for the Pilot chemicals would more adequately characterize uncertainty and variability. However, as discussed in the general comments, a probabilistic approach would more fully characterize the uncertainty.

CSF: In comparison to Pilot chemicals, EPA did not characterize uncertainty to an appropriate extent. The slope factor is extrapolated from the linear no-threshold dose-response curve. As discussed in our general comments, use of an upper-bound estimate from a linear model precludes a proper evaluation of uncertainty.

Identify all risk factors addressed by the IRIS assessment under review: e.g. Q-star or Slope Factor, RfD, RfC, etc.

CSF: 1.5E-1 $(mg/kg\text{-}day)^{-1}$

RfD: 9E-3 mg/kg-day

RfC: n/a

List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

CSF: Human: none
Animal: Nor-Am Chemical Co., 1982, 1983.

RfD: FBC Limited, 1981.

RfC: none

Identify the basis for each risk factor: (e.g. NOAEL, NOEL, LOAEL, LOEL, BMD, etc).

CSF: Classification--C; possible human carcinogen. Basis--Statistically significant increased incidence and dose related trend in liver adenomas and carcinomas (combined) in both sexes of 1 strain of mouse.

RfD: NOEL: 0.90 mg/kg-day (30 ppm)

RfC: n/a

Identify:

Risk Factor: *RfD*

Date of study: 1981

Type of study: 2-year feeding study

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
5 dogs/sex/dose

D. Number of doses in the dose range?
4 doses in the dose range; 0, 30, 135 or 600 ppm (male: 0, 0.94, 4.47, 18.1 or 28.9 mg/kg-day; female: 0, 0.90, 4.0, 18.0 or 27.5 mg/kg-day)

E. Critical effect?
Increase in serum alkaline phosphatase (SAP) and liver weights, liver histopathology

Route of exposure that yielded the critical effect?
Oral

Mechanism of action for the critical effect observed, if known?
SAP increase

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain:
Pure bred Beagle dogs

Was the species/strain known to be genetically sensitive?
Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

J. Uncertainty Factor & Basis, breaking down the UF into its component parts, as necessary. Were the following considered?

UF = 100

inter-species and intra-species variability
10 10

inter-human variability
n/a

extrapolation from less-than-chronic to chronic toxicity
n/a

extrapolation from LOAEL to NOAEL
n/a

data-base insufficiencies (e.g. too few studies, limited types of studies)
n/a

K. Identify the MF (modifying factor) used, if any, and its basis.
None

L. In your judgment, is the critical effect identified relevant to humans?
It can not be determined whether the critical effect is relevant to humans because no human information is available on the oral toxicity of prochloraz.

Is the route of exposure relevant to humans?
Because no human data are available, it can not be determined whether the route of exposure is relevant to humans.

M. What is the overall confidence rating for the data used to derive the
overall slope factor or RfD, or RfC?
High. Critical study deemed adequate and received a medium confidence rating. Supporting data deemed high, so RfD was rated high.

Risk Factor: *CSF*

Date of study: 1983

Type of study: 2-Year feeding study

Was the risk factor based on human data (describe) or on animal data?
Animal data

How many subjects in the critical stud(ies)?
52/sex/group

D. Number of doses in the dose range?
4 doses in the dose range; 0, 78, 325, or 1300 ppm

E. Critical effect?
Liver adenoma/carcinoma combined

Route of exposure that yielded the critical effect?
Oral

Mechanism of action for the critical effect observed, if known?
Not stated

For human data: n/a

Was a sensitive sub-population included?
n/a

For animal data:

Note species/strain:
CD-1 mice, male and female

Was the species/strain known to be genetically sensitive? Not stated

To have any genetic peculiarity with regard to the toxicity of the compound?
Not stated

J. Identify the MF (modifying factor) used, if any, and its basis.
None

K. In your judgment, is the critical effect identified relevant to humans?
It can not be determined whether the critical effect is relevant to humans because no human information is available on the oral toxicity of prochloraz.

Is the route of exposure relevant to humans?
Because no human data are available, it can not be determined whether the route of exposure is relevant to humans.

L. What is the overall confidence rating for the data used to derive the overall slope factor or RfD, or RfC?
Confidence in the risk estimate based on adequate number of animals, lifetime exposure and adequate dose selection.

References

FBC Limited. 1981. MRID No. 40267708. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460

Nor-Am Chemical Co. 1982. MRID No. 40267708. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460.

Nor-Am Chemical Co. 1983. MRID No. 00150409. Available from EPA. Write to FOI, EPA, Washington, D. C. 20460.

Patricia M. McGinnis, Ph.D., DABT

Patricia M. McGinnis

General Comments

As a toxicologist and risk assessor, I am a user of the Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) database. I have been involved in the preparation of draft assessments under contract to EPA for numerous chemicals, many of which are included in some form on IRIS. My comments should be taken in the context of my biologically-based background and experience with EPA risk assessment.

IRIS is intended for the general health scientist without extensive training in toxicology. It represents a summary of an EPA consensus opinion/position on chemical hazard identification, dose-response assessment, and characterization (www.epa.gov/ngispgm3.iris/intro.html). IRIS presents background documents for RfD and cancer assessments, and reference to EPA guidelines other guidance source documents (www.epa.gov/ngispgm3.iris/backgr-d.html). Many of these source documents (e.g., Neurotoxicity Guidelines) discuss variability and uncertainty. However, there is no Agency guidance or source document for RfDs. The guidelines for Exposure Assessment (U.S. EPA, 1992) and EPA's Exposure Factors Handbook (U.S. EPA, 1997) also present a discussion of variability and uncertainty, in general, as well as for many of the unit conversions and adjustments (e.g., water consumption, air intake) used on IRIS. It should be noted that the majority of these reference sources are from after 1994, whereas IRIS assessments date back to 1985.

I reviewed eight chemicals, six pre-pilot and two pilot/post-pilots, spanning from 1985 to 1999 and including RfDs, RfCs, and cancer assessments. In general, EPA characterized the uncertainty and variability in data used to develop the IRIS health assessments in a manner consistent with practices at the time that the assessment was conducted. Sometimes the characterization is in the source document and not on IRIS. There appeared to be an evolution of the approaches for the assessments with better descriptions of individual studies, their strengths and weaknesses, synthesis of the scientific data (including mechanism of action, relevance to humans), and narratives of what scientific information is known and what the data gaps are that contribute to uncertainty. The level of scientific analysis and characterization of variability and uncertainty vary amongst chemicals as well as between assessments (RfD, RfC, cancer) for the same chemical. Sometimes variability and uncertainty are noted to exist but not further characterized. This appears to be due to variations in the depth and breath of scientific information as well as a lack of a standardized approach. While post-pilot assessments generally characterize uncertainty better than the pre-pilot assessment and are moving towards describing the basis behind the interpretation of data, selection of critical effects, principal studies, applied models, data gaps, susceptible populations, and confidence, progress still needs to be made. Uncertainty is generally simply quantitated as a geometric mean, range, or uncertainty factor. (I did not review any assessments with sophisticated uncertainty analysis. I'm not sure I would have understood the latter or whether it would have significantly affected my understanding of the assessment or my review.)

I think EPA needs to further develop their efforts to characterize the range of variability and uncertainty and include scientific information that is important and relevant to human health risk assessment. These characterizations should be based on updated scientific information, be peer-reviewed, and remain primarily qualitative or simply quantitated given the IRIS audience (more sophisticated analyses could be in supporting documents). Characterizations should *explicitly* state assumptions, what is known/unknown, and what is scientific judgement/interpretation and what is an agency policy. In addition, EPA needs to be more timely in updating the assessments for important environmental chemicals.

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

Yes. The updated cancer assessment is one of the best health assessments I have reviewed for this project as far as characterizing uncertainty and variability.

I am not familiar with the primary literature on benzene. However, from reading the IRIS summary and background documents, EPA appears to have thoroughly and even-handedly presented recent scientific findings for benzene and to have discussed the important uncertainties in this health assessment. EPA laid out in narrative form uncertainty in: the exposure measurements for the principal study (Rinsky et al., 1981, 1987); reconstructing or estimating exposures for the early years of this cohort for dose-response assessment; mode of leukemogenesis and hematotoxicity; metabolism of benzene; shape of the dose response model; choice of extrapolation model; and potential sensitive subpopulations. Uncertainty is generally characterized qualitatively as a narrative. Expression of the unit risk as a range captures uncertainty in the exposure-response relationship as well as in the choice of linear models.

Use of the linear low-dose extrapolation is consistent with the 1996 proposed cancer guidelines. Some scientists might argue that a quantitative approach for determining unit risk using both linear and nonlinear models should be presented. However, EPA has adequately described the uncertainties relating to mode of action of benzene at low doses (sub-linear, linear, and even supra-linear responses). I think it would be difficult to quantitatively account for low-dose biological uncertainties without additional data as to mechanism(s) for benzene-induced leukemia.

U.S. EPA (1999) reviews the data for oral, dermal and inhalation absorption for benzene in animals and humans. Population variability in intake for various media is mentioned and refers to EPA's Exposure Factors Handbook (U.S. EPA, 1997) for further information. The basis for using absorption values other than default values in the route extrapolation appears adequately justified. It is forward move towards evaluating and utilizing the scientific information at hand to make a data-derived assessment rather than using a default procedure or waiting for more sophisticated tools before making a decision.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This assessment does a very good job of presenting a historical picture of previous Agency assessments, evaluating recent scientific information for benzene (including alternate hypotheses and approaches), explaining to the reader the rationale for decisions (whether it be data-based or science policy), and noting data deficiencies and research needs.

Compared with the pre-pilot assessments for pesticides that I have reviewed, this pilot/post-pilot assessment is a vast improvement in integrating recent science into the risk assessment and characterizing data limitations and uncertainties, and alternative approaches. This is the direction that the Agency needs to be going.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

Yes. This is particularly evident in their critical evaluation of the epidemiologic data and discussion on mode of action.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

Yes. The Additional Comments and Discussion of Confidence Sections (II.B.3, II.B.4, II.C.3, II.C.4) do a good job of summarizing these uncertainties.

D. Are there other relevant observations or comments?

I did find the inhalation quantitative risk assessment difficult to thoroughly understand. The work of Crump (1992, 1994) and Paustenbach et al. (1993) is summarized in the support document (U.S. EPA, 1998), but it is still difficult for a biology-based toxicologist to follow (e.g., where the numbers in Table 4, page 33 came from). According to the Introduction to IRIS (**http://www.epa-gov/ngispgm3/iris/intro.html)**, the information in IRIS "is intended for those without extensive training in toxicology, but with some knowledge of health sciences". I think this quantitation is above the general IRIS audience.

IRIS makes it perfectly clear that the choice of a linear extrapolation approach is a science policy default given the limitations in the state of knowledge about biological mechanisms of benzene leukemogenesis at low, environmental doses. Further, IRIS points out that this approach may under- or over-estimate the true risk. The support document does not explicitly state these points, but it should.

In the discussion of nonlinearity, the 1996 proposed cancer guidelines imply a sub-linear response. Is use of linear approach using the MLE sufficiently protective for a potential supra-linear response at low doses? Is this approach (conducted prior to proposed guidelines) consistent with proposed guidelines linear default approach?

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– No data

RfC– No data
Carcinogenicity Assessment– On line 01/19/2000; OSF and URI

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0276.html**), and Interim Quantitative Cancer Unit Risk Estimates Due to Inhalation of Benzene (U.S. EPA, 1985), Carcinogenic Effects of Benzene: An Update (U.S. EPA, 1998 and Response to the Peer Review), and Extrapolation of the Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure (U.S. EPA, 1999 and Response to the Peer Review Comments). I also looked through ATSDR (1997). It would have been helpful to have U.S. EPA (1979) just to look at quickly as IRIS states that it and U.S. EPA (1985) provide the basis for the classification of benzene as a Group A Carcinogen. Crump (1992,1994) and Paustenbach et al. (1993) are needed in order to really understand the basis of the quantitative estimate; these were not provided.

On IRIS:

RfD– NA

RfC– NA

Cancer– Several epidemiologic studies are briefly described. An overview of the database of supporting animal, metabolism, and mode of action studies is presented. Benzene is classified as "known" human carcinogen (Category A) under 1986 guidelines, and a known human carcinogen for all routes of exposure based on convincing human evidence and supporting animal evidence.

4. Identify the basis for each risk factor.

RfD– NA

RfC– NA

Carcinogenicity Assessment– Benzene is classified as a known human carcinogen by both the 1986 and 1996 (proposed) Agency guidelines. The weight-of-evidence classification is based on clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia and suggestive evidence for chronic nonlymphocytic leukemia and chronic lymphocytic leukemia. The human data are supported by animal studies showing increased risk of cancer at multiple organ sites in multiple species.

> *OSF*– 1.5E-2 to 5.5E-2 per (mg/kg)/day; approximately a three-fold range of equally plausible values derived from extrapolation of the inhalation unit risk by adjusting for differential absorption of benzene by oral and inhalation routes and converting units using standard (default) assumptions for human body weight and air intake.
>
> *URI*– 2.2E-6 to 7.8 E-6 per (µg/cu.m); approximately a three-fold range of equally plausible values derived from low-dose linear extrapolations using the MLE (by Crump, 1992, 1994 and Paustenbach et al., 1993) and (I think) two different exposure measurements from an occupational cohort showing increased leukemia (Rinsky et al., 1981, 1987). I think it is difficult (for the general toxicologist) to follow how the unit risk values were derived based only on IRIS and the support document (U.S. EPA, 1998) without being familiar with Paustenbach et al. (1993) or Crump (1992, 1994)– see also Comments 1.D. and 10.

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD – NA

RfC– NA

Carcinogenicity Assessment–

Oral Quantitative Assessment: Extrapolated from the inhalation unit risk assuming 50% absorption for the inhalation route and 100% absorption for the oral route and using standard defaults for units conversion (20 cu.m/day air intake, 70 kg body weight, 2 L/day drinking water consumption).

Inhalation Quantitative Estimate:

study for URI= Rinsky et al., 1981, 1987
species= human, occupational cohort
sex= white men

N= expanded cohort of 1165 workers (employed at least 1 day between January 1, 1940 and December 31, 1965 and followed through 1981)
exposure= based on estimated exposures before 1946, some actual measurements from 1946-1960
dose range= Not clear; presumably from 0 to more than 400 ppm-years estimated as cumulative (ambient respirable benzene multiplied by length of exposure) or weighted (how?) exposure
for a 40 year working lifetime.
type study= retrospective cohort mortality

B.1. Critical Effect (RfD, RfC)

RfD– NA

RfC– NA

B.2. Basis for Cancer Quantitative Estimate

Oral Route– Extrapolation from the inhalation route based on observations of similar toxic effects and toxicokinetic (metabolism) information from animal studies as there are few human data of oral exposure to benzene.

Inhalation Route– Human occupational retrospective mortality study (Rinsky et al., 1981, 1987). See Comments 1 and 4.

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– NA

RfC– NA

Cancer– Human epidemiological studies of occupational inhalation exposure to benzene form the bulk of the evidence for the qualitative cancer assessment. These data are supported by experimental animal studies by both inhalation and oral routes.

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– NA

RfC– NA

Cancer– IRIS and the support document explain that the mechanisms for benzene toxicity and carcinogenicity have not been fully characterized. An overview of the scientific literature on the biotransformation of benzene to a reactive species, chromosomal damage and hematotoxicity (bone marrow suppression and aplastic anemia) and pathogenesis are reviewed in U.S. EPA (1998). Two postulated metabolic pathways in animals and humans and potential quantitative differences in humans (variability owing to differences in hydroxylator phenotype and levels of CYP2E1) are discussed.

E. For human data: was a sensitive subpopulation included?

RfD– NA

RfC– NA

Cancer– Children as a sensitive subpopulation due to a variety of factors that could increase their susceptibility are discussed in U.S. EPA (1998), but are not mentioned on IRIS. See also Miscellaneous Comments.

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– NA

RfC– NA

Cancer– NA

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– NA

RfC– NA

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

Many experimental animal studies as well as metabolic and mode of action studies, support the many human studies for the classification of benzene as a known human carcinogen. These are summarized on IRIS and in supporting documentation (U.S. EPA, 1979, 1998).

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– NA

RfC– NA

A.2. Uncertainty and Limitations in Cancer Assessment

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation fro LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

Yes. Variability is handled primarily qualitatively both on IRIS and in the supporting documentation through narratives about variability/differences in response (e.g., different types of leukemias) and exposure in epidemiologic studies (intra-human) and the methodological problems in these studies; inter-species variability in tumor site response (multiple organs in animals vs. leukemia in humans), and intra-human and inter-species variability in toxicokinetics (including but not limited to absorption across routes and metabolism). Further, EPA acknowledges that population variability was not accounted for by utilizing default assumptions (body weight, air intake, water consumption) for the route conversion. Database deficiencies are delineated in Section 5 of U.S. EPA (1998) and throughout U.S. EPA (1999).

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– NA

RfC– NA

8. Identify the MF used, if any, and its basis.

RfD– NA

RfC– NA

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Yes. The critical effect is identified in humans. The scientific community at large (e.g., IARC, ATSDR, ACGIH, OSHA), recognizes the hematological system as the target for benzene, and the causal association of benzene exposure and leukemia.

Yes. Inhalation exposure is the primary route for occupational exposure. Occupational exposure is also likely to occur by the dermal route. Environmental exposures could occur by oral, dermal, and inhalation routes.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– NA

RfC– NA

Cancer– The degree of confidence (such as "high", "medium", or "low") in the quantitative assessment is not explicitly stated on IRIS or in the supporting documentation. There are a number of uncertainties in the high to low dose extrapolation (which are enumerated on IRIS, see Sections II.C.3 and 4) that cannot be resolved without additional biological information and lead to choosing a linear default and presenting a range of equally plausible unit risks.

I agree that the EPA took the best approach in laying-out the uncertainties and stating that they are presenting a quantitation that in their judgement appears to be the best approach given the state of scientific knowledge and their charge to protect public health.

Miscellaneous Comments

On Table 4, page 33, U.S. EPA 1998: missing footnotes b and c in table should be added, and scientific notation should be made consistent. Also, I cannot figure out range of risk values (MLEs?) for Crump 1992, 1994 using Crump and Allen exposure and linear model and also using Paustenbach exposure linear model– are these for two different exposures (weighted and cumulative)?

The cohort for the principal study is white men (presumably middle-aged and healthy). How/whether this contributes to uncertainty in other subpopulations (other ethnic groups, women, the elderly), including sensitive subpopulations (children) could be mentioned.

Additional References Recommended for Consideration

None.

CHEMICAL: **Danitol** **CASRN**: 39515-41-8

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

The IRIS summary accurately reflects information in the supporting DERs. This chemical assessment is consistent with the approach taken by OPP and the Agency in 1992. Other than noting variability in response (e.g., incidence of convulsions in treatment groups and sexes), there is no characterization of variability or uncertainty. The objective of this assessment does not appear to be a comprehensive review of all literature, mechanism of action, etc., but a review of information relative to OPP guidelines for pesticide registration. Since new pesticides or formulations are submitted for registration and guidelines require specific types of animal studies, there may not be human data or mechanistic information. I do not know if there is published literature for Danitol.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This pre-pilot assessment, finalized in 1992, presents more details of supporting studies and rationale for confidence than the earlier OPP pre-pilot assessments (DDT in 1985 and Prochloraz in 1988-1989) that I have reviewed.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

In 1992, EPA did not extensively address variability and uncertainty in its assessments; this assessment is consistent with Agency approaches at that time. Conversion factors and assumptions (food consumption) and are standard default values used by OPP. UF are standard default values.

D. Are there other relevant observations or comments?

OPP reviews studies for compliance with guidelines and conducts assessments for registration of pesticides. Much of the information is confidential business data and is not in the open peer-reviewed literature (which does not diminish its value in this case). There may be information on other related compounds that could be used to make the review more comprehensive. Alternatively, it could be explicitly stated that the documentation for these files differs from others on IRIS- how and why.

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– Verified 4/01/93; on line 10/01/94 (new RfD, old one withdrawn 5/01/93)

RfC– No data

Carcinogenicity Assessment– No data

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0034.html**), and:
9/2/99 memorandum from John Whalen;
undated memorandum from Bernice Fisher;
Sumitomo Chemical America, Inc. 1975; 1976 (3-month feeding-rat);
Sumitomo Chemical Company, Inc. 1979a (2-year rat feeding study);
Sumitomo Chemical Company, Inc. 1986 (2-year rat feeding study);
Sumitomo Chemical America, Inc. 1985b (2-year mouse feeding study);
Sumitomo Chemical America, Inc. 1980 (3-month feeding-dog);
Sumitomo Chemical America, Inc. 1984 (1-year feeding-dog);
Sumitomo Chemical America, Inc. 1985a (developmental toxicity- rabbit);
Valent USA Corporation, 1990 (developmental toxicity-rat);
Sumitomo Chemical America, Inc., 1979b (3-generation reproduction-rat);
Sumitomo Chemical America, Inc. 1986 (3-generation reproduction-rat).

I also looked through Casarett and Doull, 1995.

On IRIS:

RfD– 10 animal studies listed above

RfC– No data

Cancer– No data

4. Identify the basis for each risk factor.

RfD– EPA documentation (Section I.A.6) states that the assessment is not presented in any existing U.S. EPA document. The RfD is derived from the NOAEL (100 ppm= 2.5 mg/kg-day) for tremors in male and female Beagle dogs fed 0, 100, 250, or 750 ppm (0, 2.5, 6.25, or 18.75 mg/kg-day) for 1 year. The study showed a NOAEL and LEL (250 ppm = 6.25 mg/kg-day). It was assumed that 1 ppm equals 0.025 mg/kg-day (assumed dog food consumption). An UF of 100 was applied to the NOEL to derive an RfD of 2.5E-2 mg/kg-day.

RfC– NA

Carcinogenicity Assessment– NA

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD–
principal study= Sumitomo Chemical Co., Ltd. 1984
species= dog
strain= Beagle
sex= males and females
N= 4/sex/dose

doses= 0, 100, 250, or 750 ppm (0, 2.5, 6.25, or 18.75 mg/kg-day)
dose range= 7.5-fold
type study= chronic feeding study

RfC– NA

Carcinogenicity Assessment– NA

B.1. Critical Effect (RfD, RfC)

RfD– Tremors

RfC– NA

B.2. Basis for Cancer Quantitative Estimate– NA

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– Oral (feeding study)

RfC– NA
Cancer– NA

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– Not discussed on IRIS or in DERs. However, Echobichon (in Casarett and Doull, 1995) discusses target site and mechanisms of toxicity of synthetic pyrethroid insecticides (including fenpropanthrin).

RfC– NA

Cancer– NA

E. For human data: was a sensitive subpopulation included?

RfD– It is not explicitly stated on IRIS nor in the DERs whether there are human data. Ecobichon (in Casarett and Doull, 1995) note that in China, synthetic pyrethroids have been used on a large scale on cotton crops since 1982 (page 667). This leads one to think that there may be human data available. See also Comment #1.

RfC– NA

Cancer– NA

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– No, not that I'm aware of.. However, Ecobichon (1995) states that species susceptibility to pyrethroid ester toxicity appears to be highly dependent on rate of hydrolysis encountered in target and nontarget species, and level of tissue esterase activity (among other things). I don't know how the dog (most sensitive species considered) relates to human sensitivity and whether there are any differences in esterase activity. When this file is updated, it might be worth checking into relative toxicokinetic/dynamic species differences as this may affect the inter-species UF.

RfC– NA

Cancer– NA

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– Ten additional animal studies support the NOEL/LEL determination (See Comment #3).

RfC– NA

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

NA

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– Total UF= 100; 10 each to account for inter- and intraspecies differences

RfC– NA

A.2. Uncertainty and Limitations in Cancer Assessment– NA

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation of LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

Interspecies and intra-species extrapolation were considered in application of the default 10 UF for each. The database was considered as having no gaps (Confidence section, I.A.5). For the OPP, a 1-year study in dogs is considered of chronic duration, so there was no subchronic to chronic extrapolation. A NOEL was defined in the principal study.

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– No. UF appear to be default values for animal to human and human variability extrapolation, which was the practice at the time that the data were evaluated by the EPA Work
Group. When the file is updated, there may be data on synthetic pyrethroids to consider a data-derived UF for inter-species extrapolation.

RfC– NA

8. Identify the MF used, if any, and its basis.

RfD– MF of 1 (default) was used (Section IA.3).

RfC– NA

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

The critical effect appears to be relevant to humans. However, Danitol is a pesticide to be applied with spray ground equipment (Whalen, 9/2/88, page 2) so dermal and inhalation exposure seem more likely exposure routes than oral (although somewhere in the package, it says that the registrant is requesting approval for application to apples and pears). FIFRA guidelines may specify that studies are to be conducted by the oral route.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– Confidence in the study was medium because while it was well-conducted and identified a NOEL and LEL, food and test material were given *ad libitum* and there was no description of how food consumption was measured. The database and RfD were given high confidence because there are no data gaps and the supporting studies confirm the NOEL/LEL in the principal study.

RfC– NA

Cancer– NA

Miscellaneous Comments

None.

Additional References Recommended for Consideration

No specific references.

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

Characterization occurred to a limited extent, as was consistent with EPA procedures at the time of development of this IRIS file (1985). The supporting document (U.S. EPA, 1985) for the cancer assessment does a much better job than the IRIS summary of weighing the evidence and pointing out limitations in the biological information and studies. The incidence data are shown (they are not shown on IRIS), and limitations in pathological examination, study duration, survival, and dose range are discussed. Variability in response amongst species and potential underlying mechanisms are discussed as weighing the biological findings and explaining the cancer potency range. Differences in response between studies in same species and strains, differences among species, differences in sex, and degree of malignancy (e.g., only benign tumors in rats, no tumors in hamsters, differences in tumor sites amongst species, apparent complete carcinogenic activity in mice compared with apparent promotional activity in rats) are presented as contributing to the variability. Uncertainty, in general, is acknowledged in estimation of the cancer potency. Specific types of uncertainty are neither explicitly stated nor quantified, but this was not the general practice of the agency at the time of this assessment.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This is the earliest pre-pilot assessment that I reviewed, and while consistent with Agency practice at the time it was developed, it lacks in-depth discussion of data limitations and uncertainties and integration of the database, particularly in the noncancer assessment and the cancer route extrapolation.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

See Comment A.

