PUBLIC AND SCIENTIFIC REVIEW PANEL DRAFT

Air Toxics Hot Spots Program Risk Assessment Guidelines:

Technical Support Document for Describing Available Cancer Potency Factors

October, 1997

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Public and Scientific Review Panel Review Draft

Preface

The Technical Support Document for Describing Available Cancer Potency Factors (TSD) contains cancer unit risks and potency factors for 119 of the 201 carcinogenic substances or groups of substances for which emissions must be quantified in the Air Toxics Hot Spots program. The purpose of this document is to provide a summary of the data supporting the carcinogenic potential of the substance or group of substances and to provide the calculation procedure used to derive the estimated unit risk and cancer potency factors.

The Risk Assessment Advisory Committee (RAAC) report made several recommendations regarding harmonization within Cal/EPA and with US EPA. The TSD has made an effort to implement the RAAC recommendations regarding harmonization both in spirit and in substance. For example, the cancer unit risk and potency factor values developed by OEHHA that are contained in the TSD were reviewed by a Cal/EPA working group to ensure agency-wide consistency and harmonization.

Currently, OEHHA uses a toxic equivalency factor procedure for polychlorinated dibenzo-*p*-dioxins and dibenzofurans that differs slightly from the procedures used by US EPA. This document proposes adoption of US EPA's International Toxicity Equivalency Factors (ITEFs) for determining cancer unit risk and potency values for these chemicals; this is discussed in Appendix A. The document proposes to adopt 12 US EPA Integrated Risk Information System (IRIS) cancer unit risk values, in lieu of developing or using other Cal/EPA values. This is summarized in the Unit Risk and Cancer Potency Table on pages 2-6. In addition, the TSD has identified and evaluated 29 other chemicals for which Cal/EPA cancer unit risk values differ from corresponding US EPA IRIS values; this is discussed on page 18 and in Appendices E and F. Fifteen of these 29 chemicals were developed under the Toxic Air Contaminant (TAC) program; the other 14 were developed under the Proposition 65 program. All 29 of the Cal/EPA values received external peer review and public comments prior to adoption by the program of origin. Revising these numbers may require the original program to reconsider the value in an open public process. For example, the Air Resources Board and Scientific Review Panel has established a specific petition process to reconsider values adopted under the TAC program. The procedures for requesting reevaluation of cancer potency values by the programs which originated those values are listed in Appendix G. It should be noted that no new cancer unit risks or potency factors were developed for this document; all such values contained here were previously developed in documents by Cal/EPA or US EPA.

As indicated above, the document proposes for adoption 12 US EPA IRIS cancer unit risk values. Currently, US EPA is considering revisions to its cancer risk assessment guidelines. Some of the proposed changes may modify the cancer unit risk values only slightly. For example, we anticipate that some changes in potency slopes and unit risk values will result from changing the body weight scaling factor from 2/3 to 3/4 power. Additionally, US EPA has stated that cancer potency values listed in IRIS will not be revisited solely for the purpose of incorporating changes in cancer potency value calculation methods contained in the draft revised cancer risk assessment guidelines.

This document is one of five documents that will comprise the Air Toxics Hot Spots Program Risk Assessment Guidelines. The other documents to be included in the Guidelines are Part I: Technical Support Document for the Determination of Acute Toxicity Exposure Levels for Airborne Toxicants; Part III: Technical Support Document for Determination of Noncancer Chronic Reference Exposure Levels; Part IV: Technical Support Document for Exposure Assessment and Stochastic Analysis; Part V: Air Toxic Hot Spots Program Risk Assessment Guidelines.

Public workshop comments on the public comment draft of the TSD included the following suggestions:

- Change the title of the TSD from "Technical Support Document for Determining Cancer Potency Factors" to "Technical Support Document for Using Cancer Potency Factors".

- Include the procedures for submitting new scientific information on specific chemicals to the programs whose cancer unit risk and potency values were adopted in this document.