IRIS notes confidence in the cancer quantitative estimate by pointing out similarity of response and proximity of slope factors from a variety of studies in rats and mice. Some uncertainty is captured by using multiple studies and the geometric mean of slope factors.

There is no explanation as to the feasibility of the route extrapolation or how the mathematical conversions were made. It is most likely not clear to the average IRIS reader how these calculations were made or what assumptions formed the bases. The URI is not presented in the supporting documentation (U.S. EPA, 1985).

D. Are there other relevant observations or comments?

Lack of documentation, in general, for IRIS assessments is a problem for the IRIS user, but was consistent with pre-pilot agency RfD procedures.

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– Verified 12/18/85; on-line 3/31/87

RfC– No data

Carcinogenicity Assessment– Verified 6/24/87; on-line 5/01/91; OSF and URI

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for DDT (**www.epa.gov/iris.subst/0147.html,** 04/13/00), and The Carcinogen Assessment Group's Evaluation of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE, and DDD (TDE), Internal Report, January 1985, EPA-600/X-85-097. This reviewer also looked over the 1980 Ambient Water Quality Criteria for DDT, which was available in-house.

On IRIS:
RfD– 3 animal studies (Laug et al., 1950; Fitzhugh, 1948; Treon and Cleveland, 1955)

RfC– NA

Cancer– Inadequate human data; sufficient animal data (summary of 25 animal studies) in rats, mice, hamsters, and dogs

4. Identify the basis for each risk factor.

RfD– Section I.A.6 states that the assessment was not presented in any existing U.S. EPA document. Section VI.A, Oral RfD References, does not list any EPA documents. The RfD is derived from a NOEL (1 ppm diet= 0.05 mg/kg-day) for liver lesions from a 27-week rat feeding study by Laug et al. (1950). The study showed a NOEL and LOAEL (5 ppm= 0.25 mg/kg-day). An assumption was made that daily food consumption in rats approximates 5% of their body weight. An UF of 100 was applied to the NOEL to derive the RfD. It should be noted that the 1980 AWQCD used the Laug et al. study as the basis for the ADI.

RfC– No data on IRIS.

Carcinogenicity Assessment– DDT is classified as B2, probable human carcinogen. The weight-of-evidence classification is based on inadequate epidemiological data, sufficient animal data, supporting tumor promotion data, and similarity of chemical structure to DDD and DDE, other probable human carcinogens. The observation of tumors (generally of the liver) in 10 studies (3 rat and 7 mouse) in various strains comprise the sufficient animal data.

OSF– 3.4E-1 per (mg/kg)/day derived as the geometric mean of slope factors (linearized multistage procedure, extra risk) of benign and malignant liver tumors from 6 dietary studies in male and female rats (2 strains) and mice (2 strains)

URI– 9.7E-5 per (µg/cu.m) calculated from the oral data.

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD – Based on a subchronic study in rats fed commercial DDT (mixture of 81% p, p' and 19% o, p' isomers in corn oil solution mixed into powdered chow) at 0,1, 5, 10, or 50 ppm for 15-27 weeks. Rationale for choosing this as the critical study are provided in Section I.A.2: male rats appear the most sensitive animals, the study is of sufficient length to observe toxic effects, several doses were administered in the diet over the range of the dose-response curve, the study established a NOEL and LOAEL, and the LOAEL is the lowest of any observed.

principal study= Laug et al., 1950
species= rats
strain= NS
sex= male and female
N= 25/sex/dose
doses= 0, 1, 5, 10, 50 ppm
dose range= 50 fold
type study= subchronic feeding study (15-27 weeks)

RfC– NA

Carcinogenicity Assessment–
Oral Quantitative Assessment:
study for OSF= based on 6 animal studies (Turusove et al., 1973; Terracini et al., 1973; Thorpe and Walker, 1973; Tomatis and Turusov, 1975; Cabral et al., 1982; Rossi et al., 1977)
species= 2 studies rats and 4 studies mice
strain= 1 study MRC Porton and 1 study Wistar rats, and 3 studies with CF-1 and 1 study with BALB/C mice
sex= 1 rat study with males and females, 1 rat study with females only, 3 mouse studies with males and females, 1 mouse study with males
N= not specified on IRIS summary; in U.S. EPA (1985).
doses= in rats, producing increased tumor incidence= 0.15-37.5 mg/kg-day
in mice, producing increased benign liver tumors= 25-40 mg/kg-day
Doses for the 25 animal carcinogenicity studies are not specified on IRIS. U.S. EPA (1985) presents doses for some animals studies and tables with maximum dosages for other studies. Doses and tumor incidence are presented in tabular form for those studies used for cancer potency estimation in U.S. EPA (1985).
dose range= see doses
type study= chronic studies and multi-generational studies, although specific durations generally not reported on IRIS.

Inhalation Quantitative Estimate: calculated from the oral data (See B.2. below)

B.1. Critical Effect (RfD, RfC)

RfD– The critical effect is liver lesions, i.e., hepatocellular hypertrophy, cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules, in male rats. Minimal LOAEL at 5 ppm; NOEL at 1 ppm. Pathological changes were seen to a greater degree in males.

RfC– NA

B.2. Basis for Cancer Quantitative Estimate

Oral Route– Oral slope factor calculated using the LMS, extra risk, from benign and malignant liver tumors in 6 dietary mouse and rat studies. The studies encompassed 2 strains of mice (CF-1 and BALB/C) and 2 strains of rats (Wistar and MRC Porton). Four studies included males and females, whereas two studies included one sex.

Inhalation Route– A statement is made (Section II.C.2) that the inhalation risk estimates were calculated from the oral data. It is most likely not clear to the average IRIS reader how these calculations were made or what assumptions formed the bases. The URI is not presented in the supporting documentation (U.S. EPA, 1985).

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– Oral. Animals were fed commercial DDT in corn oil added to powdered chow.

RfC– NA

Cancer– Oral data formed the basis for both the oral and inhalation quantitative estimate.

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– Not discussed on IRIS. No supporting documentation cited on IRIS nor provided to reviewer.

RfC– NA

Cancer– IRIS does not present a discussion of mechanism. Mechanism as being related to metabolism and/or tumor promotion is alluded to in Sections II.A.3 and II.A.4. The former section points out that unlike mice and humans, hamsters accumulate DDT but do not metabolize it to DDD or DDE (suggesting a role of metabolism in tumorigenesis). In Section II.A.4, supporting data include tumor promotion studies, suggesting to the reader that DDT has promotional activity. The CAG report (U.S. EPA, 1985), cited as the documentation for the assessment, does a much better job laying out potential mechanism(s) for DDT tumorigenesis.

E. For human data: was a sensitive subpopulation included?

RfD– The RfD is based on animal data.

RfC– NA

Cancer– Epidemiological data were considered inadequate.

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– The strain of rats is not presented on IRIS. This reviewer did not consult the original article to obtain that information. IRIS states (Section I.A.2., last paragraph) that male rats appear to be the most sensitive animals to DDT exposure.

RfC– NA

Cancer– There were several species/strains represented in the cancer bioassays. This reviewer is not aware, nor do IRIS or U.S. EPA (1985) make any mention of, any genetic peculiarity of these species/strains.

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– Fitzhugh (1948) 2-year feeding study in rats (10-800 ppm) showing chronic LOAEL of liver lesions at 0.25 mg/kg-day. IRIS states in Section II.A.2, last paragraph, “DDT-induced liver effects were observed in mice, hamsters and dogs as well.” A one-generation rat reproduction study (Treon and Cleveland, 1955) showed increased

mortality at doses ≥0.2 mg/kg-day. However, three other reproduction studies in mice and rates showed no reproductive effects at much higher dose levels (Section I.A.4).

RfC– NA

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

Supporting data for the cancer evidence for classification as a probable human carcinogen include structural similarity to DDD and DDE (also classified by EPA as probable human carcinogens), and several studies showing that DDT acts as a tumor promoter. DDT has produced both positive and negative responses in genetic toxicity tests.

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– 10 for inter-species extrapolation and 10 to protect sensitive human subpopulations (i.e., for intra-human variability). No UF for subchronic to chronic duration extrapolation was used because of the corroborating chronic study in database (presumably corroborating the LOAEL for the critical effect in the Laug et al. study).

RfC– NA

A.2. Uncertainty and Limitations in Cancer Assessment

Positive and non-positive animal and genetic toxicity assays are presented and mention is made that in some studies, there were only benign tumors and no metastases were reported. A problem with the Tarjan and Kemeny (1969) study is noted. The confidence in the quantitative estimate (Section II.B.4) uses the 13-fold range of ten slope factors from 6 studies to support similarity of dose-response and retention of all relevant data. While the IRIS summary simply states the information, the supporting document (U.S. EPA, 1985) does a much better job discussing data limitations.

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation fro LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

Inter-species and intra-human variability were considered and a 10-fold UF was applied to account for each. Extrapolation for subchronic to chronic duration was considered, but not included because of a corroborating chronic study (Fitzhugh, 1948, 2-year study in rats establishing a LOAEL of 0.5 mg/kg-day) in the database. Extrapolation from LOAEL to NOEL was not needed as a NOEL was identified in the critical study. Database insufficiencies are not specifically mentioned on IRIS for this file (see Comment #1).

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– No

RfC– NA

8. Identify the MF used, if any, and its basis.

RfD– MF of 1 (default) was used (Section IA.3).

RfC– NA

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Yes. The liver is generally the target of (organochlorine insecticides) chlorinated hydrocarbons and the route of exposure (oral) is relevant for DDT.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– Confidence is the study, database, and RfD are all rated medium. Study confidence is medium to low due to an apparent adequate study but of shorter duration than "desired" (presumably not chronic). Moderate support for the critical effect and magnitude and lack of a clear NOEL for reproductive effects causes the database to be medium to low confidence. These lead to medium to low confidence in the RfD. At face value, this seems a bit overconfident. However, it is difficult to concur or not based on the brief presentation of the studies and lack of any supporting document.

RfC– NA

Cancer– Based on approaches in place at EPA in 1985, I concur. Use of as much of the relevant data as possible in determination of the quantitative estimate is to be encouraged. As noted in 6.A.2. above, IRIS notes confidence in the estimate by pointing out similarity of response and proximity of slope factors from a variety of studies in rats and mice. Further, it is noted that the procedure, presumably of using multiple studies and the geometric mean, is under study by EPA. However, given additional recent literature on epigenetic mechanisms of carcinogenicity and endocrine disruptors, EPA should consider updating this assessment.

Miscellaneous Comments

Types of tumors for Cabral et al., 1982 not noted in table in Section II.B.2

Additional References Recommended for Consideration

None.

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

I am not familiar with the primary literature on ethylene glycol monobutyl ether (EGBE). U.S. EPA (1999) appears to be a synthesis of all the relevant, recent literature on the toxicity and carcinogenicity of EGBE. Variability in species susceptibility, age (old and young), duration (e.g., tolerance with chronic exposure), and response/sensitivity differences in sex is presented as a narrative synthesizing the scientific literature. Uncertainties are noted and generally discussed in length (e.g., whether liver effects may be a primary or secondary toxic response).

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This pilot/post-pilot assessment is an improvement over the pre-pilot assessments in laying down a narrative of uncertainty in the database. IRIS and the supporting document appear to do a thorough job of integrating relevant experimental data for EGBE toxicity.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

EPA appears to have appropriately discussed variability in the database. There is a very good discussion of potentially susceptible subpopulations in U.S. EPA (1999).

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

When there is an uncertainty (e.g., mode of action/sequence of events for hemolysis or basis of the MCV as the critical effect), it is stated.

D. Are there other relevant observations or comments?

The toxicological review document is well-written. I am not familiar with the database for EGBE and the document appears at times as if it is arguing particular points of view (e.g., unlikely relevance to humans of hemangiosarcomas in mice based on speculation of a mechanism). The information appears to fit together so well, it is not clear whether that is the state of science or whether alternate modes of action, assumptions, or explanations of findings and what impact they might have on the risk assessment have not been considered

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– On-line 12/30/99

RfC– On-line 12/30/99

Carcinogenicity Assessment– On-line 12/30/99

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0500.html**), and Toxicological Review of Ethylene Glycol Monobutyl Ether. I also looked through the 1997 ATSDR Toxicological Profile, which we had available in-house.

On IRIS:

RfD– NTP subchronic drinking water study in rats and mice (1993); short-term human controlled studies and case reports and numerous additional pharmacokinetic, reproductive/developmental, and mechanistic studies in animals.

RfC– NTP subchronic and chronic inhalation studies in rats and mice (1998); short-term human controlled studies and case reports and numerous additional pharmacokinetic, reproductive/developmental, and mechanistic studies in animals.

Cancer– NTP bioassay in male and female rats and mice.

4. Identify the basis for each risk factor.

RfD– Alteration in MCV (mean corpuscular volume) is the critical effect identified in female rats in a subchronic drinking water study (NTP, 1993). The RfD of 0.5 mg/kg-day was derived from applying a 10-fold UF for intra-human variability to the human equivalent dose (HED) of 5.1 mg/kg-day corresponding to the BMD05 determined from the dose-response curve for MCV using internal dosimetry and back-calculated from the Corley et al. PBPK model.

RfC– Alteration in RBC count is the critical effect identified in female rats in a subchronic inhalation study (NTP, 1998). The RfC of 13 mg/cu.m was derived from applying a 30-fold UF (10 for intra-human variability and 3 for extrapolation from an adverse effect) to the human equivalent dose (HEC) of 380 mg/cu.m corresponding to the BMD05 determined from the dose-response curve for MCV using internal dosimetry and back-calculated from the Corley et al. PBPK model.

Carcinogenicity Assessment– No quantitative estimate.

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD–
principal study= NTP, 1993
species= rat
strain= F344/N
sex= female and male
N= 10/sex
doses= 0, 750, 1500, 3000, 4500, or 6000 ppm; based on drinking water consumption doses were 0, 82, 151, 304, 363, or 470 mg/kg-day for the females, and 0, 69, 129, 281, 367, or 452 mg/kg-day
dose range= approximately 6-fold
type study= subchronic drinking water study (13 weeks)

RfC–
principal study= NTP, 1998
species= rat
strain= F344/N
sex= females and males
N= 10/sex
doses= 0, 31, 62.5, 125, 250, or 500 ppm for 6 hours/day, 5 days/week
dose range= approximately 16-fold
type study= subchronic inhalation study (14 weeks)

Carcinogenicity Assessment– No quantitative estimate.

B.1. Critical Effect (RfD, RfC)

RfD– Alteration in MCV (mean corpuscular volume) in female rats.

RfC– Changes in RBC (red blood cell count) in female rats.

B.2. Basis for Cancer Quantitative Estimate

No quantitative estimates.

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– Oral; subchronic drinking water study in rats.

RfC– Inhalation; subchronic inhalation study in rats.

Cancer– No human data and two inhalation bioassays in male and female F344/N rats and B6C3F1 mice.

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– Section 4.5 of U.S. EPA (1999) summarizes the recent literature to put forth a mode of action wherein intravascular hemolysis is brought about by a change in the normal erythrocyte morphology from discocyte form to a spherocytic form. This changes is induced by the acid metabolite of EGBE, 2-butoxyacetic acid (BAA).

RfC– See RfD.

Cancer– ?– Pat??

E. For human data: was a sensitive subpopulation included?

RfD– NA; based on animal data.

RfC– NA; based on animal data.

Cancer– NA

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– Both IRIS and U.S. EPA (1999) indicate that females are more sensitive. This appears to have a pharmacokinetic basis.

RfC– See RfD.

Cancer– No

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– Supporting data include short-term human controlled studies and case reports, and numerous additional pharmacokinetic, reproductive/developmental, and mechanistic studies in animals.

RfC– See RfD.

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

No quantitative estimates for carcinogenicity were presented. The human carcinogenic potential of EGBE cannot be determined. NTP (1998) reported no evidence in male and equivocal evidence of carcinogenic activity in female F344/N rats. Some evidence was reported in both sexes of B6C3F1 mice. The relevance of the animal tumors to humans is uncertain, and there is a lack of positive responses in genetic toxicity studies and structurally-related carcinogens. Together, these preclude a determination of EGBE carcinogenic potential in humans.

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– The UF of 10 is to account for intra-human variability.

RfC– The UF of 30 is comprised of a UF of 10 for intra-human variability and 3 for extrapolation from an adverse effect to a no-effect level.

A.2. Uncertainty and Limitations in Cancer Assessment

NA; there were no quantitative estimates.

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation from LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

For the RfD and RfC, all of the above areas of uncertainty were considered and explanations are provided as to why EPA chose the current values.

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– A UF of 10 was used to account for intra-human variability. Data do not appear to be available to use other than the default value for this UF. Other UF were excluded based on use of the BMD, PBPK model, and analysis of the data for EGBE.

RfC– A UF of 30 derived from a default of 10 for intra-human variability and 3 for extrapolation from an adverse to a no-adverse effect level was used. Data do not appear to be available to use other than the default value for this UF. Other UF were excluded based on use of the BMD, PBPK model, and analysis of the data for EGBE.

8. Identify the MF used, if any, and its basis.

RfD– MF of 1 (default) was used (Section I.A.3).

RfC– MF of 1 (default) was used (Section I.B.3).

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Yes. Similar hematological effects occur in humans and animals. Occupational exposure occurs primarily through inhalation and dermal routes (ATSDR, 1997). Environmental exposures would most likely occur through oral and dermal routes (EGBE is a liquid and "slow evaporator", U.S. EPA, 1999).

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– I concur that confidence in the principal study, database, and RfD are medium, medium-to-high, and medium-to-high, respectively.

RfC– I concur that confidence in the study is high and confidence in the database and RfC are medium-to-high.

Cancer– Quantitative estimates were not derived.

Miscellaneous Comments

U.S. EPA (1999, page 67) states that the 3-fold UF_D has been retained for both the RfD and the RfC, when it has not.

Additional References Recommended for Consideration

None.

CHEMICAL: **Manganese** **CASRN**: 7439-96-5

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

Yes. EPA characterized uncertainty and variability to the extent routinely practiced in the mid-1990s.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

RfD and RfC reflect the later pre-pilot assessments, where studies are described in more detail (too much sometimes) with their limitations and strengths, the narrative synthesizes the chemical database, including possible mechanisms and data gaps, and uncertainty is at least acknowledged.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

The RfD for Manganese (Mn) is a value distilled from reputable secondary sources (WHO, NRC). IRIS notes numerous factors influence individual Mn status and the variability in physiologically required levels of Mn, human dietary content, and habits (including fasting), absorption (including interaction of other trace elements)-- these are described in narrative form. Infants as a susceptible subpopulation is discussed with supporting rationale.

D. Are there other relevant observations or comments?

It is particularly difficult to do an assessment for an essential element, as adverse health effects can occur both with deficiency and excess, and numerous environmental factors influence individual exposure.

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– Verified 5/12/95; on-line

RfC– Verified 9/23/93; on-line
Carcinogenicity Assessment– Verified 6/24/87; on-line

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0373.html**), 1984 HAD and the 1993 DWCD. I also looked over the 1998 ATSDR, which we had in-house.

On IRIS:

RfD– Overview of Mn essentiality and recommended daily intakes in humans by national and international organizations.

RfC– Description of several occupational studies and numerous animal studies.

Cancer– Description of several animal studies and no supporting genetic toxicity studies.

4. Identify the basis for each risk factor.

RfD– The RfD is based on a NOAEL for a lack of adverse CNS effects from chronic daily ingestion of manganese in the diet of large human populations. Different MF are recommended based on whether Mn is in food, water, or soil.

RfC– RfC is based on co-principal studies (Roels et al., 1997, 1992) showing LOAELs for impairment of neurobehavioral function in occupational cohorts exposed to manganese dioxide or manganese oxides and salts for 5-7 years. No NOAELs were identified in these studies.

Carcinogenicity Assessment– NA

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD– Based on a composite by EPA of estimated safe and required dietary intake of manganese in humans (adults) by the NRC, ACS, and WHO.

RfC– Roels et al. (1987) conducted a cross sectional study in 141 male workers and a matched (for SES, background environmental factors, work-load, work-shift) control group of 104 male workers. Roels et al. (1992) is comprised of 92 male workers and 101 matched (age, height, weight, schedule, smoking, alcohol and coffee consumption) controls.

Carcinogenicity Assessment– No quantitative estimates.

B.1. Critical Effect (RfD, RfC)

RfD– CNS effects in humans

RfC– Impairment of neurobehavioral function (e.g., motor coordination)

B.2. Basis for Cancer Quantitative Estimate– NA

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– Oral; dietary exposure in humans

RfC– Inhalation; occupational exposure

Cancer– Parenteral routes in animal studies. Mn was categorized as D, not classified as to human carcinogenicity.

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– Not discussed in RfD file.

RfC– IRIS briefly discusses neurochemical dopaminergic imbalance in the basal ganglia and/or mitochondrial energy metabolism (oxidative stress) as possible biochemical basis for neurobehavioral alterations.

Cancer– NA

E. For human data: was a sensitive subpopulation included?

RfD– Infants are considered a susceptible subpopulation by virtue of possible increased exposure of Mn in water. GI absorption is higher in infants and they may be fed formula that has higher Mn concentrations than human milk.

RfC– Children, pregnant women, elderly persons, individuals with liver impairment, and iron- or calcium-deficient persons were noted as susceptible subpopulations due to increased absorption or altered clearance of Mn.

Cancer– NA

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– Based on human data.

RfC– Based on human data.

Cancer– NA

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– Studies of manganese deficiency, bioavailability, human case reports, and animal studies.

RfC– Additional studies in Mn-exposed workers and laboratory animal studies.

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

No supporting data (e.g., genetic toxicity studies) were presented.

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– UF = 1 because based on large human populations consuming normal diets over a long period of time without adverse health effects.

RfC– UF = 1000, 10 for protect for sensitive individuals, 10 for extrapolation from a LOAEL to a NOAEL, 10 for limitations in the database. The latter 10 UF includes extrapolation for less than chronic exposure duration, lack of developmental data, and potential (but unquantified) differences in the toxicity of different forms of Mn.

A.2. Uncertainty and Limitations in Cancer Assessment

Some limitations in the interpretation of the animal studies were discussed (i.e., lack of dose-response, lack of increase in mean number of tumors per mouse in lung adenoma assay). The animal data were interpreted as inadequate to assess the carcinogenicity of Mn.

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation from LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

For the RfC intra-human variability, LOAEL to NOEL extrapolation, extrapolation to chronic duration, and database deficiencies were considered. The latter two were considered together in one UF. In addition, potential differences in the toxicity of different forms of Mn was considered as part of the third 10-fold UF.

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– Broad-based dietary information was used to determine that there was sufficient certainty that a UF was not needed.

RfC– The UFs for intra-human variability (10) and LOAEL to NOAEL extrapolation (10) are standard default values. The third 10-fold UF that is a composite of less than chronic duration, lack of developmental and potential toxicity differences for different Mn forms is not strictly-data derived (where the data are used quantitatively). I would call it "data-judged", where toxicological judgement as to data gaps for Mn were used to determine a UF in place of separate standard UF defaults (e.g., 10 for chronic duration extrapolation and 10 for database deficiencies).

8. Identify the MF used, if any, and its basis.

RfD– MF of 1 (default) was used (Section IA.3) when Mn exposure is from food. A MF of 3 was recommended when exposure to Mn is from water or soil for 4 reasons: increased intake in fasted individuals, concern that lifetime intake of Mn in drinking water may pose adverse effects, GI of infants absorb more Mn and their blood brain barrier less restrictive, and infants fed formula that has higher Mn concentrations than human milk.

RfC– None.

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Yes. Critical effects are identified in humans. Humans can be exposed by both inhalation and oral routes.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– Confidence in the study, database, and RfD are all considered medium. This appears to be conservative.

RfC– Confidence in the study, database, and RfC are all considered medium. Yes, primarily because no NOAELs were identified and the exposure durations were short in the co-principal studies.

Cancer– NA

Miscellaneous Comments
None.
Additional References Recommended for Consideration
None.

CHEMICAL: **4-Methylphenol** **CASRN**: 106-44-5
SYNONYM: p-Cresol

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

To a very limited degree. While uncertainties in activity of the cresols as tumor promoters or complete carcinogens and also about the applicability of mouse skin tumorigenesis are noted in the supporting document, U.S. EPA (1979), they are not raised on IRIS and should have been. U.S. EPA (1985) shows additional negative genetic toxicity data for p-cresol that apparently was not included on IRIS. The largest uncertainty, using information for the mixture of isomers to support classification of a single isomer is not mentioned.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This summary is fairly consistent with other pre-pilot assessments, and general EPA procedures during 1989, wherein uncertainty is not extensively addressed.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

To a limited degree– see Comment A.

D. Are there other relevant observations or comments?

While it is acknowledged that there are limitations in resources, there needs to be a more timely reconsideration/updating IRIS information. Two years after the file was put on IRIS, an EPA document classified p-cresol as a Group D, indicating inadequate data for categorization as a human carcinogen.

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– Withdrawn 8/01/91

RfC– Reviewed 12/11/91– data deemed inadequate

Carcinogenicity Assessment– Verified 10/05/89; on-line 9/01/90; no quantitative estimates

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0302.html**), and

The Carcinogen Assessment Group's Preliminary Risk Assessment on Cresols (U.S. EPA, 1979), Health and Environmental Effects Profile for Cresols (U.S. EPA, 1985), and Health and Environmental Effects Document for 4-Methylphenol (U.S. EPA, 1991). I also looked over the 1984 HEA and 1992 ATSDR for Cresols, which were available in-house.

On IRIS:
RfD– No data; message that assessment was withdrawn

RfC- No data; message that data reviewed and inadequate for derivation of an RfC

Cancer– Inadequate human data; limited animal data (skin painting studies in mice), genetic toxicity studies

4. Identify the basis for each risk factor.

RfD– NA

RfC– NA

Carcinogenicity Assessment– Qualitative assessment as to the weight of the evidence; no quantitative estimates of risk were reported on IRIS
OSF– NA
URI– NA

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD – NA

RfC– NA

There are no animal subchronic or chronic toxicity data by either the oral or inhalation routes for p-cresol (U.S. EPA, 1985). This remains the case for the inhalation route as stated on IRIS and as supported in the cited documentation (U.S. EPA, 1991). However, in the HEED (U.S. EPA, 1991) cited in the RfC file on IRIS, there is an RfD derived based on developmental toxicity study in rabbits. Perhaps this is why the earlier RfD was withdrawn from IRIS. There are also subchronic studies in rats (Dietz and Mulligan, 1988; U.S. EPA, 1987a).

Carcinogenicity Assessment– C, possible human carcinogen, based on increased incidence of skin papillomas in mice in an initiation-promotion study and positive results in genetic toxicity studies alone and in combination with the other cresol isomers (o-cresol, m-cresol). Only anecdotal human data were available. IRIS describes two skin application tumor promotion studies in mice, two with p-cresol (Boutwell and Bosh, 1959), one with tea (Kaiser, 1967), one with cigarette smoke condensate (Bock et al., 1971), and an acute irritation study in rabbits (Vernot et al., 1977). Female Sutter mice (27-29/group), initiated with a single dose of DMBA, received skin applications of one of the cresol isomers twice weekly for 12 weeks and were then evaluated for skin papillomas. Skin papillomas were increased in surviving p-cresol mice (7/20) relative to vehicle (benzene) controls (0/12) (Boutwell and Bosch, 1959). In a second study, these researchers applied p-cresol to mice (20/group, presumably the same sex and strain as the earlier study) twice weekly for 20 weeks following initiation by a single dose of DMBA. Control mice showed 0/18 papillomas compared to 4/14 of the p-cresol treated mice. There were no skin carcinomas. Descriptions of the animal studies with mixtures are on IRIS. Genetic toxicity studies on IRIS include some with p-cresol alone and

others with mixtures of the isomers; positive and negative results are summarized. Details of these studies are in the supporting document (U.S. EPA, 1985).

B.1. Critical Effect (RfD, RfC)

RfD– NA

RfC– NA

B.2. Basis for Cancer Quantitative Estimate

Oral Route– NA
Inhalation Route– NA

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– NA

RfC– NA

Cancer– Dermal application in rodent studies and genetic toxicity tests in bacterial and mammalian cell assays.

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– NA

RfC– NA

Cancer– Not discussed/apparently not known in IRIS, U.S. EPA (1979), U.S. EPA (1985)

E. For human data: was a sensitive subpopulation included?

RfD– NA

RfC– NA

Cancer– NA

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– NA

RfC– NA

Cancer– Not to my knowledge

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– NA

RfC– NA

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

As stated on IRIS, supporting data for a C classification include data positive for genetic toxicity. However, Table 5-1, page 22 of the HEEP (U.S. EPA, 1985), shows negative responses in a variety of tests where p-cresol was tested individually with the exception of unscheduled DNA synthesis in human lung fibroblasts (Crowley and Margard, 1978). Positive results were found in some tests where the mixture of the three isomers were tested. It appears that positive findings for the other isomers were broadly used to support the classification for p-cresol. There was no quantitative estimate on IRIS.

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– NA

RfC– NA

A.2. Uncertainty and Limitations in Cancer Assessment

U.S. EPA (1979) acknowledges that cresols are promoters for skin carcinogenesis but that there is no adequate test of tumor initiation. It points out that the overall database is weak and that "lack of understanding of the basis of promoter activity means that no theoretical basis for making a quantitative risk estimate exists." It further raises questions about the applicability of mouse skin tumorigenesis system to human cancer risk. These uncertainties are not raised on IRIS.

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation fro LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

NA

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– NA

RfC– NA

8. Identify the MF used, if any, and its basis.

RfD– NA

RfC– NA

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

The data supporting the cancer classification are dermal application tumor promotion assays in mice. Humans are dermally exposed to low concentrations of p-cresol in soaps, lotions, and perfumes and occupationally during manufacture and formulation. Humans could also be exposed through ingestion and inhalation (U.S. EPA, 1979;

U.S. EPA, 1985). While the dermal route of exposure is relevant to humans, there is uncertainty in application of the tumor initiation-promotion study design and use of rodents as models for human skin tumors.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– NA

RfC– NA

Cancer– NA

U.S. EPA (1985) reports that IARC (1979) classified the three cresol isomers as Group 3.

Miscellaneous Comments

Although documentation for cancer assessment is 1985 HEEP, in the references for the inadequate data for the RfC, more recent documents (1990 HEED, 19991 RQ) are listed. The final draft HEED (1991) classifies 4-methylphenol differently than does the earlier document on the three cresols used for the IRIS CRAVE summary. In the later document, 4-methylphenol is classified as D, not classifiable as to carcinogenicity to humans, based on insufficient evidence in animals and no data in humans. Somehow, these updates in assessments should be flagged for the reader leading to reconsideration of the assessments posted on IRIS.

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

The IRIS summary accurately reflects the data in the supporting DERs. The DERs, however, contain more explanation and synthesis of information than presented on IRIS. This RfD assessment is consistent with the approach taken by OPP and the Agency in 1988 when it was derived. The cancer assessment, developed in 1989, is consistent with the 1986 EPA Cancer guidelines and does fairly good job of synthesizing relevant information. Characterization of variability and uncertainty are clearly limited, but are consistent with Agency approaches at the time of the assessments.

The objective of this assessment does not appear to be a comprehensive review of all literature, mechanism of action, etc., but a review of information relative to OPP guidelines for pesticide registration. Since new pesticides or formulations are submitted for registration and guidelines require specific types of animal studies, there may not be human data or mechanistic information. I do not know if there are published literature for Prochloraz.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This assessment is consistent with other pre-pilot assessments and does not meet the standards of the pilot/post-pilot assessments.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

In 1988-1989, EPA did not extensively address variability and uncertainty in its assessments; this assessment is consistent with Agency approaches at that time. The standard default values for the RfD and conversion factors for the cancer assessment (body weights for interspecies surface area adjustment) are consistent with those used by the Agency at the time.

D. Are there other relevant observations or comments?

My confidence in the cancer assessment is increased seeing that it was reviewed by the OPP Peer Review Group and the FIFRA SAP. Was the RfD similarly reviewed? OPP reviews studies for compliance with guidelines and conducts assessments for registration of pesticides. Much of the information is confidential business data and is not in the open peer-reviewed literature (which does not diminish its value in this case). There may be information on other related compounds that could be used to make the review more comprehensive. Alternatively, it could be explicitly stated that the documentation for these files differs from others on IRIS- how and why.

By today's standards, the evaluations could have gone further and laid out how the other information in the database factored into the weighing the cancer evidence, i.e., the lack of positive tumorigenic response in rats, no indication of tumors in 2-year dog study (duration not sufficient?), and negative genetic toxicity information.

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– Verified 7/20/88; on-line 1/01/89

RfC– No data

Carcinogenicity Assessment– Verified 4/05/89; on-line 10/01/89

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0378.html**), and Prochloraz, Mouse Study-Qualitative Risk Assessment memorandum 4/29/87; Prochloraz- Rat Study, Qualitative Risk Assessment memorandum 1/27/88; Peer Review of Prochloraz memorandum 1/28/88; Toxicology Branch Peer Review Committee Draft Document on Prochloraz memorandum 4/29/88; OPP Tox Oneliners- Prochloraz 4/20/2000. These reports are not listed in the reference section for the RfD, but are listed in the reference section for the cancer. Many of these references are relevant for both the RfD and cancer.

On IRIS:

RfD– 2-year dog feeding study (FBC Limited, 1981), 2-year oncogenic rat feeding study (Nor-Am Chemical Co., 1982), 2-generation rat reproduction study (Nor-Am Chemical Co., 1981), rat teratology study (Nor-Am Chemical Co., 1989), rabbit teratology study (Boots Company Ltd., 1980), mouse oncogenic feeding study (Nor-Am Chemical, 1983).

RfC– NA
Cancer– 2-year chronic feeding studies in mice (Nor-Am Chemical Co., 1983) and rats (Nor-Am Chemical Co., 1982), genetic toxicity studies.

4. Identify the basis for each risk factor.

RfD– EPA documentation (Section I.A.6) states that the assessment is not presented in any existing U.S. EPA document. The RfD is derived from the NOEL (30 ppm = 0.9 mg/kg-day) for increased serum alkaline phosphatase (SAP) and liver weighs and liver histopathology in male and female Beagle dogs fed 0, 30, 135, or 600 ppm for 2 years. The study showed a NOEL and LEL (135 ppm = 4.07 mg/kg-day). An UF of 100 was applied to the NOEL to derive an RfD of 9E-3 mg/kg-day.

RfC– NA

Carcinogenicity Assessment– classified as C, possible human carcinogen, based on a statistically significantly increased incidence and dose-related trend in liver adenomas and carcinomas (combined) in both sexes of CD-1 mice.

OSF– 1.5E-1 per (mg/kg)/day, the geometric mean of two slope factors, one from combined adenomas and carcinomas in males (1.95E-1) and the other for the same tumors in females (1.14E-1) from the same 2-year dietary study (Nor-Am Chemical Co., 1983). The LMS model (with time-to-tumor analysis to adjust for mortality in the males) was used.
URI– Not available.

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD–
principal study= FBC Limited, 1981
species= dog
strain= Beagle
sex= males and females
N= 5/sex/dose (25/sex total); satellite group of 2/sex fed highest dose
doses= 0, 30, 135, or 600 ppm, based on actual food consumption males: 0, 0.94, 4.47, 18.1, or 28.9 mg/kg-day; females: 0, 0.90, 4.07, 18.0, or 27.5 mg/kg-day. After 56 weeks on study, the 600 ppm dose was increased to 1000 ppm (male: 28.9 mg/kg-day, female: 27.5 mg./kg-day)
dose range= 20-fold
type study= chronic feeding (104 weeks)

RfC– NA

Carcinogenicity Assessment–
Oral Quantitative Assessment:
study for OSF= Nor-Am Chemical Co. (1983)
species= mouse
strain= CD-1
sex= males and females
N= study design was 52/sex/ treated group; 104/sex controls; for OSF incidence, denominator was 92 males, 73 females controls, 44-49 for treated males, 39-44 treated females
doses= 0, 78, 325, or 1300 ppm (0, 3.90, 16.25, or 65.00 mg/kg-day)
dose range= 17-fold
type study= 2-year chronic feeding study in mice
type of tumor= liver adenoma and carcinomas (combined incidence)

Inhalation Quantitative Estimate: NA

B.1. Critical Effect (RfD, RfC)

RfD– Increased serum alkaline phosphatase (SAP), increased liver weights, and liver histopathology (nature and severity of pathological alterations not specified).

RfC– NA

B.2. Basis for Cancer Quantitative Estimate

Oral Route– Significant dose-related trend in incidence of liver adenoma, carcinoma, and combined adenoma/carcinoma, as well as significant increase in incidence by pairwise comparison at the mid- (not adenomas) and high-doses in the males. Significant dose-related trend in incidence for adenomas, carcinomas, and combined adenoma/carcinoma, as well as significant increases by pairwise comparisons for carcinoma (high dose) and adenomas (mid-dose) and combined (both doses) in females. It could have been noted in IRIS that were no significantly increased tumors at other sites.

Inhalation Route– NA

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– Oral (chronic feeding study in dogs)

RfC– NA

Cancer– Oral (chronic feeding study in mice)

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– Not stated on IRIS or in DERs, apparently not a ChE inhibitor (see OneLiners and DERs)

RfC– NA

Cancer– not stated on IRIS or in DERs. The DER for the oncogenicity feeding in mice (1/4/85, page 6) reports a increase in hepatocyte hyperplasia in some treated animals relative to controls, but it did not attain statistical significance (nor did non-neoplastic liver lesions, Table 7), suggesting that liver toxicity may not be involved in tumor induction (e.g., regenerative repair).

E. For human data: was a sensitive subpopulation included?

RfD– Apparently no human data

RfC– NA

Cancer– Apparently no human data

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– Not known

RfC– NA

Cancer– Not known

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– 4 studies, in addition to the principal study (FBC Limited, 1981), were considered for establishing the RfD (Section I.A.4):

- 2-year rat feeding oncogenic study with NOEL= 1.875 mg/kg-day, LEL= 7.5 mg/kg-day enlarged liver, decreased body weight (Nor-Am Chemical Co., 1982);
- 2-generation rat reproductive feeding study with fetal/maternal NOEL= 7.5 mg/kg-day, fetal/maternal LEL= 31.25 mg/kg/day (not clear what adverse effect was from study description);
- rat teratology gavage study with fetal/maternal NOEL= 5.15 mg/kg-day, fetal/maternal LEL= 21.75 mg/kg-day decreased body weight, teratogenic NOEL= 84.5 mg/kg-day (HDT);
- rabbit teratology gavage study with fetal/maternal/teratogenic NOEL= 48 mg/kg-day

Other data reviewed were mouse oncogenicity lifetime feeding study with NOEL= 195 mg/kg-day (HDT).

RfC– NA

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

The Basis Statement (Section II.A.1) does not specify supporting data that were considered in the weight-of-evidence classification. However, the summary presents a 2-year chronic rat feeding study wherein liver carcinomas were reported, but were not considered as contributing to the weight of the evidence as the tumor type is not rare, the pairwise comparison was not significant, and the incidence was within the same range as historical controls. Results were negative in several genotoxicity assays, but Prochloraz is structurally related to 2,4,6-trichlorophenol and 2,4,5-T (which induce several tumor types) and Silvex. It is not clear how the genetic toxicity data and structural analogy were weighted in the qualitative assessment.

Engler memorandum (4/29/88, page 8) gives further explanation as to why the mouse tumors were chosen for quantitation (i.e., high incidence of tumors, dose-response, clear presence of malignancy). Further, the Toxicology Branch Peer Review Committee unanimously agreed to the C classification and could not elevate the classification to B2 because they were not an uncommon or rare type nor did they have an early onset. This rationale makes EPA's decisions more transparent and could be included on IRIS.

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– UF of 100 to account for inter- and intraspecies differences (presumably 10-fold each).

RfC– NA

A.2. Uncertainty and Limitations in Cancer Assessment

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation fro LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

Interspecies and intra-species differences (variability) were considered in the UF. A rabbit teratology study is noted as a data gap. This deficiency does not impact the UF, as the assessment predates consideration of a database UF, which came into practice around 1993.

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– No, UF appear are default values for animal to human and human variability extrapolation, which was the practice at the time the data were evaluated by the EPA Work Groups. There do not appear to be any human data and pharmacokinetic data (presented in the DERs, not IRIS) appears to be insufficient to shed light on similarities/differences between animals and humans that might impact use of the default for the interspecies extrapolation.

RfC– NA

8. Identify the MF used, if any, and its basis.
RfD– MF of 1 (default) was used (Section IA.3).
RfC– NA

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?
Based on the data presented, I cannot judge whether the critical effect is relevant to humans.

Prochloraz is a fungicide submitted for registration for use on turf grasses and ornamentals (Taylor memorandum, 1/19/88). Therefore, it seems that the dermal and inhalation routes would be more likely exposure routes for humans than the oral route.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– Confidence in the critical study is medium (adequate quality). Supporting studies are also adequate and together constitute high confidence in the database and in the RfD. After looking at DERs, I concur.

RfC– NA

Cancer– I concur with confidence in the quantitative estimate as stated, i.e., based on adequacy of the study, which had adequate numbers of animals, lifetime explore, adequate dose selection (presumably because their appeared to be an MTD reached) and only decreased survival in one dose in the males that was statistically-adjusted. When the file is updated uncertainty in the model, appropriateness of combining benign and malignant tumors (e.g., liver tumors progress), appropriateness of combining male and female responses, and combining them using geometric mean, can be addressed.

Miscellaneous Comments
The route of exposure for the reproductive/developmental studies supporting the RfD should be specified.

Response to Charge

1. General Questions

A. Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?

I am not familiar with the primary literature on TDI. EPA appeared to characterize the variability in the experimental data well in this assessment. The uncertainty discussion could be improved, but it was consistent with EPA standards at the time the file was verified for IRIS.

B. How does this compare between pre-Pilot and Pilot/post-Pilot assessments?

This is a good pre-pilot assessment. However, the lack of a supporting document makes the IRIS summary long and cumbersome. A short addendum to the HEED and inclusion of a summary of the external peer review would go a long way towards bringing the file closer to today's pilot/post pilot standards. See also Comment D.

C. Did EPA appropriately address:

(i) strengths and weaknesses of the scientific evidence from available studies and sources of variability in the data used in the assessment?

Yes, strengths and weaknesses of study designs, as well as sources of variability in exposure measurements, response measurements (lung-function testing), and statistical analysis are described. Data gaps in the database are noted in Section I.B.5.

(ii) uncertainties in the underlying data, and uncertainties in the qualitative and quantitative judgments given in the assessment?

Extensive uncertainty discussions were not the general practice for IRIS in 1995. Uncertainty in peak vs. TWA exposures as the determinant of toxicity (sensitization and alterations in lung function), and in clear identification of the NOAEL and LOAEL, are noted in Section I.B.5. The summary lacks a discussion of uncertainty in mechanism of action and sensitive subpopulations. For example, there is a 3 UF for developmental effects – are the young of concern as a sensitive subpopulation? It isn't explicitly stated whether this RfC protects for asthmatic reactions in sensitized individuals (does the 10 UF for intrahuman variability protect them?).

D. Are there other relevant observations or comments?

The assessment on IRIS, while well written, is way too long (22 pages!) and detailed for the general health professional using IRIS. I understand EPA's need to include more than the usual level of detail as "This assessment is not presented in any existing U.S. EPA document". Numerous assessments on IRIS prior to around 1995 do not have a supporting document.

U.S. EPA 1988 and 1989 are cited as source documents. U.S. EPA (1988– I used the 1989 external review draft version) describes the health effects for TDI, but is not a risk assessment document. I received the 1992 HEED in the review package– a more recent version of the 1989 HEED cited on IRIS– but I'm not sure what the difference between the two are. It seems like the more recent version of the HEED should be cited on IRIS, especially since it was developed during the period in which the file was discussed by the RfD/RfC Work Group.

The 1992 HEED derived an RfC (1E-4 mg/cu.m) based on a NOAEL for the same endpoint in the same principal study using the same UF. However, there are differences in interpretation of the principal study and partitioning of the UFs between the HEED and IRIS (verified in 1995). The IRIS summary analysis is more detailed than the HEED; identifies a LOAEL from the Diem et al. (1982) study where the HEED did not; and uses the arithmetic mean for a decrement in chronic lung function where the HEED uses the geometric mean (the two means "were nearly identical" and close to the limit of analytical detection). More recent studies are also included on IRIS. The RfC apparently was under review by the RfD/RfC Work Group for approximately 7 years (Section I.B.6) . It seems like a short update/addendum to the existing HEED with the differences in interpretation could have been prepared during that time.

IRIS notes that the assessment was peer reviewed by external scientists (Section I.B.6) and the comments were evaluated and considered. The comments are in the IRIS files. Why not include a summary of these on IRIS, as is now the practice with the post-pilot toxicological reviews?

2. Identify all risk factors addressed by the IRIS assessment being reviewed.

RfD– No data

RfC– On-line; Verified 5/11/1995

Carcinogenicity Assessment– No data

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review. Were all necessary documents reviewed? If not, what was missing?

The following were reviewed: IRIS substance file for (**www.epa.gov/iris.subst/0503.html**), and Health and Environmental Effects Document for Toluene Diisocyanate (U.S. EPA, 1992).
I also looked at Casarett and Doull, 1996 and at the 1989 External Review Draft of the HAD for TDI, which we had in-house (the 1988 Workshop draft is cited on IRIS).

On IRIS:

RfD– NA

RfC– 4 epidemiological studies (Diem et al., 1982; Hughes, 1993; Jones et al., 1992; Bugler et al., 1991) are described in Section I.B.2. Several additional studies in workers and animals (mice, guinea pigs and rats) are included in Section I.B.4.

Cancer– NA

4. Identify the basis for each risk factor.

RfD– NA

RfC– The RfC of 7E-5 mg/cu.m is based on the NOAEL (HEC) of 0.002 mg/cu.m for decline in chronic lung function, determined from a NOAEL of 0.006 mg./cu.m in male TDI production workers followed prospectively for 5 years (Diem et al., 1982).

Carcinogenicity Assessment– NA

5. Identify:

A. What was the risk factor based on human data (describe) or on animal data? How many subjects in the critical stud(ies)?

RfD – NA

RfC–
principal study= Diem et al., 1982
species= human (race not specified)
sex= men
N= 223
doses= presented as 0.9 ppb for 62 months (arithmetic mean for never-smokers in the low exposure category) and 1.9 ppb for 62 months (arithmetic mean for never-smokers in the high exposure category)
dose range= not clear from write-up– limit of detection to >20 ppb??
type study= 5-year prospective occupational study of polyurethane foam production workers

Carcinogenicity Assessment– NA

B.1. Critical Effect (RfD, RfC)

RfD– NA
RfC– Decline in lung function– longitudinal decrease in FEV1

B.2. Basis for Cancer Quantitative Estimate– NA

C. Route of exposure that yielded critical effect or basis for qualitative cancer assessment

RfD– NA

RfC– Inhalation

Cancer– NA

D. Mechanism of action for the critical effect/tumors observed, if known

RfD– NA

RfC– U.S. EPA (1989) discusses possible immunologic and pharmacologic mechanisms of action for TDI-induced asthma and bronchial hyperreactivity.

Cancer– NA

E. For human data: was a sensitive subpopulation included?

RfD– NA

RfC– Apparently not, but it is not clear from the write-up. A 3 UF for developmental effects suggests a concern about young animals/children. The cohort was comprised of non-asthmatic male workers. It is not clear whether this RfC protects against the development of sensitization to TDI or for asthmatic reactions in sensitized individuals (does the 10 UF for intrahuman variability protect them?).

Cancer– NA

F. For animal data: was the species/strain known to be genetically sensitive? to have any genetic peculiarity with regard to the toxicity of the compound?

RfD– NA

RfC– NA

Cancer– NA

G.1. What were the supporting data for the critical effect (RfD, RfC)?

RfD– NA

RfC– Two occupational studies examining lung function (Bugler et al., 1991; Jones et al., 1992) did not show declines in FEV1 with TDI exposure (Section I.B). Animal studies and the occupational studies of Musk et al. (1982, 1985, 1988) and Wegman et al. (1974, 1977, 1982) support the NOAEL based on Diem et al.

G.2. What were supporting data for cancer qualitative assessment? For quantitative estimate?

NA

6. Identify:

A.1. Uncertainty factor and basis (break down UF)

RfD– NA

RfC– The UF of 30 is comprised of 10 for intra-human variability and a 3 UF to account both for subchronic to chronic extrapolation (this could be better explained) and lack of a developmental study in a second species (other than rats).

A.2. Uncertainty and Limitations in Cancer Assessment– NA

B. Were the following considered: interspecies variability? intra-human variability? Extrapolation from less-than-chronic to chronic duration? extrapolation fro LOAEL to NOAEL? database insufficiencies (e.g., too few studies, limited types of studies)?

Intra-human variability was considered in the 10 UF. Database deficiencies (lack of a developmental toxicity study in a second species) and extrapolation from a less-than-chronic duration to chronic duration were considered together in one 3-fold UF.

7. Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive the UF?

RfD– NA

RfC– A default 10 UF for intra-human variability was applied. I do not know if there is sufficient information (chronic lung function in the general population) to make a quantitative assessment of uncertainty. The UF for database deficiencies and duration extrapolation were not applied in a routine fashion. Rather than applying a

default UF of 10, or an intermediate UF of 3 for each uncertainty, a single UF of 3 was judged as adequate for both areas of uncertainty. This approach suggests the EPA Work Group discussed the UF and that it was data-derived to a certain degree. Further explanation is needed on IRIS for the reader.

8. Identify the MF used, if any, and its basis.

RfD– NA

RfC– None.

9. Is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?

Yes, the critical effect was measured in humans. Casarett and Doull (1996, pages 391 and 534) confirms that the inhalation route is relevant. Skin contact also occurs in occupational settings.

10. What is the overall confidence rating for the data used to derive the overall quantitative estimate? Do you concur?

RfD– NA

RfC– Confidence in the study, database, and RfC are all considered medium. I think that confidence in these areas is at least medium, if not somewhat higher.

Cancer– NA

Miscellaneous Comments

None.

Additional References Recommended for Consideration

None.

Bonnie R. Stern, Ph.D., M.P.H.

ACETONITRILE

(I) Noncancer Oral Risk Assessment

The oral RfD for acetonitrile has been withdrawn. Justification for the withdrawal is provided in the IRIS assessment and is comprehensive and complete.

(*II) Noncancer Inhalation RfC*

1. A. No. The critical effect is mortality, which is a frank effect. A discussion of what caused mortality at the higher doses and whether less frank effects might have been observed at lower doses if other, more relevant parameters (e.g. neurotoxicity or cardiotoxicity) had been measured would have been useful. Uncertainties are better described in supporting documents. The conflicting findings of mortality in the subchronic rodent study versus lack of mortality in the chronic bioassay with the same species could have been better discussed. Justification for not using a UF for extrapolation from subchronic to chronic exposure duration should have included toxicokinetic data, including evidence showing that acetonitrile does not accumulate in the body. Instead of a MF of 10 for forestomach toxicity ambiguities, an MF could have been considered for severity of effect, and to protect against more subtle, unreported symptoms which may preceded death. The MF of 10 was inappropriate for forestomach toxicity, and should have been either 1 or 3.

B. This assessment is an improvement over the pre-pilot assessment in that more detail is given on the studies and on the nature of the uncertainties.

C. There is insufficient discussion on the uncertainties in both the data and the assessment. Insufficient information is given on the physicochemistry, pharmacokinetics, and possible modes of action of acetonitrile, especially those which may be relevant to mortality. In this context, data on the mechanisms of acute toxicity of acetonitrile would be appropriate.

Uncertainties associated with using a frank effect such as mortality as a critical effect should have been more fully discussed. Concerns about developmental toxicity data are unfounded as the critical effect in the critical study protects against all adverse effects occurring at higher doses and developmental studies indicate that adverse effects are only observed at very high doses and usually in conjunction with maternal toxicity. Uncertainties associated with limited hematologic data and concern for these end points are not well presented. The use of a MF of 10 is not appropriately justified. The relevance of mouse forestomach lesions to human toxicity is unclear and this uncertainty was not discussed at all.