- List the documents that will comprise the Air Toxics Hot Spots Program Risk Assessment Guidelines.

- Define the term "further research" used in the table "Comparison of Hot Spots Cancer Unit Risk Values Which Differ From Corresponding US EPA IRIS Cancer Unit Risk Values" in the TSD section "How the Technical Support Document for Describing Available Cancer Potency Values (TSD) Addresses the RAAC Committee Recommendations".

- Include a discussion of how harmonization with the new draft US EPA cancer risk assessment guidelines will occur, including the question of whether the cancer unit risk and potency values will be changed to reflect new US EPA values or methodologies.

Most of the comments above resulted in revisions being made to the TSD. The title of the TSD has been changed from "Technical Support Document for Determining Cancer Potency Factors" to "Technical Support Document for Describing Available Cancer Potency Factors". The procedures for submitting new scientific information on specific chemicals to the programs whose cancer unit risk and potency values were adopted in this document have been added to the TSD as Appendix G. The documents that will comprise the Air Toxics Hot Spots Program Risk Assessment Guidelines have been listed above in this Preface.

Harmonization with the new draft US EPA cancer risk assessment guidelines will be dependent on the extent to which the programs which generated the cancer unit risk and potency values adopt those guidelines when finalized, and the decisions those programs make about cancer potency values which predate the new guidelines. For example, US EPA has stated that cancer potency values listed in IRIS will not be revisited solely for the purpose of incorporating changes in cancer potency value calculation methods contained in the draft revised cancer risk assessment guidelines. It should be noted that once this document is

approved by the Air Resources Board, statute (SB1082, Statutes of 1992, Calderon; SB1731, Statutes of 1994, Calderon) would require that future revisions undergo external peer review by the ARB Scientific Review Panel, a public comment period, and public workshops.

We believe the RAAC report has provided useful insight to the Cal/EPA risk assessment processes. Our intent has been to move forward to consider RAAC recommendations and to incorporate them into existing processes and programs on an ongoing basis.

INTRODUCTION

The Technical Support Document (TSD) for Describing Available Cancer Potency Factors provides technical information support for the Air Toxics Hot Spots Program Risk Assessment Guidelines. The TSD consists of 9 sections:

1. The TSD introduction.

2. A lookup table containing unit risk and cancer potency values.

3. A description of the methodologies used to derive the unit risk and cancer potency values listed in the lookup table.

4. Chemical-specific summaries of the information used to derive unit risk and cancer potency values.

5. A description of the use of toxicity equivalency factors for determining unit risk and cancer potency factors for polychlorinated dibenzo-*p*-dioxins and dibenzofurans (Appendix A).

6. A listing of Toxic Air Contaminant documents approved by the California Air Resources Board (Appendix B).

7. Descriptions of the International Agency for Research on Cancer (IARC) and U.S. Environmental Protection Agency (US EPA) carcinogen classifications (Appendix C).

8. An asbestos quantity conversion factor for calculating asbestos concentrations expressed as 100 fibers/m^3 from asbestos concentrations expressed as $\mu g/m^3$ (Appendix D).

9. US EPA IRIS inhalation unit risk and oral cancer potency factors available for chemicals listed in the TSD (Appendix E).

10. A listing of Hot Spots cancer unit risk values which differ from corresponding US EPA IRIS inhalation unit risk factors. (Appendix F).