2. The RfC is the only risk factor available for acetonitrile.

3. A toxicological review, on EPA's web site, is available for background data. Supporting data is well presented and well organized; each study is briefly summarized in a discrete paragraph, and the corresponding LOAEL and NOAEL are identified, if available from the data. Supporting data includes 3 developmental studies, 1 reproductive study, 5 subacute, subchronic or chronic inhalation studies in mice or rats, 1 specialized investigating hematologic and immunotoxic responses, and two older subchronic inhalation studies with rats, dogs, and rhesus monkeys. Given the nature of the toxicity of acetonitrile, it would have been appropriate to include a section on physicochemical properties and pharmacokinetics.

4. The RfC is based on a mouse NOAEL from a subchronic chronic inhalation study (NTP 1996) The IRIS file was last updated in 1999.

5. The critical study for derivation of an inhalation RfC was conducted by NTP in 1996.
B6C3F1 mice (10/sex/group) were exposed to vapor concentration of acetonitrile of 0, 100, 200, 400, 800, or 1600 ppm, for 6 hours/day, 5 days/week for 13 weeks. Mortality was observed at doses of 400 ppm or higher. Incidences of forestomach squamous epithelial hyperplasia were significantly increased in males exposed to 800 ppm and females exposed to 200 ppm or higher. Forestomach hyperplasia was considered adverse because it was associated

with infiltration of inflammatory cells and at the highest concentration in females, focal ulcers. Increased absolute liver weight in males at doses of 400 ppm or higher was not considered to be adverse in the absence of other liver effects such as histopathology. Exposures at 400 ppm was considered to be a frank effects level (FEL) because of the mortality of one female, followed by increased mortality at higher concentrations. The NOAEL of 200 ppm was identified in this study, based on mortality as an end point.

A follow up study was conducted (NTP 1996) in which B6C3F1 mice (50/sex/group) were exposed to acetonitrile vapor concentrations of 0, 50, 100, or 200 ppm for 111 weeks . In contrast to the 13-week study, no differences in the survival of the treated animals, as compared with control animals were observed, and there were no concentration-related effects on liver weights. The incidence of forestomach squamous cell hyperplasia was significantly increased in males and females exposed to 200 ppm, the highest dose tested. Because it is likely that grooming of contaminated fur and/or mucociliary clearance followed by ingestion contributed to the observed increase in forestomach hyperplasia, the role of inhalation exposure is uncertain. Therefore, an inhalation LOAEL or NOAEL was not identified for this effect. The critical effect was considered to be mortality in the 13-week study, and the NOAEL, adjusted for intermittent dosing and human equivalent concentration, was determined to be 60 mg/cu.m.

No human data were presented and the test species is not known to have genetic sensitivity to the toxicity of acetonitrile.

6. Uncertainty factors applied to the human NOAEL were: a factor of 10 for within-species variability; a factor of 3 for interspecies extrapolation, in accordance with EPA guidelines, and a factor of 3 for data base deficiencies, specifically lack of a comprehensive reproductive study and hematology in mice. It is not clearly stated what is meant by “hematology in mice”. Two mice studies reported significant decreases in hemoglobin, hematocrit, and red blood cell counts; however, these findings were considered by the study authors to be of questionable biological significance. It is likely that the data base deficiency reference to “hematology in mice” indicates a cause for concern for hematologic effects which have not been adequately investigated. This should be more fully explained in the Uncertainty Section.

The total UF was 100. No UF was applied to the use of a subchronic study because there was no mortality in the chronic mouse bioassay at exposure concentrations of 200 ppm or less. The use of a partial UF of 3 for data base insufficiencies, instead of a full factor of 10, was justified on the basis of (1) lack of evidence to suggest that acetonitrile accumulates in the body; (2) fetal developmental effects are marginal and occur only at doses which are maternally lethal.

This justification is confusing because the critical effect was mortality and the critical study was a subchronic inhalation bioassay, not a reproductive or developmental toxicity study. Summaries of the developmental toxicity studies in the IRIS assessment demonstrated (1) a significant increase in the percent of supernumerary ribs per litter in the lowest dose tested in the Mast et al. (1994) study, which was not concentration-related, (2) increased incidences in fetal deaths and resorptions per litter only at a dose which was maternally lethal in the Saillenfait et al (1993) study; and (3) increases in fetotoxicity and birth defects only at doses that were maternally lethal in the Willhite (1983) study. The use of a partial UF of 3 for data base insufficiencies is justified, but not for the reasons presented in the IRIS assessment.

7. The UF were, in part, data-derived. Specifically, no UF was applied to the use of a subchronic study because there was no mortality in the chronic mouse bioassay at exposure concentrations of 200 ppm or less. The use of a partial UF of 3 for data base insufficiencies is justified based on the lack of a comprehensive multi-generation reproductive study, not for the reasons presented in the IRIS assessment.

8. A MF of 10 was applied because of the uncertainty in the role of inhalation exposure in causing the concentration-related increase observed in the incidence of forestomach lesions in male and female mice. It is thought that grooming of contaminated fur and/or mucociliary clearance followed by ingestion contributed to the observed increase in forestomach hyperplasia and thus the contribution of inhalation exposure is unclear. However, the relevance to humans of forestomach hyperplasia is unclear, as humans do not have a forestomach. The application

of a MF of 10 is too conservative, given the ambiguity of the effect of inhalation on forestomach exposure to acetonitrile and the questionable relevance of forestomach toxicity to human toxicity.

9. Mortality is relevant to humans. The route of exposure is also relevant to humans because of the likelihood of occupational and possible consumer exposure to acetonitrile via inhalation.

10. The confidence rating for critical study, data base and RfC is given as medium. I would agree, but not for the reasons cited in the Confidence Section. The critical study appears to be well conducted. The lack of mortality in the chronic bioassay suggests that this frank end point is not of concern at concentrations of 200 ppm or lower and supports the IRIS assessment conclusion that acetonitrile does not accumulate in the body. It would have been useful to present pharmacokinetic data justifying this conclusion. Concern for forestomach toxicity is questionable, based on the ambiguous contribution of inhalation exposure and the fact that humans do not have a forestomach. The rationale for the concern that acetonitrile may affect heart rate, ventilatory parameters, and blood pressure is not given. My medium confidence rating in the data base and the RfC is due to the nature of the critical effect, i.e., mortality. A MF could have been considered for severity of effect, and to protect against more subtle, unreported symptoms which are likely to have preceded death.

(III) Carcinogenicity Assessment

1. A. A quantitative risk estimate for carcinogenicity was not performed due to the equivocal nature of the animal inhalation data and the lack of any human data. The basis for not deriving a quantitative cancer risk estimate is well described and justified.

B. This cancer assessment is a major improvement over the pre-pilot assessments. First, the cancer classification is given with a cogent discussion of why acetonitrile was classified as Category D according to the 1986 cancer guidelines and "cannot be determined" using the 1996 guidelines. Second, the two animal cancer bioassays are described and summarized appropriately, clearly presenting information on statistical and toxicological significance and other factors relevant to the cancer classification.

C. The strengths and weaknesses of the cancer data are well described. However, no conclusions are drawn about the weight-of-evidence for genotoxicity, leaving the reader uncertain about the relevance of the information presented to acetonitrile mutagenicity/genotoxicity and potential carcinogenicity. Pharmacokinetic information is lacking.

(I) Noncancer Oral Risk Assessment

1. A. No. Uncertainties were summarized in a paragraph in the Confidence Section. and default uncertainty factors were applied to the BMD_{10}. Existing data were not used to derive the UF. In particular, toxicokinetics were not discussed, even though some toxicokinetic information is available which would have been useful for interpretation of the principal study results. First, adverse effects were only in the oral dog study and consisted of gastrointestinal inflammation in the small intestine, stomach, and large intestine. These findings can be considered a portal of entry effect. There were no adverse effects observed in either rat or mice oral feeding studies. The lack of concordance of results among animal species for several toxic end points suggest that there also may be a lack of concordance between dogs and humans and therefore the relevance of these findings to humans is questionable. Also, the relevance of beryllium speciation to beryllium toxicity was not discussed.

Another uncertainty which could be reduced by the use of toxicokinetic data concerns the lack of studies on the potential immune effects of oral exposure to beryllium. The concern for immunotoxicity results from the findings that beryllium sensitization and progression to immune-mediated chronic beryllium (lung) disease is the critical effect for inhalation exposure. However, toxicokinetics were not discussed. According to EPA (1991) cited in the Toxicological Review, oral administration results in <1% absorption and storage; most of ingested beryllium passes through the gastrointestinal tract unabsorbed and is excreted in the feces.. Therefore, systemic effects would not be anticipated to occur when exposure is by the oral route because very little of the compound is absorbed. Therefore uncertainty regarding the potential immunotoxic effect of oral exposure is reduced.

The toxicological relevance of the findings in the critical study is uncertain, as is the choice of the critical study. The IRIS file reports in error that adverse effects were seen at the two highest dose levels. Statistical significance was not reported but it is unlikely that the 1/10 incidence of gastrointestinal lesions reported in the second highest dose group tested is significant. Therefore, there were no significant adverse findings in this dose group. The only animals to demonstrate significant gastrointestinal toxicity were in the 500 ppm group, the group which was terminated after 33 weeks of exposure because of “overt signs of toxicity”. This toxicity was not well described but appeared to involve system blood infection resulting from perforation of the gastrointestinal tract and consequent bacterial invasion. Because the toxicity were severe enough to warrant termination of exposure after 33 weeks, the Maximum Tolerated Dose was exceeded. Therefore, the critical effect, observed only in this group, is not appropriate.. Further, the study cannot be considered to be of chronic duration because the only dose group to show significant incidence of the critical effect was terminated at week 33. If the 500 ppm-dose group were to be excluded from the study, then the study NOAEL would be 50 ppm, the highest dose group to undergo long-term exposure (172 weeks)..

The use of the BMD model to characterize the dose-response is questionable, because the dose-response is steeply concave-upward. If the 400 ppm-dose group were to be excluded from the study, there would be no dose-response.

B. Numerous uncertainties are better described in the Confidence Section but are not well discussed. Default UF values are used without consideration of data which might reduce uncertainty. This evaluation is not an improvement of pre-pilot assessments, although it is more detailed.

C. No. The strengths and weaknesses of the scientific evidence and uncertainties in qualitative and quantitative judgements are poorly addresed. Neither toxicokinetic nor mechanistic information is given to support the critical effect of intestinal inflammation. The likelihood that beryllium is a severe irritant and repeated oral administration erodes the gastrointestinal lining, causing inflammation and perforation, was not discussed. Although this was a feeding study, animals were only allowed to feed for 1 hour per day. Therefore, it is likely that food was eaten very quickly; rapid ingestion of a large quantity of treated food would be similar to the “bolus dosing” which is characteristic of oral gavage. It is possible that the observed gastrointestinal inflammation was associated with the manner in which the compound was ingested; this was not discussed in the IRIS assessment. The negative results observed in the rat and mouse studies may have been related to the mode of administration, because beryllium was administered in either drinking water or ad *lib* feed. These dosing regimes result in a more gradual, intermittent

uptake of compound. The adequacy of the principal study design and findings is not discussed, nor is the lack of concordance of the results with other animal studies. See Section 1B for additional comments..

D. This is a poorly done assessment. In general, the toxicokinetics and toxicity of metal compounds differ markedly by route of exposure. Therefore, the use of inhalation data to raise concerns about oral exposure is of limited relevance. A metals toxicologist should review each of the metal assessment on IRIS.

2. The RfD, RfC, and inhalation cancer slope factor were derived for beryllium. .

3. Both a Tox Review and a Health Assessment document are available. Relevant toxicokinetic data and mode of action information were not discussed in the IRIS assessment.

4. The BMD_{10} from a chronic dog studied is used to derive the RfD.

5. The IRIS assessment was last revised in 1997. The principal study was a long-term feeding study by Morgareidge et al. (1976) in which groups of beagle dogs (5/sex/group) were fed diets containing 0,5,50, or 500 ppm beryllium as beryllium sulfate tetrahydrate for 172 weeks. The high-dose group was terminated at week 33 because of overt signs of toxicity (not described in the text) and replaced by a low-dose group fed a diet containing 1 ppm beryllium for 143 weeks. It should be noted that significant adverse effects were only observed at 500 ppm, the highest dose tested and the group which was terminated at 33 weeks because of "overt signs of toxicity" (undescribed). One animal in the 50 ppm group died at week 70 and had gastrointestinal lesions similar but less severe than those observed in the 500 ppm group. In the group terminated at week 33, 9/10 animals exhibited erosive and inflammatory lesions of the gastrointestinal track as well as generalized systemic infection, attributed to bacterial invasion through the damaged intestinal mucosa.

There is no discussion of (1) the mechanism of toxic action, likely related to severe irritation associated with of bolus-like food dosing; and (2) the implications adverse effects observed only at a dose which exceeded the MTD. None of the additional animal literature supports the findings in this study. The test species was not known to be genetically sensitive.

6. Default UF totalling 300 were applied as follows: 10 each for interspecies extrapolation and within-species variability, 3 for data base deficiences. A long list of data base deficiences is provided, and includes lack of human toxicity data by the oral route, lack of oral reproductive/developmental studies; lack of studies investigating immunotoxic end points (considered to be important because it is the critical effect for inhalation exposure).

7. These UF were not data-derived. A consideration of mode of action and toxicokinetic information would have resulted in a reduction in the qualitative assessment of uncertainty, although a factor of 3 for data base deficiences might still be warranted by the absence of a muti-generation reproductive study and developmental studies. Concern for developmental toxicity is based on findings in an inhalation study which demonstrate that beryllium crosses the placenta. However, toxicokinetics indicate that <1% of beryllium is absorbed from the gastrointestinal tract and thus beryllium is unlikely to be a developmental toxicant when exposure is via the oral route.

8. The MF is 1.

9. The critical effect is of questionable relevance to humans. The route of exposure has some relevance because humans may ingest food, soil, or drinking water containing low doses of beryllium.

10. The confidence in the principal study is rated as medium, in the data base and RfD as low-to-medium. I would rate the confidence in the principal study as low, for reasons cited in Sections 1 and 5. I do not consider adverse effects as having been demonstrated at two dose levels, only at the highest dose tested. I do not think that the additional chronic study in dogs improves the confidence in the data base because of the problems with the study previously cited. I would similarly rate the confidence in the RfD as low.

(*II) Noncancer Inhalation RfC*

1. A. The uncertainty and variability were reasonably well described. The RfC derivation utilized human data; therefore no adjustment for interspecies extrapolation was needed. No adjustment was made for within-species variability, which was amply justified by a cohesive discussion of the evidence (including genetic data) demonstrating that individuals who develop CBD are the most sensitive subpopulation.

B. Uncertainty was much better characterized than in the pre-pilot assessments and included a section on the genetics of beryllium sensitivity and a review of the animal models. Exposure uncertainties were adequately discussed.

C. The strengths and weaknesses of the scientific evidence and the uncertainties in the qualitative and quantitative judgments are incompletely addressed. UF of 3 applied to account for the "sensitive nature of the end point" is unclearly explained and appears to have more to do with the use of a LOAEL to derive the RfC than with the nature of the observed toxicity. A UF of 3 for data base deficiencies, specifically the poor quality of the exposure data, is appropriate. The authors note that although there are no developmental studies or multi-generation reproductive toxicity studies, a limited continuous breeding study found that beryllium does not cause reproductive or developmental effects following intratracheal administration. These findings are presumably used to justify the lack of concern for reproductive/developmental toxicity which is inconsistent with the application of a UF for data base deficience in the oral RfD derivation. Furthermore, the sentence stating that systemic distribution of beryllium is less than 1% may apply only to oral exposure.

The inhalation section is reasonably well organized, uncertainty factors and confidence ratings are well presented.

2. The RfD, RfC, and inhalation cancer slope factor were derived for beryllium. .

3. Both a Tox Review and a Health Assessment document are available. Toxicokinetic data and mode of action information were not discussed in the IRIS assessment.

4. The RfC is based on a human LOAEL from an occupational epidemiology study.

5. The IRIS assessment was last revised in 1997. The co-principal studies by Kreiss et al. (1996) and Eisenbud et al. (1949) were occupational epidemiology studies, using measures of beryllium sensitization in workers and progression to chronic beryllium disease (CBD) as the critical effect. Three measures of exposure were recorded. The Kreiss et al. (1996) cohort consisted of 136/139 workers occupationally exposed to beryllium. Supporting information confirming the association between beryllium exposure and CBD, but not sensitization, was provided by the Eisenbud et al. (1949) study.

6. The UF was 10. No UF were applied for either interspecies extrapolation (because the critical study was with humans) or for within-species variability (because individuals developing beryllium sensitization and CBD comprise the most sensitive subpopulation) A UF of 3 applied to account for the "sensitive nature of the end point" is unclearly explained and appears to have more to do with the use of a LOAEL to derive the RfC than with the nature of the observed toxicity. A UF of 3 for data base deficiencies, specifically the poor quality of the exposure data, is appropriate. The authors note that although there are no developmental studies or multi-generation reproductive toxicity studies, a limited continuous breeding study found that beryllium does not cause reproductive or developmental effects following intratracheal administration. These findings are presumably used to justify the lack of concern for reproductive/developmental toxicity. A section on the genetic susceptibility of the sensitive subpopulation is included and supports the choice of a UF of 1 for within-species variability.

7. The UF was data-derived.

8. The MF was 1.

9. The critical effect was observed in a human occupational study of inhalation exposure. Therefore, both the effect and the route are relevant to humans.

10. The overall confidence rating is medium for the RfC, the data base, and the principal study. I would agree.

(III) Carcinogenicity Assessment

1. A. No. The uncertainty and variability were very poorly characterized, both qualitatively and quantitatively. It should be noted that a comprehensive and cohesive discussion of uncertainty was presented in both the Tox Review and the Health Assessment document. Qualitatively, there was no comprehensive weight-of-evidence evaluation integrating the results of the human studies with the supporting animal studies. Shortcomings in the cancer epidemiology studies which may have lead to an overestimate of excess lung cancer risk associated with beryllium exposure were not clearly described. There were no exposure measurements in any of the principal epidemiology studies and a convoluted method for using estimates by NIOSH of the upper and lower bounds of airborne exposure concentrations (spanning one order of magnitude) for quantitative assessment of unit cancer risk was incompletely presented. It is unclear how NIOSH arrived at these estimates, whether they can be justifiably applied to the principal study data, and how excess relative risks were converted to excess cancer incidences to derive the inhalation unit risk.

B. There is more detail than in a pre-pilot assessment but the information is not well integrated and uncertainties are not appropriately addressed. Too much detail was presented on individual studies and not enough characaterizing uncertainties.

C. No. The strengths and weaknesses of the scientific evidence, and the uncertainties in both the data and the qualitative and quantitative judgments are poorly addressed. Each of the studies, human and animal, has many deficiencies and these were not well summarized. The weight-of-evidence for human carcinogenicity is qualitative, and I do not understand why EPA chose to develop a unit cancer risk estimate using human data in the absence of exposure data, instead of waiting for NIOSH to complete the results of its study which has clearly-defined exposure matrices. The relationship of lung toxicity to carcinogenicity is not discussed. Individuals with pre-existing disease appear to be more susceptible to the development of lung cancer. However, because the principal studies were mortality analyses, the association of lung disease with the etiology of lung cancer was not examined. In addition, the relationship between beryllium speciation and toxicity/ carcinogenicity is not well covered.

D. Uncertainties in the data base are much better presented in both the Tox Review and the Health Assessment document.

2. The RfD, RfC, and inhalation cancer slope factor were derived for beryllium.

3. Both a Tox Review and a Health Assessment document are available. Toxicokinetic data and mode of action information were not discussed in the IRIS assessment. Uncertainty and variability, well described in both supporting documents, is very poorly described in the IRIS assessment.

4. A unit risk was derived for excess lifetime cancer from inhalation exposure.

5. The weight-of-evidence for the inhalation carcinogenicity of beryllium was upgraded from B2 to B1, based on the IRIS assessment of limited human data and sufficient animal data, according to 1986 cancer RAGs. Using the 1996 guidelines, the classification is “likely” carcinogen in humans via inhalation and “cannot be determined” for ingested beryllium.

The critical study was a 1980 cohort mortality inhalation exposure study by Wagoner et al. (1980) supported by a 1992 beryllium case mortality study by Ward et al. (1992). The studies had information on duration of exposure, but no data on exposure levels. The studies showed a small excess of lung cancer mortality and a larger increase in mortality from nonneoplastic respiratory diseases. Limitations are noted, the most important of which were the lack of exposure measurements and the presence of numerous confounding variables including incomplete smoking histories and no data on concurrent or prior exposure to other potential lung carcinogens.

Mechanism of action information, other than limited genotoxicity data, are not presented. The association of lung toxicity with lung carcinogeniciity are not discussed.

Supporting data from animal studies included a number of carcinogenicity bioassays in which no excess tumor incidence was observed and several older studies with increased tumor incidences in exposed animals but no reported statistical significance and no dose-response (only one dose was tested in each of the older studies). In genotoxicity data, clastogenic effects were observed in some studies but most mutagenicity studies gave negative results.

6-8. Not applicable to carcinogenicity.

9. Yes, the principal study was a human carcinogenicity study.

10. The discussion of confidence for the inhalation exposure cancer analysis briefly mentions the limitations of the epidemiologic study but concludes that the animal data support the human data and quantitation of risk is justified. In the absence of exposure data from the principal studies, a quantitative inhalation risk assessment is not warranted. Further, the weight-of-evidence suggests that beryllium is a high-dose lung carcinogen; however no information is given on the likely shape of the dose-response curve in the low-dose region.

An oral cancer slope factor was not derived due to inadequate data. I agree with this conclusion.

The relationship of lung toxicity to carcinogenicity is not discussed. Individuals with pre-existing disease appear to be more susceptible to the development of lung cancer. However, because the principal studies were mortality analyses, the association of lung disease with the etiology of lung cancer was not examined. This reduces confidence in the use of a linear model for quantitative cancer assessment because the relationship between exposure and carcinogenicity might be dose-depended. In addition, the relationship between beryllium speciation and toxicity/ carcinogenicity is not well covered.

CHLORDANE - POST

(I) Noncancer Oral Risk Assessment

1. A. No. Although the studies were comprehensively presented, and some background information on physicochemical properties, tissue distribution, and important metabolites was given, the uncertainty and variability in the data were not well discussed.

B. The file is much more comprehensive that pre-pilot assessment, with (1) physicochemical information; (2) conclusions stated at the end of each study summary; (3) description and discussion of the data gaps and health concerns for other end points.

C. The strengths and weaknesses could have been better addressed, especially with regard to uncertainties and variability. The relevance of the critical effect (i.e., liver toxicity) to humans, data base deficiencies and uncertainties (i.e., other end points such has hematopoietic or neurological toxicity which may be more critical than the effect used to derive the RfD) were not appropriately addressed. It is also not clear why EPA selected this study as the critical one, except for historical reasons (i.e., it was the study used for the original oral noncancer assessment in 1989). It seems as if other studies with end points more relevant to humans might have been more appropriate for RfD derivation. Toxicokinetic differences related to species differences might have been used to justify a lower UF for interspecies extrapolation.

Specifically, the assessment did not discuss (1) uncertainties in interspecies extrapolation, where there are no supporting data to suggest that chlordane is a human liver toxicant (although there are data to suggest it induces human toxicity in the nervous and hematopoietic systems); (2) uncertainties in within-species variability; (3) data base deficiencies which include not only the lack of a multi-generation reproductive study but also the lack of a second developmental toxicity study in rabbits in accordance with current test guidelines. The reproductive study by Narotsky and Kavlock (1995) is not cited; this study found a significant increase in the percent loss of pups per litter at both doses tested.

D.

2. The RfD, RfC, oral cancer slope factor, and inhalation cancer slope factor were derived for chlordane. Therefore, this is a complete IRIS assessment.

3. A toxicological review and health effects criteria document are available for background data. The toxicological review is on EPA's website. Other cited reports and peer-reviewed literature and presented in the reference sections for each risk factor.

Information on pharmacokinetics especially metabolism and possible mode(s) of action are missing from the IRIS file.

4. The RfD is based on a mouse NOAEL from a chronic dietary study.

5. The most recent assessment of the oral RfD was conducted in 1999. The critical study was a 24-month chronic toxicity/carcinogenicity study (Khasawinah and Grutsch 1989) in which ICR mice (80/sex/group) were fed either 0, 1, 5, or 12.5 ppm (corresponding to average daily doses of 0, 0.15, 0.75, and 1.875 mg/kg) technical chlordane in the diet for 104 weeks. Treatment-related effects were only observed in the liver and consisted of (1) increased absolute and relative liver weights in high-dose mice of both genders; (2) increased absolute (but not relative) liver weight in the low- and mid-dose females; (3) hepatocellular hypertrophy (swelling) in both genders of mice at the two highest dose groups; (4) hepatic fatty degeneration in males exposed to the highest dose and females exposed to the two highest doses; and (5) hepatic necrosis in the mid-dose group males. The critical effect was considered to be hepatic necrosis although what is meant by necrosis is not clear because it does not appear to have been observed in any group but mid-dose males. The rationale for identifying liver toxicity as the critical effect for this study was presented and a LOAEL and NOAEL for ingested chlordane were identified.

Supporting data were presented and included: (1) discussion of the physicochemical properties of chlordane, including its lipid solubility and persistence in adipose tissue; (2) brief mention of the three major metabolites of chlordane; (3) summary discussion of epidemiologic studies whose results do not support the animal finding that the liver is the critical target organ of toxicity; (4) detailed summary and conclusions from two chronic toxicity/carcinogenicity studies in rats -- only one of which showed evidence of liver toxicity; (5) summary of one additional chronic toxicity study with mice which reported no statistically significant increase in liver toxicity as compared with controls; (6) preliminary results from a tissue distribution rodent study which was interpreted as suggesting that chlordane may have an affinity for reproductive tissue in both pregnant and nonpregnant rats; (7) lack of a multigeneration reproductive toxicity study; (8) brief summary of developmental toxicity studies suggesting possible neurobehavioral, neurological, and blood system effects; (9) evidence from one study suggesting possible reproductive hormone effects.

Very little data was presented on pharmacokinetics: specifically, absorption, distribution, metabolism, and excretion. Metabolic pathway information was not presented. These data were available at the time of the IRIS assessment.

Most strains of laboratory mice tend to be sensitive to liver effects from exposure to chlorinated hydrocarbons.

6. UF totaled 300. Three uncertainty factors were applied to the animal NOAEL: a factor of 10 each for interspecies extrapolation and within-species variability, and a factor of 3 for data base insufficiencies, specifically the lack of a multi-generation reproductive study.

7. The UF were not data-derived. They were default factors applied appropriately to the data base. The numerous uncertainties were not well documented. Specifically, the assessment did not discuss (1) uncertainties in interspecies extrapolation, where there are no supporting data to suggest that chlordane is a human liver toxicant; (2) uncertainties in within-species variability; (3) data base deficiencies which include not only the lack of a multi-generation reproductive study but also the lack of a second developmental toxicity study in rabbits to measure a range of end points in accordance with current test guidelines. The reproductive study by Narotsky and Kavlock (1995) is not cited; this study found a significant increase in the percent loss of pups per litter at both doses tested. The developmental studies cited in the IRIS assessment appear to be geared toward specific end points and it is not clear whether all standard developmental end points were assessed.

8. The MF was 1.0.

9. In my judgment, the critical effect does not appear to be relevant to humans because there are no supporting data in the literature demonstrating adverse liver effects in humans. Presentation of available pharmacokinetic data for humans and rodents might elucidate species differences in absorption, distribution, metabolism or excretion which may be related to differences in toxicity. Further, chlorinated hydrocarbons tend to induce both liver toxicity and benign liver tumors in a number of strains of laboratory mice, and, therefore, the relevance of these findings to humans are questionable.

The route of exposure is relevant because chlordane is an agricultural pesticide and dietary residues are possible.

10. The confidence rating in the critical study, data base, and RfD is medium. I agree with the confidence rating for the critical study but not with the ratings for data base and RfD. In my judgment, the confidence ratings for the data base and RfD are low. There is lack of concordance between human and animal findings. Preliminary evidence from other studies suggest that other end points may be (1) more relevant to humans, and (2) more critical than liver toxicity (i.e. they may have lower LOAELs/NOAELs). Data base deficiencies appear to include the lack of second developmental toxicity study in rabbits, as well as pharmacokinetic information.

(*II) Noncancer Inhalation RfC*

1. A. Although the studies were comprehensively presented, and some background information on physicochemical properties, tissue distribution, and important metabolites was given, the uncertainty and variability in the data were not adequately described. Considerable discussion was given to the likelihood that other end points, specifically neurotoxicity, hematopoietic toxicity, and reproductive toxicity were more relevant to humans than liver toxicity; however, no quantitative assessment of these uncertainties was presented. Default uncertainty factors were applied to the NOAEL (i.e., the assessment did not integrate the concerns about human relevance of the critical effect into the uncertainty analysi or utilize toxicokinetic data or information from other studies).

B. The file is much more comprehensive that pre-pilot assessment, with (1) physicochemical information; (2) conclusions stated at the end of each study summary; (3) description and discussion of the data gaps and health concerns for other end points.

C. No. The weaknesses of the scientific evidence from the rodent studies was not well discussed. The relevance of the critical effect (i.e., liver toxicity) to humans, data base deficiencies and uncertainties were not appropriately addressed. It is also not clear why EPA selected this study as the critical one, except for historical reasons (i.e., it was the study used for the original oral noncancer assessment in 1989). It seems as if other studies with end points more relevant to humans were appropriate for RfD derivation. These include the 90-day inhalation study by Khasawinah et al (1989) with cynomologous monkeys in which the only effect observed was an increase in mean liver and thyroid weights at the highest dose tested, without accompanying histopathology; these effects were not judged to be adverse. Differences in species sensitivity evident from pharmacokinetic studies are not presented.

D. There was considerable redundancy in the supporting data presented in support of the RfC as all cited studies were previously discussed in the RfD section.

2. The RfD, RfC, oral cancer slope factor, and inhalation cancer slope factor were derived for chlordane. Therefore, this is a complete IRIS assessment.

3. A toxicological review and health effects criteria document are available for background data. The toxicological review is on EPA's website. Other cited reports and peer-reviewed literature and presented in the reference sections for each risk factor..

4. The RfC is based on a rat NOAEL from a subchronic inhalation study.

5. The critical study for derivation of an inhalation RfC was conducted in 1989 (Khasawinah et al. 1989), in which Wistar rats (35-47 animals/sex/group) were exposed to 0., 0.1, 1.0, or 10 mg/cum. Technical chlordane for 8 hours/day, 5 days/week for 13 weeks followed by a 13 week recovery period. Alterations in blood chemistry indicative of changes in liver function were observed only at the highest dose tested and were considered to demonstrate hepatic toxicity. The LOAEL was 10 mg/cu.m. and the NOAEL, 1 mg/cu.m. The animal NOAEL was adjusted for intermittent dosing and converted to a human NOAEL of 0.65 mg/cu.m. The test species is not known to be genetically sensitive to chlordane toxicity.

Supporting data were well documented; however, as with the supporting data for the RfD, no mention is made of the Narotsky and Kavlock (1995) developmental study in rats or the Khasawinah et al. (1989c) monkey study. Furthermore, the supporting studies were the same as those cited for the RfD and thus, there was considerable redundancy in the IRIS file.

6. UFs applied to the human NOAEL were: a factor of 3 for interspecies extrapolation, in accordance with EPA guidelines), a factor of 10 for extrapolation from a subchronic to a chronic study, and a factor of 3 for data base deficiencies, specifically a lack of a multi-generation reproductive study. The critical study established a NOAEL; therefore, there was no adjustment needed for extrapolation from a LOAEL to a NOAEL.

7. The UF was not data-derived; default UFs were utilized. All information was not used in the uncertainty assessment, in particular, the findings of the 90-day inhalation study in cynomologus monkeys by Khasawinah et al. (1989c) which did not show any adverse effects at the highest dose tested

8. The modifying factor was 1.

9. The identified critical effect does not appear to be relevant to humans because of (1) the absence of reports in the human literature suggesting liver effects, and (2) the study by Khasawinah et al. (1989c) on cynomologus monkeys which did not demonstrate adverse effects at the highest dose tested. The route of exposure is relevant to humans because chlordane is an agricultural pesticide and workers are likely to be exposed via inhalation to this compound.

10. The confidence rating for the critical study is medium; the confidence for the data base, and RfC is low. The choice of critical effect is supported by a shorter 28-day study in which a progression of effects with increasing dose -- from alterations in blood chemistry at 28.2 mg/c.m to liver histopathology at 413 mg/cu.m -- was observed in the same species of rats. However, no mention is made of the monkey study in which adverse effects were not observed. Monkey data are more likely to be relevant to humans than rodent data and therefore, the choice of critical study is questionable. I would rate the confidence in the critical study as low. I agree with the low rating for confidence in the data base and the RfC.

(III) Carcinogenicity Assessment

1. A. The uncertainty and variability is poorly characterized. The human relevance of the mouse liver tumors is not discussed, neither qualitatively nor quantitatively. Chlordane is classified in as a "nongenotoxic murine hepatocarcinogen" in the Supporting Data for Carcinogenicity Section. However, discussion of the evidence for sublinearity or nonlinearity of the dose-response of chlordane carcinogenicity in the low-dose region of the dose-response curve is restricted to a single sentence in the Confidence Section. The results of the cell proliferation study, the numerous mutagenicity/genotoxicity studies, the evidence supporting the sublinearity/nonlinearity at low doses, and the cytotoxicity accompanying the high-dose tumorigenic findings (which are supportive of a cytotoxicity-mediated carcinogenic response) are not appropriately presented or integrated into the discussion. There is insufficient discussion on the implications of the findings of increased incidences of *malignant* mouse liver carcinoma, as compared with increases in *benign* mouse liver adenomas.

B. There is more extensive coverage of the carcinogenicity studies in this post-pilot assessment. The gentoxicity section is too short and would benefit from a more detailed discussion of the "limited evidence for mutagenicity" in the contest of the classification of chlordane as a "nongenotoxic murine heaptacarcinogen". The conclusions are tentative at best.

C. The strengths and weaknesses of the data and uncertainties in the data with regard to implications for the potential human carcinogenicity of chlordane are not appropriately addressed. There are conflicting human and animal data that are not adequately resolved. Mode of action information is not well integrated into the assessment. The route-to-route extrapolation for derivation of an inhalation cancer slope factor is not fully justified and the use of a default inhalation absorption rate of 100% is likely to be an overestimate due to the semi-volatile nature of chlordane.

D. The conclusions are confusing, as the authors of the IRIS assessment themselves question their own quantitative evaluation. The summary reads: "Although the evidence for chlordane exposure leading to cancer in humans is tentative at best, it indicates that the target is the hematopoietic system rather than the liver. Therefore, it is prudent to regard mice liver cancer as an indicator of human hazard, and to regard the extrapolated linear no-threshold dose-response curve as a health-protective estimate of the doses at which human hazards could occur." This summary talk is about hazard, not quantitative assessment, and seemingly discounts the validity of the cancer dose-response analysis to estimate excess lifetime human cancer risk. Because there are no data concerning the dose-response of chlordane for hematopoetic cancer, it is not known whether a cancer risk factor based on liver.tumors would be protective. Thus, the summary negates the dose-response and focuses on hazard.

2. The RfD, RfC, oral cancer slope factor, and inhalation cancer slope factor were derived for chlordane. Therefore, this is a complete IRIS assessment.

3. A toxicological review and health effects criteria document are available for background data. The toxicological review is on EPA's website. Other cited reports and peer-reviewed literature and presented in the reference sections for each risk factor.

Existing human data are well summarized. However, information on pharmacokinetics especially metabolism and possible mode(s) of carcinogenic action are missing from the IRIS file.

4. The basis for the oral cancer slope factor was the geometric mean of 5 slope factors using liver carcinoma incidence from 5 mice data sets. Two modeling approaches were utilized: (1) the linearized multistage model for derivation of q1*, and (2) a linear extrapolation based on the lower 95% confidence limit for BMD_{10}. However, the q1* was used for risk estimates because the 1996 proposed cancer risk assessment guidelines have not yet been accepted. The inhalation cancer slope factor was conducted using a route-to-route extrapolation from oral data, and assumed 100% inhalation absorption and a human breathing rate of 20 cu.m/day..

5. Five sets of mouse cancer bioassay data were used for derivation of the oral cancer slope factor. The data came from three studies: (1) a 1973 IRDC study in which groups of 100 male and 100 female CD-1 mice were fed diets containing technical chlordane at concentrations of 0, 5, 25, or 50 ppm for 18 months; (2) a 1977 NCI study in which groups of 50 male and 50 female B5C3F1 mice were exposed to dietary concentrations of chlordane of 0, 29.9, and 56.2 ppm for 80 weeks and then observed for an additional 10 weeks; and (3) a study by Khasawinah and Grutsch (1989a) in which ICR mice (80/sex/group) were fed 0, 1, 5, or 12.5 ppm technical chlordane in the diet for 104 weeks. The critical effect for cancer was a statistically significant increase in the incidence of liver carcinoma Mouse carcinoma tumors were accompanied by both increases in liver adenomas and significant hepatotoxicity. In two chronic rat bioassays with either Osborne-Mendel or F-344 rats, no treatment-related increase in liver neoplasms or other tumors was observed.

Supporting data on genotoxicity and mutagenicity were briefly reviewed; chlordane was evaluated as having limited evidence of mutagenicity and classified as a "non-genotoxic murine hepatocarcinogen". However, the mode of carcinogenic action is described as being uncertain.

The weight-of-evidence classification was given as B2 (limited data in humans, sufficient data in animals) using the 1986 cancer guidelines, and as a likely human carcinogen by all routes of exposure under the 1996 proposed cancer risk assessment guidelines, using as justification (1) human epidemiology studies suggesting an association between chlordane exposure and non-Hodgkins lymphoma and aplastic anemia; (2) animal studies showing increases in benign and liver tumors in four strains of mice but not tumors in rats; and (3) structural similarity to other rodent liver carcinogens.

6-8. Not applicable to carcinogenicity.

9. There is little evidence to suggest that the mouse liver carcinogenicity of chlordane is relevant to humans. Laboratory mice tend to be sensitive to liver tumorigenesis from lifetime exposure to chlorinated hydrocarbons. Strains of this species tend to have a high background occurrence of benign liver tumors. The route of exposure is relevant because of the potential for dietary exposures to chlordane resulting from its use as an agricultural pesticide.

10. The confidence expressed in the Discussion of Confidence Section for Oral Exposure is high regarding the likelihood that chlordane is a mouse liver carcinogen at dietary concentrations above 10 ppm. In my judgment, the confidence is low regarding the likelihood that the rodent liver cancer findings are relevant to humans. The confidence is also low regarding the use of a linearized multi-stage model to assess the shape of the dose-response curve at low exposure concentrations because "there is indication that the dose-response curve is sublinear in the dose region between 5 and 60 ppm". However, "linearity at low doses cannot be ruled out on theoretical grounds".

I agree with the low confidence rating. The conclusions, however, are confusing, as the authors of the IRIS assessment themselves question their own quantitative evaluation. The summary reads: "Although the evidence for chlordane exposure leading to cancer in humans is tentative at best, it indicates that the target is the hematopoietic system rather than the liver. Therefore, it is prudent to regard mice liver cancer as an indicator of human hazard, and to regard the extrapolated linear no-threshold dose-response curve as a health-protective estimate of the doses at which human hazards could occur." This summary talk is about hazard, not quantitative assessment, and seems to discount the validity of the cancer dose-response analysis. There are no data concerning the dose-response of chlordane for hematopoetic cancer and therefore it is not known whether a cancer risk factor based on liver.tumors would be protective. Thus, the summary negates the dose-response and focuses on hazard.

(I) Noncancer Oral Risk Assessment

No data are available for an oral RfD assessment.

(*II) Noncancer Inhalation RfC*

1. A. The critical study was well conducted and the uncertainty and variability in the critical study was well characterized. However, uncertainty in the data base with regard to other toxic effects is only briefly mentioned. Concern about the uncertainties associated with respiratory and irritant effects of repeated exposure to DBCP and the lack of data to characterize hazard and quantify dose-response for these endpoints is discussed briefly in the section on supplemental documentation. However, uncertainty regarding female reproductive toxicity is not well characterized. The use of a full UF of 10 for subchronic to chronic exposure duration was justified in the file because there were sporadically lower sperm counts observed in rabbits at the NOAEL and these findings may have become toxicologically and statistically significant with increased exposure duration. However, according to current guidelines, when a reproductive study is used to derive a noncancer risk factor, a UF for subchronic to chronic exposure duration is not applied to the NOAEL. Therefore, the use of this UF factor is questionable.

B. This is a well-documented pre-pilot assessment, although it tends to focus primarily on the critical effect, testicular toxicity, to the exclusion of other toxic end points.

C. The strengths of the scientific evidence from available studies on male reproductive toxicity in both humans and animals are adequately discussed. However, uncertainties in the underlying data concerning other target organs of toxicity are not well addressed. The similarities in male reproductive toxicity between animals and humans are captured in the IRIS evaluation but are not captured in the uncertainty assessment. The use of available pharmacokinetic data might have reduced the uncertainty associated with interspecies extrapolation and and may have also reduced uncertainty associated within-species variability. Although weaknesses in the scientific evidence regarding respiratory tract effects are presented; weaknesses and uncertainties regarding female reproductive toxicity and liver and kidney toxicity are not adequately dealt with in the assessment. However, it is not known whether addressing uncertainties associated with other target organs of toxicity would have altered the quantitative uncertainty analysis.

D. This IRIS assessment is biased toward the presentation of toxicological data on the critical effect, testicular toxicity. While the bias is understandable because of the frank occurrence of testicular toxicity in humans, the IRIS assessment does not appropriately address other toxic end points. Also, it would have been instructive to examine the epidemiologic data more quantitatively. Although human exposure information was extremely limited, it is interesting to note that the use of a human study to calculate the RfC would have yielded an RfC very similar to the one derived from the animal study; however, the uncertainty factors would have differed. This similarity increases confidence in the RfD.

2. The inhalation RfC was assessed in the IRIS review. An oral RfD assessment was not conducted.

3. There was extensive review of supplemental documentation pertaining to testicular toxicity. However, a MEDLINE search for scientific literature available at the time the IRIS assessment revealed that other documentation relevant to a toxicity evaluation of DBCP was not included in the IRIS file. The IRIS file focussed on male reproductive toxicity in humans and animals, and on standard animal bioassay data (i.e., chronic and subchronic studies). Information available at the time but not included in the supplemental documentation included studies on female reproductive toxicity, pharmacokinetics and metabolism, mutagenicity/genotoxicity, and liver/kidney toxicity.

Eight epidemiology studies of workers occupationally exposed to DBCP were briefly summarized. Although many of these studies reported occupational exposure duration in terms of hours or years, only one study measured DBCP airborne concentrations in the work place. All human studies reported testicular effects in workers exposed to DBCP vapors. A number of animal bioassays employing a range of exposure routes (i.e., drinking water, inhalation, oral gavage) and doses confirmed the findings in human studies and were also summarized. Rats, mice, and rabbits were tested, with rabbits judged to be the most sensitive test species for assessing quantitatively the critical effect of testicular toxicity. The testicular toxicity parameters investigated in reproductive studies were extensive and included hormone levels, sperm counts, motility, and viability, reproductive histopathology and recovery/regeneration (upon cessation of exposure), fertility indices including measures of fetal loss and litter size, and teratology. The most detailed reports presented in the IRIS files were of the 1982 NTP inhalation carcinogenesis bioassay comprised of four different studies involving rats and mice. Limitations of the animal tests in terms of study design, analysis, and reporting are also given.

4. The basis for the RfC was a rabbit NOAEL, rabbits having been previously identified as the most sensitive animal test species.

5. Although there were numerous reports in the scientific literature of testicular toxicity in humans, only one study reported a workplace exposure concentration. Therefore, a quantitative dose-response analysis could not be conducted on humans because of insufficient exposure data. However, the critical adverse effect on which the RfC was based was identified from human data.
The animal studies were designed to measure a range of reproductive toxicity parameters and to examine the effect of exposure duration on reproductive toxicity.

The inhalation RfC was conducted in 1991, using as the critical study a reproductive toxicity inhalation study with New Zealand white rabbits, conducted by Rao et al. (1982). Male rabbits (10/group) were exposed to atmospheric concentrations of DBCP vapors (adjusted for 97.3% purity) of 0, 0.1, 1, or 10 ppm for 6 hours/day, 5 days/week for 14 weeks. Semen was collected and evaluated during exposure and during a 32-38 week recovery period. Adverse effects including reduced sperm counts; abnormal spermatozoa; increased FSH serum levels; reduced testes weight; and atrophy of testes, epididymides, and accessory sex glands including the prostate were observed at the two highest doses. At the lowest dose tested, sperm counts were sporadically lower than control values although this finding was only statistically significant during exposure week 12. Mating of exposed male rabbits to unexposed females at weeks 14 and 41 induced the following effects: (1) at 14 weeks, no pregnancies occurred in mating with males exposed to 10 ppm, indicating infertility, and a decrease in the mean number of implantations/litter was observed in the 1 ppm-treated group; (2) at 41 weeks, all rabbits in the two lowest dose groups (0.1 ppm and 1 ppm) produced normal litters and 2/5 males in the 10 ppm group regained fertility and produced normal litters. Based on the results of the study, the LOAEL is 1 ppm and the NOAEL is 0.1 ppm, with the critical effect being testicular toxicity. Adjustments for intermittent-to-continuous exposure duration and calculation of a human equivalent dose concentration (HEC) yielded a NOAEL (HEC) of 0.17 mg/cu.m

No mode of action information is presented. The testicular toxicity of DBCP was confirmed by the findings of numerous occupational epidemiology studies. Therefore, there is good interspecies concordance. The test species had previously been determined to be the most sensitive animal species.

6. All appropriate uncertainty factors were considered in the uncertainty section, with a very brief synopsis of the rationale for the use of each. For interspecies variability, a UF of 3 was used, in accordance with EPA guidelines when dosimetric adjustment is conducted. For intraspecies variability, a default UF of 10 was applied. The RfC was based on an animal NOAEL; therefore, no adjustment was necessary for the use of a LOAEL. A UF of 10 was applied for the use of a subchronic study rather than a chronic study. Justification for the use of a full UF of 10 was made on the basis of (1) the finding of marginal decreases in sperm count at the NOAEL consistent with more severe effects seen at higher doses including the LOAEL, and (2) concern that the marginal effects observed at the NOAEL might become significant with continued, chronic exposure. A UF of 3 was applied to the animal NOAEL because of

the lack of a multigenerational reproductive study and an inhalation developmental toxicity study. Thus, UFs totaled 1000.

7. The UF was, in part, data-derived. First, a dosimetric adjustment was used to convert the inhalation animal NOAEL to an inhalation human NOAEL, and the interspecies extrapolation UF was correspondingly reduced to 3. Pharmacokinetic and pharmacodynamic information was not employed to further reduce the interspecies extrapolation. Given the similarity in findings between animal and human studies, it is highly likely that the mode of action for testicular toxicity is similar across species. Use of pharmacokinetic data might have resulted in a further reduction in the UF for interspecies extrapolation. Second, the use of a full UF of 10 for subchronic to chronic exposure duration was justified on the basis of the results observed at the NOAEL (i.e., sporadically lower sperm counts which may have become toxicologically and statistically significant with increased exposure duration). However, according to current guidelines, when a reproductive study is used to derive a noncancer risk factor, a UF for subchronic to chronic exposure duration is not applied to the NOAEL. Therefore the use of this UF factor is questionable.

8. A MF of 1 was used.

9. The critical effect is directly relevant to humans, because of the concordance in findings between animal and human studies. The route of exposure is relevant to human occupational exposure. However, a data gap is the lack of evaluation of DBCP toxicity via the oral route. Because DBCP is used in agriculture, it is likely that dietary residues are another route of human exposure.

10. The study, data base, and RfC were rated of medium confidence, due to failure of investigators to report respiratory effects in the principal study, and uncertainty about whether respiratory tract effects would be observed at doses lower than those inducing testicular toxicity. I would add uncertainty regarding the effects on female reproductive toxicity which were not well discussed in the IRIS assessment. DBCP is also a liver and kidney toxicant and quantification of the dose-response for these end points was not well presented.

(III) Carcinogenicity Assessment

A carcinogenicity assessment was not conducted for DBCP, despite the existence of sufficient evidence from NTP (1982) bioassays of DBCP-induced rodent tumorigenesis. There was also extensive information at the time of the IRIS assessment on the mutagenicity and genotoxicity of DBCP.

HEXACHLOROBENZENE - PRE-PILOT

(1) Noncancer oral risk assessment

1. A. No. Uncertainty and variability are not discussed at all in the IRIS assessment. The UF applied to the animal NOAEL are default values.

B. This is a pre-pilot assessment. The lack of presentation of supporting study information makes this assessment notably short and incomplete, even by pre-pilot assessment standards.

C. No. There is no discussion of the strengths and weaknesses of the scientific evidence or the uncertainties and variability in the qualitative and quantitative judgments. There is reference to other studies but very little information is presented. This is typical of a non-pesticides risk assessment at the time.

2. An RfD and oral and inhalation cancer slope factors are presented. The RfC was not derived.

3. Supporting documentation include a drinking water criteria document and a health assessment document. No supporting data from these documents were included in the IRIS file.

4. The RfD was derived from a NOAEL obtained from a rat chronic feeding study.

5. The IRIS assessment was performed in 1988. In a rat chronic feeding study (Arnold et al. 1985) 50 male and 50 female Sprague-Dawley rats (Fo) were exposed to hexachlorobenzene in the diet at concentrations of 0, 0.32, 1.6, 8.0, or 40 ppm for 90 days prior to meeting and until 2 days after parturition. The number of offspring (F1) was reduced to 50/sex/dose group and fed diets containing the same hexachlorobenzene concentrations as the diets of their parents. Although not stated, it is assumed that the F1 generation was treated with dietary hexachlorobenzene for 2 years. No treatment-related adverse effects were reported in the two lowest dose groups. The 8 ppm F1 groups exhibited a significant increase in hepatic centrilobular basophilic chromogenesis. The highest dose group (40 ppm) F1 animals exhibited pup mortality, liver effects, and severe kidney effects (males only).

6. The UF totaled 100, consisting of a UF of 10 for interspecies extrapolation and a UF of 10 for within species variability.

7. The UF were default values. No discussion was presented.

8. The MF was 1.

9. There is some evidence from human studies that the liver is one of several target organs of hexachlorobenzene toxicity. The route of exposure is relevant because hexachlorobenzene is an ingredient of some agricultural fungicides..

10. The confidence rating in the principal study and the RfD is medium. These medium ratings are given because of (1) the "... unusual dosing scheme" in the principal study (i.e., animals were dosed prenatally and throughout their lifetimes; their parents were also dosed prior to mating) and (2) the finding of increased porphyrin levels in the liver, kidney, and spleen in a supplemental subchronic rat study which was an end point not evaluated in the principal study. Although it is not clearly stated in the assessment, concern for the finding of increased porphyrin levels in rodents is relevant to humans because this effect was observed in humans who ingested hexachlorobenzene-contaminated seed grain. The high confidence rating given the data base is cited as being due to the extensive number of quality research studies available. However, these are not documented or discussed in the IRIS assessment.

(II) Noncancer inhalation risk assessment

An RfC was not derived.

(III) Carcinogenicity Assessment

1. A. Variability and uncertainty were not characterized. The strengths and weaknesses of the scientific evidence were not discussed. Although the study summaries were short, the animal tumor data were consistent across species and across studies and supported the weight-of-evidence classification. There were no relevant human data. The performance of an oral route-to- inhalation route extrapolation for derivation of an inhalation unit cancer risk is consistent with the standards at the time the assessment was conducted. Oral to inhalation route extrapolation was consistent with the then state-of-the-science in that the observed liver tumors constituted a systemic effect and therefore, oral data could be used to quantitatively estimate inhalation cancer risk.

B. This pre-pilot assessment and is brief and lacks detail, but is likely to have been considered adequate according to the standards at the time.

C. There is little discussion of scientific strengths and weaknesses. The weight-of-evidence for B2 cancer classification and confidence is the carcinogenicity assessment are summarized in 1-2 sentences and emphasize the concordance in tumor findings in three rodent species and multiple rodent studies. Gentoxocity/mutagenicity data to support the tumor results and dose-response information are not presented.

Hexachlorobenzene is classified as Category B2, i.e., probable human carcinogen based on inadequate human data and sufficient data in three rodent species via the oral exposure route.

Sprague-Dawley rats (94/sex/group) were fed 0, 75, or 150 ppm in the diet for up to 2 years in a study by Erturk et al. (1986). Treated animals of both sexes surviving past 12 months showed significant increases in liver and renal tumors. Females were more susceptible to developing liver tumors and males were more likely to develop renal tumors. The time-to-tumor onset was generally longer than 1 year. Syrian golden hamsters (30-60/sex/dose group) ingested 0, 50, 100, or 200 ppm hexachlorobenzene in the diet for a lifetime (Cabral et al. 1977). A signficant dose-related increase in the incidence of hepatomas and liver hemangioendotheliomas was observed in both genders of hamsters. The incidence of thyroid alveolar adenomas was also increased in males in a dose-related manner but was statistically significant only in the high dose group.. Male and female Swiss mice exposed to 0, 50, 100, or 200 ppm hexachlorobenzene in their diet for up to 120 weeks exhibited a dose-related increase in hepatomas which was significant among females in the high dose group as compared with controls. *In vitro* mutagenicity data produced both positive and negative results. In an *in vivo* dominant lethal mutation assays, hexachlorobenzene administered to rats via gavage did not induce mutagenic effects.

The Ertuk et al. (1986) study was used to derive the oral cancer slope factor, which was based on an increased incidence in liver carcinoma in female rats.

The confidence in the oral slope factor was supported by 14 different data sets in 3 species. The slope factors of these data sets were within the range of 1 order of magnitude of the slope factor from the Ertuk et al. (1986) study.

The inhalation unit risk was derived from the oral carcinogenicity data.

MANGANESE

1. A. Yes. The quantitative assessment discusses and takes into account both the essentiality and toxicity of manganese, the lack of a reliable animal model for manganese toxicity, individual variability with regard to toxicity and essentiality requirements, pharmacokinetic information, putative mechanisms of neurotoxicty, and the limitations of deriving an RfD for an essential trace elements (i.e., the RfD is estimated to be an average daily dose which is not associated with toxicity in the general population; intakes above the RfD are not necessarily associated with toxicity). Further, differences in absorption associated with different oral sources of manganese (i.e., food, drinking water, soil) are noted and modification of the RfD is suggested for drinking water and soil intake.

B. This assessment is much more comprehensive and thorough than most pre-pilot assessments. The assessment was conducted in 1995. Because manganese is an essential trace element, there would be concern for adverse health effects resulting from manganese deficiency, and thus a comprehensive review and evaluation of the literature was needed..

C. The principal studies address both toxicity and essentiality. The strengths and weaknesses of the scientific evidence are well documented. Uncertainties concerning pharmacokinetics, individual variability, and sensitive subgroups such as infants and persons with pre-existing liver disease are thoroughhly discussed.

D. This is a well done assessment.

2. The RfD and RfC were derived for manganese.

3. Both a drinking water criteria document and a health assessment document are available for manganese. All necessary documents were well reviewed and support the IRIS evaluation.

4. The RfD for manganese was derived using a chronic NOAEL estimated from composite human data from large populations consuming normal diets over an extended period of time without evidence of adverse effects.

5. The IRIS assessment was completed in 1995. Information on the toxicity of manganese was derived from one epidemiology study (Kondakis et al. 1989) on neurotoxicity associated with with a range of exposures to manganese in natural well water, and analysis by NRC (1989), (Freeland-Graves et al.1987), and WHO (1973) on manganese essentiality and the minimum daily dose required for health. In the epidemiology study, an increase in the incidence of neurologic symptoms was associated with an increase in drinking water exposure to manganese. However, because of variability in the study population of manganese exposure from food intake, this study could not be used to establish a quantitative dose-response. The RfD was based on a composite of data from large human populations consuming normal diets over an extended period of time with no adverse effects. Putative mechanism of toxic action is discussed. The number of human subjects is not specified in the essentiality studies but is very large. Sensitive subpopulations, specifically infants and individiuals with pre-existinag liver disease, were considered.

6. The UF was 1.

7. Yes. The UF of 1 is justified because (a) the data used to derive the chronic NOAEL was from numerous cross-sectional investigations in humans; (b) no adverse effects were observed at this dose level; and (c) manganese is an essential element and deficiency will cause adverse health effects. The chronic NOAEL is conservative, in that intakes above this value are not assumed to be toxic, and individuals vary in their manganese requirements. Because the RfD is conservative, a UF for within-species variability is not necessary. The chronic NOAEL is assumed to be protective of a range of potential toxic end points because no adverse effects were observed at this dose level.

8. The MF is 1 for food intake of manganese. Because neurotoxicity has been associated with drinking water exposure (gastrointestinal absorptoin is greater in the absence of food in the gut), a MF of 3 is recommended for drinking water and soil intakes. Pharmacokinetic data and data on sensitive subpopulations are presented to support the use of this MF for drinking water and soil ingestion exposures.

9. The critical effect is absence of toxicity and is relevant to humans, as is the route of exposure.

10. Confidence rating is medium for the studies, the data base and the RfD. Variability in the absorption and elimination of manganese by humans support this confidence rating.

(II) Noncancer Inhalation RfC

1. A. Yes. Uncertainties and variability are well documented. Uncertainties discussed include lack of identification of a NOAEL, lack of individual exposure data and information on the particle size distribution of manganese dusts, and insufficient information about differences in toxicity of different forms of manganese.. The results of the principal studies are consistent with those of other human studies. Pharmacokinetic data including mode of action and a discussion of sensitive subgroups are included in the Supporting Studies Section. Supporting animal data on pharmacokinetics and mode of action are presented. The duration of exposure in the principal studies was less-than-chronic and this uncertainty is discussed. The reproductive toxicity data are limited but suggest that an RfC based on neurological dysfunction is likely to be protective of reproductive toxicity. Data on developmental toxicity are inadequate and this uncertainty is also discussed. What is lacking is a discussion of essentiality in the context of inhalation exposure.

B. This assessment is pre-pilot. However, it is comprehensive and cohesive and thoroughly discusses the numerous uncertainties associated with derivation of the RfC.

C. The strengths and weaknesses in the scientific evidence and uncertainties in the qualitative and quantitative judgments are well presented.

2. The RfD, and RfC were derived for manganese.

3. Both a drinking water criteria document and a health assessment document are available for manganese. All necessary documents were well reviewed and support the IRIS evaluation.

4. The RfC is based on a human LOAEL from occupational exposure studies.

5. The IRIS assessment was conducted in 1993. T he principal studies are is by Roels et al. (1992, 1987). An epidemiologic investigation of workers exposed to manganese dioxide, oxides, and salts examined the effects of inhalation exposure in the work place on neurological and respiratory symptoms, neurobehavioral function and fertility. In the 1992 cross-sectional study, the cohort consisted of 92 exposed male workers and 101 matched controls. The principal adverse findings were an increase in neurobehavioral dysfunction as measured by visual reaction time and five measures of eye-hand coordination, and increase in self-reported respiratory symptoms. Exposure to respirable manganese dusts was measured. A C x T analysis, using 8-hour TWA occupational exposures for various job classifications multiplied by the individual work histories in years was performed, and used to derive the LOAEL. In the 1987 cross-sectional study, the cohort consisted of 104 workers and 104 matched controls. Exposure to total manganese dusts were measured. Neurological and respiratory function were examined. Significant differences were found for a range of neurological function and symptoms. The populations in both studies were not known to have any genetic sensitivity to inhaled manganese.

6. The total UF was 1000, consisting of a factor of 10 for within-species sensitivity, a factor of 10 for the use of a LOAEL, and a factor of 10 for data base limitations including a less-than-chronic exposure duration, the lack of developmental toxicity studies, and lack of information on differences in toxicity of different forms of manganese.

7. The UF were default values and were not data-derived.

8. An MF of 1 was used.

9. The critical effect and route of exposure are relevant to humans.

10. The confidence rating in the study, data base, and RfC are medium. Uncertainties discussed include lack of identification of a NOAEL, lack of individiual exposure data and information on dust particle size distribution. However, the results of the principal studies are consistent with those of other human studies. Pharmacokinetic data including mode of action and a discussion of sensitive subgroups are included in the Supporting Studies Section. The duration of exposure was less-than-chronic. The reproductive toxicity data are limited but suggest that an RfC based on neurological dysfunction is likely to be protective of reproductive toxicity. Data on developmental toxicity are inadequate. A medium confidence rating for study, data base, and RfC is warranted.

(III) Carcinogenicity Assessment

Manganese is classified as Category "D", not classifiable as to human carcinogenicity because existing studies are inadequate to assess manganese carcinogenicity.

(I) Noncancer Oral Risk Assessment

1. A. Yes. Uncertainty and variability are reasonably well documented. The UF of 3 for interspecies extrapolation was data-derived, based on pharmacokinetic data. MMA is metabolized more slowly in humans and this information is used to justify a reduction in the rat-to-human UF. An additional factor discussed in the IRIS assessment was the lack of a forestomach in humans, which is cited in the IRIS assessment as the portal-of-entry target organ of MMA toxicity in the Borzelleca et al (1964) principal study. The relevance of forestomach toxicity is unclear because no mention of a forestomach effect in either the IRIS assessment or the Tox Review was located. Therefore, it is unclear why this rodent target organ was discussed in the Uncertainty Section. The critical effect for oral exposure to MMA was no effect. A UF of 3 for interspecies extrapolation was warranted, according to the assessment, because of the lack of human oral exposure information and the uncertainty of MMA's potential to induce adverse effects in humans. The UF of 3 for data base deficiencies is applied to the animal NOAEL because (1) no information on human toxicity is available; (2) there is no chronic study in a second species; (3) there are no data for neurologic, developmental and reproductive toxicity when exposure is via the oral route. However, the lack of reproductive and developmental toxicity effects in inhalation studies suggest that these end points are unlikely to occur when exposure is by the oral route.

B. This post-pilot assessment is succinctly yet comprehensively presented, addresses all major uncertainties, uses a data-derived UF for interspecies extrapolation, and integrates information.

C. The relevant scientific evidence, its strengths and weaknesses are well discussed. Qualitative and quantitative judgments are supported by the data presented in the assessment.

D. This is the only assessment I have reviewed which addresses uncertainties clearly and succinctly, in a focused, integrated manner.

2. The RfD and RfC were derived for MMA. Cancer slope factors were not derived because MMA was classified as Category "E", not carcinogenic in four well-designed animal studies.

3. A Tox Review is available.

4. The RfD was based on a chronic NOAEL from a rat drinking water study.

5. The IRIS assessment was conducted in 1998. The principal study is a chronic bioassay by Borzelleca et al. (1964) in which Wistar rats (25/sex/group) were exposed to MMA in drinking water at initial concentrations of 6, 60, and 2000 ppm. The low and medium expousres were increased to 7 and 70 ppm, respectively at the beginning of the fifth month of the study. No statistically and toxicologically significant effects were observed and the NOAEL was the highest dose tested.

6. The total UF was 100: a factor of 10 for within species variability, a factor of 3 for interpecies differences and a factor of 3 to account for data base deficiencies.

7. The within-species variability UF was the default value. The UF of 3 for interspecies extrapolation was data-derived, based on pharmacokinetic data. MMA is metabolized more slowly in humans and this information is used to justify a reduction in the rat-to-human UF. An additional factor discussed in the IRIS assessment was the lack of a forestomach in humans, which is cited as the portal-of-entry target organ in the Borzelleca et al (1964) principal study. However, no mention of a forestomach effect in this study was located in either the IRIS assessment or the Tox Review. Therefore, it is unclear why this rodent target organ was discussed in the Uncertainty Section. A UF of 3 was warranted, according to the assessment, because of the lack of human oral exposure information and the uncertainty of MMA's potential to induce adverse effects in humans. The UF for data base deficiencies is applied to the animal NOAEL because of lack of an identified adverse critical effect in humans, lack of a chronic study in a second species, the lack of a neurologic study, and the lack of developmental and reproductive toxicity studies when

exposure is via the oral route. However, the lack of reproductive and developmental toxicity effects in inhalation studies suggest that these end points are unlikely to occur when exposure is by the oral route.

8. The MF is 1.

9. The critical effect was no effect. It is unclear whether lack of oral toxicity would also be observed in humans because no human studies are available. The route of exposure is likely relevant as MMA is used in dental cement and might be ingested. However, oral exposures are anticipated to be rare.

10. Confidence rating in the study, data base, and RfD is low to medium. The principal reasons for these confidence ratings are (1) the Borzelleca study is an older study which does not appear to have been performed according to current GLP standards, and (2) no LOAEL was identified. However, it should be noted that the highest dose tested in the principal study was 2000 ppm; human exposures are unlikely to reach this level, and thus MMA toxicity at higher doses is not relevant to humans. The data base lacks reproductive, developmental, and neurologic toxicity studies. There are also no human studies. I would rate the critical study, data base, and RfD as medium.

(II) Noncancer inhalation risk assessment

1. A. Uncertainty and variability are well characterized. Toxicokinetic and toxicodynamic data as well as mode of action information are adequately presented in the text. Uncertainty factors associated with within-species variability and data base deficiencies are data-derived and the data to support the use of these UF is well documented. Interspecies differences are discussed in detail. The lack of significant variability in the portal of entry critical effect is discussed and the likelihood that an RfC based on this effect is protective of systemic effects, even those which have not been well studied, is supported. Two different statistical models used to calculate the BMC_{10} gave similar concentration-response curves and goodness-of-fit, which increases confidence in the BMC_{10}.

B. This post-pilot assessment is succinctly yet comprehensively presented, addresses all major uncertainties, and uses data-derived UFs for within species variability and data base deficiencies.

C. The scientific evidence is well characterized. Quantitative and qualitatiave judgments are supported by a comprehensive and cohesive presentation of scientific data and justifiable assumptions. Rather than describing each supporting study in detail, which is a characteristic of many IRIS assessments, supporting studies are comprehensively summarized in an organized manner.

2. The RfD and RfC were derived for MMA. Cancer slope factors were not derived because MMA was classified as Category “E”, not carcinogenic in four well-designed animal studies.

3. A Tox Review is available. The data are well summarized in the IRIS assessment.

4. A BMC_{10} from a rat chronic inhalation study is used to derive the RfC.

5. The IRIS assessment was conducted in 1998. The principal study (Hazelton 1979) is a rat chronic inhalation studies. F344 rats (70/sex/group) were exposed to mean atmospheric concentrations of 0, 24, 99.79, or 396.07 ppm MMA for 6 h/day, 5 days/week for 2 years. Nasal lesions which were not concentration-dependent were observed in exposed animals in all groups at the end of the study. Thus, initially, the association of these lesions to MMA exposures was considered to be questionable. However, histopathological reexamination of nasal tissue (Lomax 1992, 1997) revealed an increase in the incidence of degeneration/atrophy of the olfactory epithelijm in male rats which was concentration-dependent. This effect was used for derivation of the BMC_{10}. Two models were used and generated similar concentration-response curves and reasonable goodness of fit.

6. The total UF was 10, with a UF of 3 applied to the BMC_{10} to adjust for interspecies extrapolation and a UF of 3 to account for within-species variability.

7. A partial UF of 3 for interspecies extrapolation was used because of dosimetric adjustment in derivation of the RfC and because.toxicodynamic differences between rats and humans suggest that humans may be less capable of recovering from olfactory injury than rats. Data from human occupational studies and case reports demonstrate that irritation is the primary human toxic effect resulting from MMA inhalation exposure. A partial UF of 3 for within-species variability is used because little intraspecies variability is observed in laboratory animals and there are no data to suggest that this type of effect is highly variable in humans. The observation of a portal of entry effect is consistent with other data in both humans and animals. There are no multigeneration reproductive toxicity studies with MMA. However, pharmacokinetic information is available which suggest that the portal-of-entry effects are likely to occur at doses lower than those inducing reproductive toxicity. Developmental studies in rodents show effects only at very high doses and the RfC based on olfactory damage is likely to be protective of potential reproductive and developmental effects in humans. This data-derived information is used to support the use of a data base deficiency UF of 1.

8. The MF is 1.

9. The critical effect and route of exposure are relevant to humans.

10. Confidence rating in the principal study is high, and is medium to high for the data base the RfC. Reasons for these confidence ratings are discussed. The key data deficiency is the lack of a mutilgeneration reproductive study. However, an RfC based on portal of entry effects is likely to be protective of systemic effects including those associated with reproduction. I agree with the confidence rating.

(III) Carcinogenicity Assessment

1. A. There is little variability in the animal tumor findings because none of the animal studies showed evidence of carcinogenicity. These findings were reflected in the cancer classification. It is extremely rare to see a chemical classified as Category E, i.e., evidence of non-carcinogenicity. However, based on the IRIS assessment and the Tox Review, this classification is warranted. Based on the weight-of-evidence, MMA is considered to be a Category E compound, i.e. demonstrating evidence of non-carciongenicity in humans, under the 1986 cancer guidelines, and as not likely to be carcinogenic to humans by any route of exposure under the 1996 proposed cancer risk assessment guidelines. The animal bioassay tumorigenicity data is summarized and all studies (in 4 species) are shown to yield consistent results by two routes. Confidence is thus high that MMA is not an animal carcinogen. Human data are briefly summarized and do not suggest that MMA causes cancer in humans.

B. This post-pilot assessment summarizes and integrates the data in a succinct yet comprehensive manner.

C. The data base for animal carcinogenicity is robust and the human data are inadequate. Both these sets of data are adequately addressed. The scientific judgments are appropriately based on available information.

Hazelton (1979) conducted chronic bioassays in which F3434 rats and Charales River golden hamsters were exposed to MMA vapors at either 0, 25, 100, or 400 ppm for 6 h/day, 5 d/wk for 2 years and 18 mon, respective. No evidence of treatment-related tumorigenicity was observed. In a two-year NTP inhalation bioassay, rats and mice exposed to MMA vapors at unspecified concentrations did not show evidence of carcinogenicty. A study by Borzelleca et al (1964) exposed male and female dogs (2/sex/group) to MMA in a dietary gelatin capsule at concentrations of 10, 100, or 1473 ppm, daily for 1 year without evidence of carcinogencitiy. Borzelleca et al. (1964) also administered MMA in drinking water to Wistar rats (25/sex/group) for 104 weeks at initial concentrations of 6,60 and 2000 ppm; the low and medium doses were increased to 7 and 70 ppm respectively at the beginning of the fifth month of the study. No excess tumors were identified in any of the exposed groups.

MMA is not mutagenic in *in vitro* bacterial assays when tested at cytotoxic concentrations, but has shown evidence of *in vitro* clastogenicity in mammalioan cell gene mutations and chromosomal aberration assays. However, no clastogenic effects or dominant lethal mutations have been observed in *in vivo* oral and inhalation studies, and clastogenic effects from *in vivo* human data are equivocal. A comparison of structure-activity

relationships (SAR) among acrylate compounds indicates that the introduction of methyl group to the acrylate moiety negates the carinogenic activity observed with the acrylate moietry alone (i.e., ethyl acrylate).

The weight-of-evidence supports the cancer classification.

These data are succinctly and comprehensively presented and include four well-conducted chronic inhalation studies in three appropriate animal studies (rats, hamsters, mice) which do not demonstrate carcinogenic effects. A chronic oral bioassay with rats and a 1-year study with dogs also did not show evidence of carcinogenicity; these studies were conducted in the 1960's and may not have followed current GLP guidelines. The weight-of-evidence for genotoxicity indicates that MMA is unlikely to be an *in vivo* mutagen or genotoxin. Comparative SAR supports the Category E designation.

NAPHTHALENE

(I) Noncancer Oral Risk Assessment

1. A. The uncertainty with regard to interspecies extrapolation and the protectiveness of the Rf\D for human hematologic toxicity is succinctly summarized in the Confidence Section. However, numerous species and tissue differences differences between rodents and primates and their implications for interspecies extrapolation are not well characterized. The relevance of the critical rodent finding to humans is not discussed except to state that it is not possible to determine whether the RfD is protective of hemolytic anemia in humans. Infants are thought to be more sensitive than adults to napthalene-induced hemolytic anemia because incomplete development of the infant liver is associated with a deficiency in the G6PDH enzyme and G6PDH is involved with the detoxification of napthalene. More discussion should have been given to pharmacokinetics and enzyme variability in sensitive subgroups, with a statement emphasizing that the factor of 10 applied to the animal NOAEL to account for within species variability is considered to be protective of all sensitive subgroups. It is possible that a factor other than the default value of 10 for extrapolation from subchronic to chronic exposure duration could have been data-derived using toxicokinetic information.

B. This is overall a good assessment, although there is too little detail presented on suppporting studies, specifically the effects in humans of napthalene exposure, the similarity of adverse ocular effects (cataract formation) in animals and humans , and the developmental toxicity studies in animals. Justification for selection of the critical study is well presented, and a reasonable discussion of the uncertainties associated with inter-species extrapolation is given in the Confidence Section. A brief summary of the rationale for the UF for data base insufficiencies is presented in the Uncertainty and Modifying Factor Section. No discussion of the use of a UF of 10 for subchronic to chronic exposure duration is given; toxicokinetics may support the choice of the default value or reduce it.

C. Specific uncertainties in the underlying data and in the qualitative and quantitative judgments are discussed, specifically: (1) uncertainty associated with whether the RfD based on decreased rat body weight is protective of hemolytic anemia, the major adverse effect observed in humans; and (2) uncertainty in the data base regarding reproductive toxicity; (3) concern for a sensitive subgroup, infants, which justifies the use of a full factor of 10 for within-species variability.

2. The RfD and RfC were derived for napthalene. Animal cancer data were evaluated and deemed insufficient or inconclusive to warrant quantitative cancer risk estimation for either the oral or inhalation routes. This is a complete IRIS assessment.

3. A toxicological review, on EPA's web site, is available for background data. Supporting data for the principal study is well presented. However, a review of other data, specifically reproductive and developmental toxicity is not presented, nor are data on pharmacokinetics.

4. Both LOAEL/NOAEL and BMD values are given; however, "it was decided to use the LOAEL/NOAEL". Rationale for this decision is not given.

5. The critical study was conducted in 1980 by Battelle's Columbus Laboratories and the IRIS file was completed in 1998. Napthalene in corn oil was administered by gavage to F-344 rats (10/sex/dose group) at doses of 0, 25, 50, 100, 200, or 400 mg/kg/day 5 days per week for 13 weeks. The critical effect was a statistically significant > 10% decrease in terminal body weights in male rats, which was not associated with a concomitant decrease in food consumption. The test species is not known to exhibit genetic sensitivity to napthalene toxicity.

A supporting study, in which significant decreases in the absolute weight of brain, liver, and spleen, and relative weight of spleen were observed, is also presented,. A rationale is given for using the Battelle study rather than the supporting study to derive the RfD.

Other data (e.g., reproductive and developmental toxicity studies) are very briefly reviewed in the IRIS assessment. Human studies demonstrating hemolytic effects of napthalene, and animal and human studies showing

cataract formation are not adequately summarized in the IRIS assessment and this is an omission. These studies are well reviewed in the Toxicological Review.

6. Uncertainty factors totalled 3000: a factor of 10 for interspecies extrapolatin, a factor of 10 for within-species variability, a factor of 10 for extrapolation from subchronic to chronic exposure, and a factor of 3 for data base deficiences (including the lack of a chronic oral study and 2-generation reproductive toxicity study).

7. No, the UF are not data derived. Default factors ere used.

8. The MF is 1.

9. It does not appear that the critical effect is relevant to humans because there are no data to suggest that decreased body weight occurs in humans exposed to napthalene. The primary effects observed in humans are blood effects including hemolytic anemai and cataracts. Humans may be exposed to napthalene via accidental ingestion because of its use in moth balls and as a deodorizer. Case studies of poisoning from moth balls have been reported. Therefore, the route of exposure is relevant.

10. The study confidence rating is high, the data base and RfD low. The study was adequately conducted; however, exposure was via oral gavage in corn oil and bolus dosing tends to overestimate ingestion toxicity. Therefore, I would rat the study confidence as medium. The data base is limited because of the lack of adequate chronic oral studies, lack of a two-generation reproductive toxicity study, and most importantly, insufficient information about the dose-response characteristics of napthalene-induced hemolytic toxicity and cataract formation, which are the two human end points of concern. Therefore, I agree that the data base and the RfD confidence ratings should be low.

(*II) Noncancer Inhalation RfC*

1. A. Default UF were used and the uncertainty was not appropriately characterized. The critical effect was a portal of entry effect and the RfC based on this effect may not be protective of human systemic effects. The effects most relevant to humans (blood effects and cataract formation) were not adequately studied in the principal study. The inhalation data base is limited and uncertainty factors were default-derived.

B. Detail on the principal study and calculation of the HEC was more extensive than in the pre-pilot assessments. However, the level of data review and discussion of UF were not different from those contained in pre-pilot assessments.

C. The strengths and weaknesses of the scientific evidence were not well addressed, nor were sources of variability in the data. Specifically, pharmacokinetics and modes of toxic action are not discussed at all. There is some suggestion in the literature that different napthalene metabolites induce different toxic effects in different species and the uncertainties associated with these findings are not addressed at all. Other than the caveat in the Confidence Section that the RfC derived from nasal lesions in mouse may not be protective of hemolytic effects and cataracts in humans, the level of discussion of data base and scientific uncertainties is similar to those contained in the pre-pilot assessments.

2.. The RfD and RfC were derived for napthalene. Animal cancer data were evaluated and deemed insufficient or inconclusive to warrant quantitative cancer risk estimation for either the oral or inhalation routes. This is a complete IRIS assessment.

3. A toxicological review, on EPA's web site, is available for background data. Supporting data for the principal study is well presented. Additional studies are well summarized, and information is presented in an integrated manner, including the lack of animal data on relevant human endpoints, the rationale for the critical study, and supporting metabolic and acute toxicity data. This information is not well integrated into the uncertainty analysis, however. Data used for the RfC derivation are presented in tabular form, and a separate section for calculation of

the Human Equivalent Concentration(HEC), divided into two parts: (1) dose conversion, and (2) dose-response modeling, explains how the HEC is caluclated and why the NOAEL/LOAEL approach was used instead of BMD modeling.

4. The RfC is based on a LOAEL derived from a chronic mouse inhalation bioassay.

5. The critical study is a mouse inhalation bioassay (NTP 1992), in which B6C3F1 mice (75/sex/group) were exposed to napthalene at atmospheric concentrations of 0, 10, and 30 ppm for 6 hr/day, 5 days/week for 103 weeks. The primary adverse effects were nasal and respiratory epithelial lesions, considered to be a treatment-related generalized inflammatory/regenerative process in the nasal tissues. Effects were observed at both dose levels. No other statistically signficant non-neoplastic effects were observed.

The critical effect is thus a localized portal-of-entry effect, due either to direct contact by napthalene or to localized absorption and metabolism to reactive oxygenated species. Supporting data for a reactive metabolite-induced effect is presented and the calculation of the HEC takes this mechanism into account. The test species is not known to have any particular genetic sensitivity to the toxicity of napthalene.

6. The total UF was 3000 and included (1) a factor of 10 to extrapolate from mice to humans, (2) a factor of 10 to protect sensitive subgroups, (3) a factor of 10 to extrapolate from a LOAEL to a NOAEL, and (4) a factor of 3 for data base deficiencies including lack of a 2-generation reprodutive toxicity study and chronic inhalation data for other animal species. Usually, when an animal LOAEL/NOAEL is dosimetrically adjusted to yield a human equivalent concentration (HEC), the UF for interspecies extrapolation is 3. The use of a UF of 10 may have been due to the fact that the critical effect is portal-of-entry nasal inflammation. However, this is not clearly discussed. Calculation of the HEC takes into account the proposed mechanism, which is nasal absorption followed by localized metabolism which yields a reactive metabolite in the nasal passage. In my judgment, a factor of 3 should have been used for interspecies extrapolation. It is also not clear why the lack of chronic data in a second animal species is considered to be a data base deficiency for noncancer inhalation effects; however, a UF of 3 would still be used for lack of a 2-generation reproductive study. There are also no inhalation developmental toxicity studies. Furthermore, napthalene may exhibit neurotoxicity and there are no studies which evaluate its effects on the nervous system.

7. The UF were not data-derived. The default factors for uncertainty were used. Based on my judgment of the appropriate UF for interspecies extrapolation (3 instead of 10), the total UF should be 1000, not 3000. Usually, when an animal LOAEL/NOAEL is dosimetrically adjusted to yield a human equivalent concentration (HEC), the UF for interspecies extrapolation is 3. The use of a UF of 10 may have been due to the fact that the critical effect is portal-of-entry nasal inflammation. However, this is not clearly discussed. Calculation of the HEC takes into account the proposed mechanism, which is nasal absorption followed by localized metabolism to yields a reactive metabolite *in situ*. In my judgment, a factor of 3 should have been used for interspecies extrapolation

8. A MF of 1.0 was used.

9. The critical effect may be relevant to humans as it occurs along the portal of entry (i.e., the nasal passages); humans occupationally exposed to high atmospheric concentrations of napthalene may develop nasal inflammation. Similarly, the route of exposure is also relevant to humans.

10. The confidence in the critical study is medium, in the data base -- low-to-medium, and in the RfC -- medium. The principal study, in my judgment, should be rated low-to-medium, because of the high mortality in the male control group (which is likely to have affected the reliability of statistical comparisons between treated and control male groups), the lack of a NOAEL, the lack of hematologic analysis of treated animals beyond day 14. The data base is appropriately rated low-to-medium, and the RfC should also be rated low-to-medium.

(III) Carcinogenicity Assessment

Quantitative estimate of the inhalation carcinogenic risk was not estimated because the evidence of an increase in female mouse liver tumorigenesis is only suggestive of a napthalene carcinogenic effect. The study is fully described and the rationale for not calculating a quantitative cancer risk estimate is given. Quantitative estimation of the oral carcinogenic risk is not possible because there are no oral carcinogenicity studies.

The weight-of-evidence classification for napthalene was Group C using the 1986 cancer risk assessment guidelines (i.e., a, possible human carcinogen, based on no human data and limited animal data), and "cannot be determined" using the 1996 cancer guidelines.

There is one inhalation bioassay (NTP 1992), in which B6C3F1 mice (75-150/sex/group) were exposed to vapors of napthalene at concentrations of 0, 10, and 30 ppm for 6 hr/day, 5 days/week, for 2 years. The only statistically significant neoplastic effect was an increase in the incidence of alveolar/bronchiolar adenomas in the high-dose females relative to controls. Similar increases in the incidences of adenomas alone and combined adenomas/carcinomas in h igh-dose males was judged not to be statistically significant when adjusted for intercurrent mortality. Extensive mortality in the control male group (> 40%) may have compromixed the significance of these findings, although the tumor incidence in the high-dose group was also within the range of historical control incidence. Oral studies are inadequate to assess the carcinogenicity of napthalene by this route. The mutagenicity/genotoxicity data appears to be equivocal and a a genotoxic mode of carcinogenic action is deemed unlikely in the Weight of Evidence Characterizatiom.

The test species has a high background rate of spontaneous tumor occurrence in the liver; therefore, it is possible that this species is genetically sensitive to the effects of napthalene exposure.

Curtis Travis, Ph.D.

EPA's IRIS Uncertainty Review for 2,4-/2,6-Toluene diisocyanate mixture (TDI)

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TDI exists primarily in the vapor phase in the ambient environment. Human exposure is primarily via inhalation. There is limited data on oral administration of TDI in animals. Subchronic TDI inhalation exposure data exists for dogs, guinea pigs, hamsters, rabbits, mice and rats. Most of these exposures were above 20 ppb. Rats appear to be the most sensitive of these species to respiratory tract and systemic effects. Rats exposed to 100 ppb TDI for 6 hr/day, 5 days/week for 3 months showed advanced bronchiolitis fibrosa in their lungs. CD-1 and Sprague-Daweley rats were exposed to 50 and 150 ppb TDI for 110 weeks. Both species showed a concentration-related increase in chronic rhinitis.

Reports of chronic industrial exposures of worker are abundant, with long-term exposures at about 1 ppm showing decreases in lung function. Development of hypersensitivity has been reported for exposures ranging from 0.3 to 3 ppb. However, most studies have confounding factors such as exposure to complex mixtures, lack of control for smoking, and inadequate personal exposure data.

The LOAEL for subchronic inhalation exposure of TDI is 1.9 ppb based on asymptomatic deterioration of lung function in industrially exposed human male workers. The decline in lung function correlated not only with average exposure levels, but also time spent in peak exposures.

1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      EPA did identify the UF and discuss its derivation. However, the discussion simply identified the standard factor of 10 to account for sensitive sub-populations and a factor of 3 to account for both subchronic to chronic extrapolation and the lack of developmental toxicity data in a second species. Other important sources of uncertainty were not identified. These include: 1) the question of whether peak exposure or chronic exposure is the proper exposure variable to consider, 2) the fact that in an occupational setting, exposure is likely to occur in combination with other chemicals and thus increase degradation of lung functions, 3) the fact that the LOAEL is based on an measurable decrease in lung function, but the most sensitive end point may be hypersensitivity to low, nonirritating concentrations of TDI, 4) the fact that hypersensitivity has been shown to occur following acute exposures and, thus, that the LOEAL may not be protective for hypersensitivity, 5) the mechanism of action for both decreased lung function and hypersensitivity, and 6)sensitive subpopulations.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      This IRIS assessment falls into the pre-Pilot assessment class. It used the standard factor of 10 uncertainty factor and provided less discussion of factors that may have contributed to uncertainty. No use is made of the additional human studies. The is no discussion of whether the calculated RfC will be protective of hypersensitivity, a critical effect known to

occur in humans. The assessment uses an additional uncertainty factor of 3 to account both for subchronic to chronic extrapolation and the lack of developmental toxicity data in a second species. The document does not explain why a five-year occupational study is considered subchronic, nor does the document explain why an additional uncertainty factor is needed because of the lack of developmental studies in a second species. Very few of the IRIS assessments I looked at in this review had reproductive/developmental studies in a second species. They did not add an additional uncertainty factor. I believe the additional uncertainty factor is needed, but not for the reasons stated. It should be added to allow for the uncertainty concerning hypersensitivity.

C. *Did EPA appropriately address:*

1) *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*

In some respects this was an easy study for which to develop uncertainty factors. The principle study was a human study of 5 years duration. There were many additional studies of occupational exposures and one chronic animal inhalation study. There was a multigenerational reproductive/developmental study. Thus, there was no need to do interspecies extrapolation. The EPA applied a factor of 10 uncertainty to account for variability in humans. However, the document did not discuss mechanism of action, metabolism, and sensitive sub-populations.

2) *Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?*

There is not adequate discussion of the uncertainties in the judgments made in the assessment.

D. *Are there other relevant observations or comments that you would like to raise?*
No

2. *Identify all risk factors addressed by the IRIS assessment under review:*

Inhalation RfC for TDI.

3. *List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.*

See below.

4. *Identify the basis for each risk factor.*

The risk factor was based on a 5-year occupational study of lung function decline in TDI production workers (Diem et al, 1982). Strengths of the study were that 1) exposure was to TDI alone, 2) breathing-zone exposure measurements were available, and 3) baseline lung-function was measured before the start of exposure. A weakness of the study was that no exposure data were available during the first 2 years of the study.

5. *Identify:*

   A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*

      The risk factor was based on human data. TDI production workers (277 males) were followed prospectively over a 5-year period for evidence of respiratory tract dysfunction. Pulmonary-function measurements were taken at nine survey points over a 5-year period, with baseline pulmonary-function measurements taken in 168 individuals with no previous exposure to TDI approximately 6 months before manufacturing and TDI exposure started.

   B. *Critical effect*
      Chronic lung-function decline

   C. *Route of exposure that yielded the critical effect*
      Inhalation

   D. *Mechanism of action for the critical effect observed.*

      The respiratory tract is the critical target tissue for both acute and chronic TDI exposures. Effects include irritation, TDS-induced asthma, and progressive impairment of lung function as a result of long-term exposures. The mechanism of action for the critical effect is not known. It is thought that TDS-induced asthma is immunologically mediated, but TDI-specific immunoglobulin E (IgE) is found in only a small fraction on individuals with symptoms.

   E. *For human data: was a sensitive sub-population included?*

      The primary study was an occupational study of TDI production workers. It is presumed that the study group included a representative sample of workers, both sensitive and non-sensitive, that might be exposed. However, it is likely that sensitive individual workers may have left the study early because of voluntary termination of employment. The study, by its nature did not include non-occupationally exposed sensitive sub-populations.

   F. *For animal data: was the species/stain known to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?*

6. *Identify:*

   Uncertainty Factor & Basis. Were the following considered?

   A. *Inter-species and intra-species variability*
      Yes
   B. *Inter-human variability*
      Yes
   C. *Extrapolation from less-than-chronic to chronic toxicity*
      Yes
   D. *Extrapolation from LOAEL to NOAEL*
      No

E. Data-base insufficiencies

More discussion of database insufficiencies was needed. Only one occupation human study was considered to provide sufficient data from which to identify a LOAEL. However, the LOEAL identified (1.9 ppb) was at or above the level of exposure reported to cause effects in other less well-controlled studies.

7. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

The UF was not data-derived. There was not sufficient information to make a quantitative assessment of uncertainty. An UF of 30 was used. This accounts for a factor of 10 to account for intrahuman variability and a factor of 3 to account both for subchronic to chronic extrapolation and the lack of developmental toxicity data in a second species. The principal study was a five-year occupational study. The document did not discuss why a five-year study was considered to be subchronic.

8. *Identify the MF (modifying factor) used, if any, and its basis.*

No MF was used.

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

Both the critical effect and the route of exposure were relevant to humans since the critical study was an inhalation exposure occupational study in humans.

10. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

The overall confidence ratings given to both the data and the RfC were medium. I agree with these ratings. The critical study was of high quality, even though personal monitoring data were not available for the first 2 years (possibly the years of highest exposure). However, lack of knowledge concerning the mechanism of action for the critical effect is a major limitation in interpreting the study. It is not know whether peak exposures or long-term average exposure is the most important factor in enhancing lung function decline. EPA assumed that long-term exposure was the proper exposure variable to use.

EPA's IRIS Uncertainty Review For 4-Methylphenol

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1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      The oral RfD was withdrawn in 1993. The IRIS document only contains a classification of carcinogenicity. There is no discussion of uncertainty.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      This is a pre-Pilot assessment. However, with regard to the weight-of-evidence classification, there is not much difference in the discussion of uncertainty between pre-Pilot and post-Pilot assessments. There is very little discussion of uncertainty is the carcinogenicity assessments.

   C. *Did EPA appropriately address:*
      1) *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*

         No

      2) *Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?*

         No

   D. *Are there other relevant observations or comments that you would like to raise?*

      No

2. *Identify all risk factors addressed by the IRIS assessment under review:*

   Carcinogenicity assessment

3. *List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.*

   See below.

4. *Identify the basis for each risk factor.*

The classification of 4-Methylphenol as a Class C possible human carcinogen was based on limited animal data involving dermal application that resulted in skin papillomas. No cancer data following oral exposure were available. Mutagenicity and genotoxicity testing on 4-methylphenol were negative.

5. *Identify:*
   - A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*
     Animal data
   - B. *Critical effect*
     Skin papillomas
   - C. *Route of exposure that yielded the critical effect*
     Dermal application
   - D. *Mechanism of action for the critical effect observed.*
     Not stated
   - E. *For human data: was a sensitive sub-population included?*
     No human data
   - F. *For animal data: was the species/stain known to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?*
     No

6. *Identify:*
   Uncertainty Factor & Basis. Were the following considered?
   - A. *Inter-species and intra-species variability*
     No
   - B. *Inter-human variability*
     No
   - C. *Extrapolation from less-than-chronic to chronic toxicity*
     No
   - D. *Extrapolation from LOAEL to NOAEL*
     No
   - E. *Data-base insufficiencies*
     No

7. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

   The UF was not data-derived. There was not sufficient information to make a quantitative assessment of uncertainty.

8.. *Identify the MF (modifying factor) used, if any, and its basis.*

   None were used

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

The data has medium relevance to humans. The critical effect was skin papillomas. The route of exposure was skin application. Thus, the data were limited.

10. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

No quantitative estimate of carcinogenicity was derived. No discussion of the uncertainty in the weight-of-evidence classification was given. However, I would rate the confidence as low.

EPA's IRIS Uncertainty Review of Chromium III

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1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      No. The major difficulty in establishing a NOAEL in this IRIS assessment is the lack a good principal study with clear effects. Thus, EPA developed the best estimate of the oral RfD that it could, given the data that it had. However, the IRIS assessment could have done a better job discussing the uncertainty. Even though the IRIS assessment for Chromium III was updated on 9/3/98, it still has the flavor of the pre-pilot assessments. It is as if, even though EPA knows that the pre-Pilot assessments are substandard, when they revisit them, they are reluctant to change the format and add more discussion of uncertainties.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      The Chromium III assessment is a post-Pilot assessment that is inadequate given the new post-Pilot culture. It actually should not be classified as a post-Pilot assessment, since it only received minor modification in 98.

   C. *Did EPA appropriately address:*
      1) *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*

         NO. The post-Pilot IRIS assessment of Chromium should include a discussion of the toxicokinetics of Cr(III). The low absorption rate (0.4-0.5%) explains the difficulty in obtaining sufficiently high doses to obtain a critical effect. Cr (III) is cleared rapidly from the blood. The liver appears to be to preferred organ of accumulation, followed by kidney. Thus, any systemic toxicity study should look at these organs. Cr(VI) is reduced to Cr(III) in all tissues. O'Flaherty (1996) developed a physiologically based model for chromium disposition in the rat. This model should have been mentioned in the IRIS RfD assessment. The fact that Cr(VI) is rapidly reduced to Cr(III) raises the question of whether animal exposures to Cr(VI) can be used to evaluate the toxic effects of Cr(III). This issue is discussed in the Toxicity Review of Trivalent Chromium, but should have also been discussed in the IRIS assessment.

         A short statement about the one chronic and several subchronic oral studies in mice and rates at doses less than 1.0 mg/kg/day should be made. The text does state that "other subchronic oral studies show no indication of adverse effects, but dose levels were

considerably lower" I think this statement should have stated that the studies were in both rats and mice and given a quantitative statement of the dose range.

2. *Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?*

NO. The post-Pilot IRIS assessment of Chromium should have had a larger discussion of uncertainty. The O'Flaherty physiologically based model for chromium disposition is an example of data that should have been discussed. Could this model be used to reduce the factor of 10 uncertainty for interspecies extrapolation? Two of the other post-Pilot assessments that I read reduced the interspecies UF to 3 based on the existence of a pharmocokinetic model.

The major difficulty in the discussion of uncertainty is that EPA did not acknowledge that the true RfD might be higher or lower than the one calculated in the IRIS assessment. Since there was no observed critical effect in the principal study, other studies might produce a NOAEL at even higher doses. Since the principal study only looked at body weight loss and gross histological impacts, there is no way of knowing if other studies looking at more sensitive endpoints (kidney impacts or neurological impacts, for example) might find an RfD lower than the one calculated. This kind of discussion should appear in the assessment

D. *Are there other relevant observations or comments that you would like to raise?*

Only that the above comments should not be taken as critical of EPA. In developing the RfD, EPA did the best job possible. However, the discussion of uncertainties is not up to post-Pilot standards.

2. *Identify all risk factors addressed by the IRIS assessment under review:*

Oral RfD
An inhalation RfC is discussed, but insufficient data are available. A carcinogenicity assessment is discussed, but insufficient data are available.

3. *List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.*

4. *Identify the basis for each risk factor.*

The oral RfD is based on the chronic feeding study in rats of Ivankovic and Preussman (1975).

5. *Identify*:

A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*

The RfD was based on animal studies. Groups of 60 male and female rats were fed chromic oxide (Cr_2O_3) baked in bread at dietary levels of 0, 1%, 2%, or 5%, 5daus/week for 600

feedings (840total days). Body weight and food consumption were monitored. The animals were maintained on control diets following termination of exposure. All major organs were examined histological. Other toxicologic parameters were not mentioned explicitly. No effects due to chromic oxide treatment were observed at any dose level.

B. Critical effect
No critical effects were observed.

C. Route of exposure that yielded the critical effect
The route of exposure was oral exposure through chromic oxide baked in bread.

D. Mechanism of action for the critical effect observed.
Since no effects were observed, no mechanism of action was given.

E. For human data: was a sensitive sub-population included?
No human data were used.

F. For animal data: was the species/stain known to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?
The animal species was not known to be genetically sensitive, nor have any genetic peculiarity.

6. Identify:

Uncertainty Factor & Basis. Were the following considered?

A. Inter-species and intra-species variability
Yes

B. Inter-human variability
Yes

C. Extrapolation from less-than-chronic to chronic toxicity
No

D. Extrapolation from LOAEL to NOAEL
No

E. Data-base insufficiencies
No

7. *Was the UF data-derived? Was there sufficient information to make a uantitative assessment of uncertainty? If not, how was available information used to derive UF?*

The UF was not data derived. The standard factor of 10 was used to account for interspecies extrapolation. No justification for selection of 10 as the factor was given. A standard factor of 10 was used to account for inter-human variability. No justification for selection of 10 as the factor was given.

8. Identify the MF (modifying factor) used, if any, and its basis.

A MF of 10 was used. This was to account for the lack of a non-rodent mammal study and the lack of data on reproductive impacts. This study was last revised in 9/3/98. The value of the MF was not changed from the previous IRIS entry.

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

No critical effect was identified. The route of exposure is relevant to humans.

10. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

The overall confidence in the RfD was rated as low. The principal study was rated low because of the lack of detail on study protocol and results. (In addition, I would rate the principal study as low because it did not produce an effect and no effects were looked for except loss of body weight). The database was rated as low due to the lack of high-dose supporting data. (I do not agree with this statement either. The principal study was weak because it did not use sufficiently high doses to elicit critical effects. The database was weak because it did not include supporting studies in other species and did not include reproductive studies and multi generational studies).The RfD was rated as low because of the lack of an observed effect level.

However, the IRIS assessment states that the calculated RfD should be considered as conservative since “the MF addresses only those factors that might lower the RfD”. This sentence does not make sense to me. To say that the RfD is conservative means that it is lower than it true value. EPA has no way of knowing this. The true RfD may be higher or it may be lower. Since there was no observed critical effect in the principal study, other studies might produce a NOAEL at even higher doses. Since the principal study only looked at body weight loss and gross histological impacts, there is no way of knowing if other studies looking at more sensitive endpoints (kidney impacts or neurological impacts, for example) might find an RfD lower than the one calculated.

Thus, while I concur with the low rating given the principal study, the database, and the RfD, I do not agree with the statements given by EPA justifying these ratings. The principal study is not of low quality only because it was not explicit in providing detail on study protocol and results. It was of low quality because it was not designed to study systemic toxicity, did not include sufficiently high doses to have observed effects, and did not look for effects other than body weight loss.

EPA's IRIS Uncertainty Review for Danitol

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1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      EPA did identify the UF and state that it represented the standard factor of 10 to account for intraspecies variability and the standard factor of 10 to account for interspecies extrapolation. Confidence in the database was high, multiple species were tested in chronic long-term studies, and both reproductive and developmental studies have been done. All of the additional studies supported the NOEL/LEL established in the principal study. However, there were no data on mode of action and metabolism upon which to base a reduction in the estimate of uncertainty. Thus, I conclude that EPA correctly characterized the extent of uncertainty and variability in the data.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      While I believe that EPA followed the correct procedure in characterizing the uncertainty, the document should have given more discussion of possible sources of uncertainty (like the fact that Danitol in the principal study was contained in food, which might affect absorbability; the mechanism of action is unknown; the lack of human data; no discussion of possible sensitive subpopulations). While I conclude that EPA correctly followed EPA policy in characterizing the uncertainty, the lack of discussion to justify the UFs identifies this as a pre-Pilot study.

   C. *Did EPA appropriately address:*
      1. *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*

         There was some discussion of these issues in the text, but not at the same level as the post- Pilot studies. The IRIS document cites 11 studies in support of the RfD. In addition to the principal study described below (one-year feeding study in beagle dogs that found a NOEL of 100 ppm), there was one 2-year mouse feeding study, two 2-year rat feeding studies, two 3-generation reproductive studies in rats, and two developmental toxicity studies; one in rats and one in rabbits. Thus, the database had high confidence and no data gaps and the document provided a good survey of the data. However, it did not provide a satisfactory discussion of the uncertainty associated with the data.

2. *Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?*

   No

D. Are there other relevant observations or comments that you would like to raise?

This is an example of one of the better pre-Pilot studies. There was high confidence in the database and no data gaps. However, the IRIS document provides little discussion of uncertainties in the underlying data or the judgments made in selecting the uncertainty factors.

2. *Identify all risk factors addressed by the IRIS assessment under review:*

Oral RfD for Danitol.

3. *List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.*

See below.

4. *Identify the basis for each risk factor.*

The risk factor was based on a Sumitomo Chemical Company (1984) study of beagle dogs fed diets containing Danitol for one year.

5. *Identify:*

A. Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?

The risk factor was based on animal data. Groups of beagle dogs (4/sex/dose) were fed diets containing 0, 100, 250 or 750 ppm (0, 2.5, 6.25, or 18.75 mg/kg-day) of Danitol for 1 year. All animals were terminated after week 52. Incidences of ataxia were noted at 750 ppm. Incidences of tremor were observed at 250 ppm and 750 ppm. No other significant effects were noted. Based on tremors, the LOAEL for systemic toxicity is 250 ppm. The NOEL for systemic toxicity is 100 ppm.

B. Critical effect
The critical effect was tremors.

C. Route of exposure that yielded the critical effect
The route of exposure was ingestion.

D. Mechanism of action for the critical effect observed.
The mechanism of action is unknown.

E. For human data: was a sensitive sub-population included?
There was no human data.

F. For animal data: was the species/stain known to be genetically sensitive? To have any genetic peculiarity with regard to the toxicity of the compound?

The animal species was no known to be genetically sensitive, nor was it known to have any genetic peculiarity with regard to the toxicity of the compound.

7. ***Identify:***

Uncertainty Factor & Basis. Were the following considered?

A. *Inter-species and intra-species variability*
   Yes
B. *Inter-human variability*
   The document does not mention Inter-human variability.
C. *Extrapolation from less-than-chronic to chronic toxicity*
   No. It was not necessary.
D. *Extrapolation from LOAEL to NOAEL*
   No
E. *Data-base insufficiencies*
   No

8. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

The UF was not data-derived. There was not sufficient information to make a quantitative assessment of uncertainty. An UF of 100 was used. This accounts for a factor of 10 for intraspecies variability and a factor of 10 for interspecies extrapolation. The document was not clear as to whether the factor of 10 for intraspecies variability was to account for sensitive human sub populations.

9. *Identify the MF (modifying factor) used, if any, and its basis.*

A MF of 1 was used. No basis for this factor was given.

10. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

The critical effect used in the study was tremors. As an indication of systemic effects, it is relevant to humans. The route of exposure was ingestion and is relevant to humans.

11. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

The principal study was given a medium confidence rating. The database was given a high confidence rating. The RfD was given a high confidence rating. The principal study was well conducted. Its only weakness was that the study did not describe in detail how the amount of food ingested by each dog was measured. The database had no data gaps and contained a number of additional studies that support tie NOEL/LOAEL established in the study. The database was therefore given a high confidence rating. The high confidence rating of the RfD follows. I concur with these rates.

2. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      YES. EPA went to great extent to characterize the uncertainty in the data used to develop the IRIS assessment for EGBE.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      This is an excellent example of a post-Pilot assessment. This IRIS assessment has several innovations.

      First, there is a good discussion of metabolism and the mechanism of action. It is believed that an oxidative metabolite, BAA, is the causative agent for EGBE-induced hemolysis.

      Second, the maximum concentration of the metabolite BAA in blood was used as the dose metric. This was an innovative step forward in using biological data to reduce uncertainty. It was made possible by the existence of a PBPK model for EGBE metabolism in the rat (Corley et al. 1997). The maximum concentration of BAA in arterial blood can be determined from the model under different experimental conditions.

      Third, the PBPK model and biological data were used to extrapolate to humans, eliminating the need for the standard uncertainty factor of 10 to account for interspecies extrapolation. An interspecies extrapolation UF of 1 (1 for pharmacodynamics times 1 for pharmacokinetics) was used. The factor of 1 was used for pharmacodynamics since humans are less sensitive than rats or mice. The factor of 1 for pharmacokinetics was used since a PBPK model was used to account for interspecies differences in metabolism. This was another excellent example of the use of data to quantitatively reduce uncertainty, and at the same time, provide a mechanistically more realistic approach to estimating the RfD.

      This IRIS assessment is a vast improvement over the pre-Pilot assessments.

   C. *Did EPA appropriately address:*
      1. *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*
         The mechanism of action is well known and was discussed adequately in the IRIS document. The acid metabolite, BAA, has been shown to be the causative agent of the critical effect, hemolysis.

         The metabolism of EGBE has been extensively studied and the IRIS document uses this fact to select the maximum concentration of BAA in blood as the proper dose metric.

         Data exist showing that humans are significantly less sensitive to the hemolytic toxicity of EGBE than mice, rats, or rabbits. Based on the rat toxicity data, and making the

conservative assumption that humans are equally as sensitive as rats, the PBPK model was used to back calculate a human equivalent dose for the RfD. This is an innovative approach that utilizes existing data and understanding on mechanism to significantly reduce uncertainty.

The Toxicology Review of EGBE provides an excellent discussion of potentially susceptible subpopulations. A primary factor would be populations with enhanced metabolism or decreased excretion of BAA. There is an excellent discussion of childhood susceptibility and the effect of age and gender.

The Toxicology Review has a discussion of the uncertainty associated with the choice of the measure of dose. Two alternatives were considered: maximum blood concentration or the area under the curve of the blood concentration. First, data clearly indicate that the dose metric should measure BAA. Second, the critical effect appears to be dependent on dose rate, indicating that maximum blood concentration is the proper dose metric. However, the observation of a dose rate effect comes from two different studies (they do use the same strain of rat), introducing some uncertainty. Thus there is some uncertainty as to the proper dose metric, a fact that is not pointed out in the IRIS assessment.

2. Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?

Yes

D. Are there other relevant observations or comments that you would like to raise?
No

2. Identify all risk factors addressed by the IRIS assessment under review:

Oral RfD
Inhalation RfC
Carcinogenicity assessment

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

4. Identify the basis for each risk factor.

The oral RfD was based on an NTP (1993) toxicity study of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol administered in drinking water to F344/N rats and B6C3F1 mice.

The inhalation RfC was based on an NTP (1998) inhalation toxicity study of 2-butoxyethanol in F344/N rats and B6C3F1 mice.

No quantitative estimate of carcinogenicity was made. EGBE was judged to be a possible human carcinogen (Group C) using existing EPA guidelines (1986) and limited evidence of carcinogenic activity in B6C3F1 mice. Under the recently proposed guidelines (1996), the human carcinogenic potential of EGBE cannot be determined.

5. *Identify:*

   A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*

      Both the RfD and the RfC were based on animal data. The oral RfD was based on a 13-week subchronic toxicity study in Fisher 344 rats and B6C3F1 mice using 2-butoxyethanol (EGBE). Groups of 10/sex/species received EGBE in drinking water at doses of 0, 750, 1500, 3000,4500, and 6000 ppm.

      The inhalation RfC was based on a 14-week toxicity study in Fisher 344 rats and B6C3F1 mice using EGBE. Groups of10/sex/species were exposed via inhalation to concentrations of 0, 31, 62.5, 125, 250, and 500 ppm of EGBE 6 hours/day, 5 days/week.

      The classification of EGBE as a Group C carcinogen was based on a two-year NTP (1998) inhalation study in F344/N rats and B6C3F1 mice. Groups of 50/sex F344/N rats were exposed to 0, 31,62.5, and 125 ppm. Groups of 50/sex B6C3F1 mice were exposed to 0, 62.5, 125, and 250 ppm.

   B. *Critical effect*

      For the oral RfD, the critical effect was changes in mean corpuscular volume (MCV).

      For the inhalation RfC, the critical effect was changes in red blood cell (RBC) count.

      For the carcinogenicity weight-of-evidence characterization, the observed cancers were benign and malignant pheochromocytoma of the adrenal medulla in the female rat and both hemangiosarcoma of the liver and forestomach squamous cell papilloma or carcinoma.

   C. *Route of exposure that yielded the critical effect*

      For the oral RfD, the route of exposure was ingestion of drinking water.

      For the inhalation RfC, the route of exposure was inhalation.

   D. *Mechanism of action for the critical effect observed.*

      It is believed that an oxidative metabolite, BAA, is the causative agent for EGBE-induced hemolysis. EGBE-induced hemolysis appears to be dependent on dose rate. For this reason, it appears that the maximum concentration of BAA in blood is the most appropriate dose metric. The first event in the mechanism of action is the interaction between BAA and cellular molecules in erythrocytes. The second event is erythrocyte swelling, followed by

cell lysis mediated by an increase in osmotic pressure. The exact hematological endpoint that should be used as the basis for an RfD/RfC is not known.

E. For human data: was a sensitive sub-population included?
There were no human data in these studies.

F. For animal data: was the species/stain known to be genetically sensitive? The have any genetic peculiarity with regard to the toxicity of the compound?
No

6. *Identify:*
Uncertainty Factor & Basis. Were the following considered?
A. Inter-species and intra-species variability
Yes
B. Inter-human variability
Yes

C. Extrapolation from less-than-chronic to chronic toxicity
Yes
D. Extrapolation from LOAEL to NOAEL
Yes
E. Data-base insufficiencies
Yes

7. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

Parts of the UF were data derived. This IRIS is a good example of making maximum use of data to obtain the best estimates of UF possible and therefore minimum use of default values. There was sufficient information to make a quantitative assessment of uncertainty in interspecies extrapolation. The uncertainty factor for intrahuman sensitivity was derived in the standard fashion.

For the oral RfD, an UF of 10 was used to account for intrahuman sensitivity. Potentially susceptible subpopulations include individuals with enhanced metabolism or decreased excretion of the metabolite BAA, and individuals whose red blood cell walls are less resistant to the lysis caused by BAA. An UF of 1 (1 for pharmacodynamics times 1 forpharmacokinetics)was used to account for interspecies extrapolation. The factor of 1 was used for pharmacodynamics since humans are less sensitive than rats or mice. The factor of 1 for pharmacokinetics was used since a PBPK model was used to account for interspecies differences in metabolism. This is a reduction by a factor of 3 in the UF for interspecies extrapolation.

A value of 1 was used for extrapolating from a subchronic study to chronic exposures since toxicity studies show that there does not appear to be an increase in severity of hemolytic effects beyond 1-3 weeks of oral and inhalation exposure.

For the inhalation RfC, an UF of 30 was used based on a factor of 10 to account for intrahuman sensitivity and a factor of 3 to account for an adverse effect level. A PBPK model was used to account for interspecies extrapolation. A value of 3 was selected to extrapolate from an adverse effect level to a NOAEL.

8. *Identify the MF (modifying factor) used, if any, and its basis.*

   A MF of 1 was used.

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

   For the toxicity studies, the answer is yes. Both the critical effect and the routes of exposure are relevant to humans.

   For the carcinogenicity assessment, it was not known whether the observed tumors had relevance in humans.

10. *What is the overall confidence rating of r the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

    For the oral RfD, confidence in the principal study was medium because it was not a chronic study. However, the study employed both male and female rats and mice.

    Confidence in the data base was rated as medium-to-high because data were available for a variety of animal species, including humans. However, the potential for adverse liver effects in humans from long-term exposure has not been investigated. Thus, confidence in the oral RfD is rated as medium-to- high.

    For the inhalationRfC, confidence in the principal study was rated as high because it was a chronic study; it employed both male and female rats and mice; and it had a wide range of exposure levels.

    Confidence in the data base was rated as medium-to-high because data were available for a variety of animal species including humans. However, the potential for adverse liver effects in humans from long-term exposure has not been investigated. Thus, confidence in the oral RfD is rated as medium-to- high.

    I concur with the confidence rating.

EPA's IRIS Uncertainty Review for Methyl methacrylate

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1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      Yes.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      This is clearly a post-Pilot study. There is a much more extensive discussion of the uncertainties used in deriving the uncertainty factors. The lower rate of metabolism in humans is used to justify a factor of 1 for extrapolation of pharmacokinetics (however, the document does not describe it in terms of pharmacokinetics. This identifies it as in the early wave of post-Pilot studies). The document introduces an uncertainty factor of 3 to account for uncertainties in the database. This also identifies the document as being a post-Pilot assessment. Thus, I would say that this document is an improvement over pre-Pilot assessments, but that it does not provide as complete of a discussion regarding its assumptions as do the later post-Pilot assessments.

   C. *Did EPA appropriately address:*
      1. *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*

         MMA is a liquid with a strong acrid odor. It is readily absorbed into the blood via the lungs, gastrointestinal tract, and skin.
         Metabolism. Data indicate that MMA is rapidly by blood serum enzymes and enzymes in the olfactory tissue of both rats ans humans. The rate of metabolism in both tissues is much higher in rats than in humans. This fact was used to justify a factor of 3 for the interspecies extrapolation.
         Human Studies. Thirteen human studies were reviewed. Most of the studies were confounded by co-exposure to other chemicals and lacked information of individual exposures. However, the studies supported the observation that exposure to MMA in the range of 1 to 50 ppm did not produce lasting effects in humans. These additional studies reduce uncertainty in the protectiveness of the RfC.

      2. *Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?*

Yes. The document has a discussion of the uncertainties in the judgments made in the assessment.

D. *Are there other relevant observations or comments that you would like to raise?*

This document has a good discussion of uncertainties surrounding judgments made during the assessment. The presentation and description of issues is not as clear as later assessments. For example, there is not a separate section on mechanism of action and metabolism. Nor does the document discuss interspecies extrapolation in terms of pharmacokinetics and pharmacodynamics.

2. *Identify all risk factors addressed by the IRIS assessment under review:*

Oral RfD
Inhalation RfC
Carcinogenicity assessment

3. *List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.*

4. *Identify the basis for each risk factor.*

For the oral RfD, the principal study was the Borzellece et al. (1964) study of Wistar rats exposed to MMA in drinking water.

For the inhalation study, the principal study was the Hazelton Laboratories America (1979) study of MMA inhalation exposure of F344 rats.

For the carcinogenicity assessment, the principal study was a NTP inhaltion study in F344 rats and B6C3F1 mice.

5. *Identify:*
   A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*

Both risk factors were based on animal data.
For the oral RfD, groups of 25 male and 25 female Wistar rats were exposed to MMA in drinking water continuously for 104 weeks. The initial exposure concentrations were 6, 60, and 2,000 ppm MMA. The low and medium exposures were increased to 7 and 70 ppm, respectively, at the start of the fifth month, resulting in time weighted average exposure concentrations of 6.85 and 68.46 ppm MMA.

For the inhalation RfC, groups of Fisher 344 rats (70 for each sex per group) were exposed to mean concentrations of 0, 25, 99.79, or 396.07 ppm for 6 hr/day, 5 days/week for 2 years.

The carcinogenicity assessment was based on several animal studies showing negative results in carcinogenicity testing. The principal study was an NTP 2-year inhalation study on F344 male and female rats.

B. Critical effect

For the oral RfD, there was no critical effect.

For the inhalation RfC, the critical effect was degeneration/atrophy of olfactory epithelium in male rats.

C. Route of exposure that yielded the critical effect

For the oral RfD, the route of exposure was ingestion of drinking water.

For the inhalation RfC, the route of exposure was inhalation.

D. Mechanism of action for the critical effect observed.

For the oral RfD, no critical effect was noted in the principal study. Thus there is no mechanism of action that needs explanation. However, it is know that, both in animals and humans, following oral exposure MMA is rapidly metabolized to methacrylic acid and methanol.

For the inhalation RfC, the mechanism of action for the cytotocicity on the olfacatory region is thought to be the hydrolysis of MMA by carboxylesterase enzymes and subsequent releases of methacrylic acid in the olfactory tissues.

E. For human data: was a sensitive sub-population included?

There were no human data.

F. For animal data: was the species/stain known to be genetically sensitive? The have any genetic peculiarity with regard to the toxicity of the compound?

No

6. Identify:

Uncertainty Factor & Basis. Were the following considered?

A. *Inter-species and intra-species variability*
Yes

B. Inter-human variability
Yes

C. Extrapolation from less-than-chronic to chronic toxicity
No

D. Extrapolation from LOAEL to NOAEL

No

E. Data-base insufficiencies
Yes

7. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

The UF was partially based on data.

For the oral RfD, an UF of 100 was used. A threefold uncertainty factor was used to account for interspecies extrapolation. The slower blood metabolism of MMA in humans combined with the fact that humans do not have a forestomach was cited as justification. A full uncertainty factor of 10 was used to account for potentially sensitive human subpopulations. An uncertainty factor of 3 was used to account for a deficient database.

For the inhalation RfC, an UF of 10 was used. A threefold uncertainty factor was used to account for sensitive human subpopulations. The justification of this UF was that there exist extensive human occupational studies identify the irritant properties of MMA as the principal effect of concern from MMA inhalation exposure. There is also little reason to expect a high degree of intraspecies variability from this type of effect. A factor of 3 was used to account for uncertainty in interspecies extrapolation. The justification of this factor is that most evidence shows that rat nasal passages are likely to be affected at lower MMA concentrations than those of humans. No uncertainty factor was applied for data base deficiencies.

8. *Identify the MF (modifying factor) used, if any, and its basis.*

MF= 1 was used.

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

Yes, the critical effect is relevant to humans. Yes, the route of exposure is relevant to humans.

10. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

For the oral RfD, the confidence in the principal study was low to medium. The Borzelleca (1964) study is well documented, but EPA did not consider it to be conducted in accordance with what would now be considered to be Good Laboratory Practice and did not identify a LOAEL. Confidence in the database was judged to be low to medium. Relevant quantitative human subchronic or chronic studies are not available. Multiple inhalation studies bolster the weak oral database. However, no developmental or reproductive studies are available by the oral route, and no multi generational studies are available by any route of exposure. Thus, the overall confidence in the oral Rfd is low to medium. I concur with this confidence rating.

For the inhalation RfC, the confidence in the principal study was high. The principal study was a long-term rat inhalation study with large group sizes and through histopathologic analyses on all relevant tissues. The primary target organ, the nasal passage, was well described. The confidence in the database is medium to high. Development studies were carried out in two species, rats and mice, with effects only observed in offspring at levels more than 10-fold higher than the LOAEL. Multigenerational reproductive studies are not available for MMA, but protection against the low levels that cause port-of-entry effects is likely to also protect against multigenerational reproductive effects. The overall confidence in the RfC was rated as medium to high. I concur with this confidence rating.

EPA's IRIS Uncertainty Review Naphthalene

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1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      Yes. EPA used a UF of 3,000 for both the oral RfD and the inhalation RfC. This UF seems reasonable given the lack of data in both cases. The IRIS document provides an adequate discussion of the extent of uncertainty and variability. However, the IRIS document has no discussion of mechanism of action, metabolism, or sensitive subpopulations. This identifies it as an early post-Pilot assessment.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      The uncertainty analysis in this IRIS assessment is of high quality and is reflects its post-Pilot status. There are no adequate chronic oral dose-response data for naphthalene in humans or animals. The limited subchronic oral data identify decreased body weight in rats as the critical effect. There are no reproductive studies. The discussion in the IRIS document of uncertainty is good. The uncertainty factors applied are reasonable given uncertainties in the data. However, the document should have discussed mechanism of action, metabolism, and sensitive subpopulations.

   C. *Did EPA appropriately address:*
      1) *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*
         Yes

      2) *Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?*

         The document could have used a more extensive discussion of uncertainty. Little justification or discussion of the uncertainty factor selected is given. The critical effect was decreased terminal body weight. No discussion of possible other effects was given.

   D. *Are there other relevant observations or comments that you would like to raise?*
      No

2. *Identify all risk factors addressed by the IRIS assessment under review:*

The risk factors addressed in the IRIS assessment are the Oral RfD, the Inhalation RfC, and a Carcinogenicity Assessment.

3. *List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.*

4. *Identify the basis for each risk factor.*

   The oral RfD was supported by an unpublished subchronic toxicity in Fisher 344 rats and a toxicology and immunotoxicology study in CD-1 mice.

   The inhalation RfC was based on an inhalation study in B6C3F1 mice.

   The carcinogenicity weight-of-evidence characterization was based on an NTP inhalation study in B6C3F1 mice.

5. *Identify:*

   A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*

      All risk factors were based on animal data.

      The oral RfD was based on an unpublished subchronic toxicity study in Fisher 344 rats. Corn oil was administered by gavage to groups of 10 male and 10 female Fisher 344 rats at dose levels of 0,25,50,100,200, or 400 mg/kg, 5 days a week for 13 weeks.

      The inhalation RfD was based on an inhalation study conducted by the National Toxicological Program in B6C3F1 mice. The mice (75/sex/group) were exposed to naphthalene at concentrations of 0, 10, and 30 ppm for 6 hr/day, 5 days/week, for 103 weeks. The critical effect was respiratory lesions (hyperplasia in respiratory epithelium and metaplasia in olfactory epithelium)that were considered to result from a generalized inflammatory and regenerative process.

      Naphthalene is classified in Group C, a possible human carcinogen. This is based on inadequate data (actually no data) of carcinogenicity in humans exposed to naphthalene via the oral and inhalation routes, and the limited evidence of carcinogenicity in animals via the inhalation route. No human studies were located upon which to base an assessment of the carcinogenicity of naphthalene in human populations. IRIS cites the 1992 NTP inhalation study in B6C3F1 mice in its discussion of animal carcinogenicity data.

   B. *Critical effect*

      The critical effects were body weight loss for the oral RfD, respiratory lesions for the inhalation RfC, and respiratory tract tumors for the carcinogenicity assessment.

C. *Route of exposure that yielded the critical effect.*

For the oral RfD, the route of exposure was corn oil gavage.

For the inhalation RfC, the route of exposure was inhalation.

D. *Mechanism of action for the critical effect observed.*

In the oral toxicity study, no mechanism of action for the observed loss of body weight was given.

In the inhalation toxicity study, naphthalene-related effects on the nasal epithelium were assumed to follow from absorption of naphthalene and subsequent metabolism to reactive oxygenated metabolites, rather than being a result of direct contact. It is not know whether the metabolite is formed in the liver or the respiratory tract.

The mechanism of action of naphthalene as a possible human carcinogen is unknown. The genotoxic potential of naphthalene has been evaluated in many test systems (with and without activation) and found negative in most studies.

E. *For human data: was a sensitive sub-population included?*

No human data were used.

F. *For animal data: was the species/stain known to be genetically sensitive? The have any genetic peculiarity with regard to the toxicity of the compound?*

No

6. *Identify:*

Uncertainty Factor & Basis. Were the following considered?

A. *Inter-species and intra-species variability*
Yes

B. *Inter-human variability*
Yes

C. *Extrapolation from less-than-chronic to chronic toxicity*
Yes

D. *Extrapolation from LOAEL to NOAEL*
Yes

E. *Data-base insufficiencies*
Yes

7. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

The UF was not data derived. There was not sufficient information to make a quantitative assessment of uncertainty. The uncertainty factor was derived in the standard fashion.

For the oral RfD, an uncertainty of 3,000 was used (10 to extrapolate from rats to humans, 10 to protect sensitive humans, 10 to extrapolate from subchronic to chronic exposure, and 3 for database deficiencies including the lack of chronic oral exposure studies and 2-generation reproductive toxicity studies).

For the inhalation RfC, an uncertainty factor of 3,000 was used. This UF accounts for 10 to extrapolate from mice to humans, 10 to protect sensitive humans, 10 to extrapolate from a LOAEL to a NOAEL, and 3 for database deficiencies including the lack of a 2-generation reproductive toxicity studies and chronic inhalation data for other animal species.

8. *Identify the MF (modifying factor) used, if any, and its basis*.

   A modifying factor of MF = 1 was used. No basis for this number was given.

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*

   Yes, in both cases.

10. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

    For the oral RfD, the principal study was given high confidence rating because adequate numbers of animals were included and experimental protocols were adequately designed, conducted, and reported.

    Confidence in the database was rated low because of the lack of adequate chronic oral data for naphthalene: lack of any dose-response data for naphthalene-induce hemolytic anemia, probably one of the most well-known health hazards to humans exposed to naphthalene; and the lack of two-generation reproductive toxicity studies.

    Confidence in the RfD was rated low because of the low rating of the available database and because of the absence of an appropriate animal model for hemolytic anemia, the most observed effect in humans.

    For the inhalation RfC, the principal study was given a medium confidence rating because adequate numbers of animals were used, and the severity of nasal effects increased at the higher exposure concentration. However, the study produced high mortality and the hematological evaluation was not conducted beyond 14 days.

Confidence in the database was rated low to medium because there are no chronic or subchronic inhalation studies in other animal species, and there are no reproductive or developmental studies for inhalation exposure.

Confidence in the RfC was rated medium because of medium confidence in the database. I believe that confidence in the RfC should be rated as low for the same reason as the confidence in the RfD was rated low: because of the absence of an appropriate animal model for hemolytic anemia, the most observed effect in humans.

EPA's IRIS Uncertainty Review for DDT

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1. *Answer the following questions:*
   A. *Did EPA characterize to an appropriate extent the uncertainty and variability in data used to develop these IRIS health assessments?*

      No. The document contains very little discussion of uncertainty and variability. There is no discussion of the mechanism of action, metabolism, or sensitive subpopulations. I agree with the uncertainty factors selected in the assessment (10 for interspecies and 10 for variability in human populations), but believe that more discussion of the surrounding uncertainties was needed.

   B. *How does this compare between pre-Pilot and Pilot/post-Pilot assessments?*

      This is clearly a pre-Pilot assessment. There is little or no discussion of uncertainty in the database not discussion of the judgments made during the assessment.

   C. *Did EPA appropriately address:*
      1) *Strengths and weaknesses of the scientific evidence from available studies, and sources of variability in the data used in the assessment?*

         No. The studies are reviewed, but no discussion of the uncertainties in the studies or the judgments made in interpreting the studies was given.

      2) Uncertainties in the underlying data and uncertainties in the qualitative and quantitative judgments given in the assessment?

         No. The document provides little discussion of uncertainty.

   D. *Are there other relevant observations or comments that you would like to raise?*

      This was a very early assessment (originally made around 1985). Even though it had an update in 1996, it still is not up to the standards for discussing uncertainty found in post-Pilot assessments. Again, it is not correct to be critical of EPA for the quality of the uncertainty discussion in this assessment. This assessment was perfectly acceptable in 1985 given the culture at the time. However, it does not meet the requirements for discussion of uncertainty of post-Pilot assessments. The comparison of the discussion of uncertainty in this assessment with post-Pilot assessments definitely shows the improvements that EPA has made.

2. *Identify all risk factors addressed by the IRIS assessment under review:*

   Oral RfD
   Carcinogenicity assessment

3. List what relevant background data for each risk factor were available, either on EPA's website, or as bibliographic information, which required review.

   See below.

4. *Identify the basis for each risk factor.*

   For the oral RfD, the principal study was Laug et al. (1950), a study of weanling rats fed commercial DDT. The database also includes a three-generation rat reproduction study.

   For the carcinogenicity assessment, the classification of DDT as a B2 carcinogen was based on liver tumors results in seven studies in various mouse strains and three studies in rats. There were no human data.

5. *Identify:*
   A. *Was the risk factor based on human data or on animal data? How many subjects in the critical stud(ies)?*

      The RfD was based of animal data. The principal study was on weanling rats (25/sex/group) fed commercial DDT in corn oil solution mixed with powered chow at levels of 0, 5, 10, or 50 ppm for 15-27 weeks.

   B. *Critical effect*

      The critical effect for the oral RfD was liver lesions.
      The critical effect for the cancer assessment was benign and malignant liver tumors.

   C. *Route of exposure that yielded the critical effect*
      Ingestion

   D. *Mechanism of action for the critical effect observed.*
      The mechanism of action is not known.

   E. *For human data: was a sensitive sub-population included?*

      There were no human data in these studies.

   F. *For animal data: was the species/stain known to be genetically sensitive? The have any genetic peculiarity with regard to the toxicity of the compound?*

No

6. *Identify:*

Uncertainty Factor & Basis. Were the following considered?

A. Inter-species and intra-species variability
Yes

B. Inter-human variability
Yes

C. Extrapolation from less-than-chronic to chronic toxicity
No

D. Extrapolation from LOAEL to NOAEL
No

E. Data-base insufficiencies
No

7. *Was the UF data-derived? Was there sufficient information to make a quantitative assessment of uncertainty? If not, how was available information used to derive UF?*

The UF was not data-derived. There was not sufficient information to make a quantitative assessment of uncertainty. An UF of 100 was used. This accounts for a factor of 10 for intraspecies variability and a factor of 10 for interspecies extrapolation. An uncertainty factor for subchronic to chronic conversion was not included because of the corroborating chronic study in the database.

8. *Identify the MF (modifying factor) used, if any, and its basis.*
None

9. *In your judgment, is the critical effect identified relevant to humans? Is the route of exposure relevant to humans?*
Yes

10. *What is the overall confidence rating of the data used to derive the overall slope factor or RfD, or RfC? Do you concur?*

The principal study was given a medium confidence rating. It was adequate, but of shorter duration than desired. The database was given a medium rating since it was only moderately supportive of both the critical effect and the magnitude, and since it lacked a clear NOEL for reproductive effects. The RfD was given a medium confidence rating.

I do not concur with the confidence rating. The entire IRIS assessment only cites three studies: the principal study, a 15-27 week study of weanling rats, a 2-year diet study in rats which supported the critical effect and the LOAEL of the Laug et al.(1950) study, and a 3-generation rat reproduction study which showed increased offspring mortality at all dose levels, the lowest of which corresponds to about 0.2 mg/kg-day. The write up in the IRIS document does not provide sufficient breath or detail on the database to support a confidence rating of medium. Given the widespread potential of human exposure to DDT, I believe more attention needs to be given to

characterizing the critical effect, the mechanism of action, and summarizing studies on other species.

The derivation of cancer slope factors was based on ten slope factors from six studies in mice and rats. The final slope factor was the geometric mean of the ten slope factors. The document does not state a level of confidence in the estimate of the slope factor. The appropriateness of the reviewed bioassays for deriving cancer slope factors was not discussed in the document.