11. Procedures for revisiting or delisting cancer potency factors by the program of origin (Appendix G).

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
Acetaldehyde		75-07-0	TAC	2.7 E-6	1.0 E-2	B2	2B
Acetamide		60-35-5	RCHAS-E	2.0 E-5	7.0 E-2	NC	2B
Acrylamide		79-06-1	IRIS	1.3 E-3	4.5 E+0	B2	2A
Acrylonitrile		107-13-1	RCHAS-S	2.9 E-4	1 .0 E+0	B1	2A
Allyl chloride		107-05-1	RCHAS-S	6.0 E-6	2.1 E-2	C	3
2-Aminoanthraquinone		117-79-3	RCHAS-E	9.4 E-6	3.3 E-2	NC	3
Aniline		62-53-3	IRIS	1.6 E-6	5.7 E-3	B2	3
Arsenic (inorganic)	(inhalation)	7440-38-2	TAC	3.3 E-3	1.2 E+1	A	1
	(oral)		IRIS		1.5 E+0		
Asbestos		1332-21-4	TAC	6.3 E-2	NA	A	1
				1.9 E-4[#]			
Benz[*a*]anthracene[BaP]	(inhalation)	56-55-3	TAC	1.1 E-4	3.9 E-1	B2	2A
	(oral)				1.2 E+0		
Benzene		71-43-2	TAC	2.9 E-5	1.0 E-1	A	1
Benzidine		92-87-5	RCHAS-S	1.4 E-1	5.0 E+2	A	1
Benzo[*a*]pyrene	(inhalation)	50-32-8	TAC	1.1 E-3	3.9 E+0	B2	2A
	(oral)				1.2 E+1		
Benzo[*b*]fluoranthrene[BaP]	(inhalation)	205-99-2	TAC	1.1 E-4	3.9 E-1	B2	2B
	(oral)				1.2 E+0		
Benzo[*j*]fluoranthrene[BaP]	(inhalation)	205-82-3	TAC	1.1 E-4	3.9 E-1	NC	2B
	(oral)				1.2 E+0		
Benzo[*k*]fluoranthrene[BaP]	(inhalation)	207-08-9	TAC	1.1 E-4	3.9 E-1	B2	2B
	(oral)				1.2 E+0		
Benzyl chloride		100-44-7	IRIS	4.9 E-5	1.7 E-1	B2	2B
Beryllium	(inhalation)	7440-41-7	IRIS	2.4 E-3	8.4 E+0	B2	1
	(oral)				4.3 E+0		
Bis(2-chloroethyl) ether		111-44-4	RCHAS-S	7.1 E-4	2.5 E+0	B2	3
Bis(chloromethyl)ether		542-88-1	RCHAS-S	1.3 E-2	4.6 E+2	A	1
1,3-Butadiene		106-99-0	TAC	1.7 E-4	3.4 E+0	B2	2A
Cadmium (and compounds)		7440-43-9	TAC	4.2 E-3	1.5 E+1	B1	1
Carbon tetrachloride		56-23-5	TAC	4.2 E-5	1.5 E-1	B2	2B
Chlorinated dibenzo-*p*-dioxins[A]		1746-01-6	TAC			B2	2B
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin				3.8 E+1	1.3 E+5		
1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin				1.9 E+1	6.5 E+4		
1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin				3.8 E+0	1.3 E+4		
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin				3.8 E+0	1.3 E+4		
1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin				3.8 E+0	1.3 E+4		
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin				3.8 E-1	1.3 E+3		

Footnotes

A see Appendix A
BaP see benzo[a]pyrene TAC document
C see Appendix C
NA not available
NC not classified
[100 PCM fibers/m3]-1 ; see Appendix D
* can be calculated using PEF factors contained in the benzo[a]pyrene TAC document
P1 For use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs
P2 For use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs

Source Key

TAC Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S Standard Proposition 65 document, OEHHA
IRIS Integrated Risk Information System, U.S. Environmental Protection Agency (US EPA)
RCHAS-E Expedited Proposition 65 document, OEHHA
ATES Air Toxicology and Epidemiology Section document, OEHHA
PETS Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
1,2,3,4,5,6,7,8-Octachlorodibenzo-*p*-dioxin				3.8 E-2	1.3 E+2		
Chlorinated dibenzofurans[A]		5120-73-19	TAC			B2	NC
2,3,7,8-Tetrachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,7,8-Pentachlorodibenzofuran				1.9 E+0	6.5 E+3		
2,3,4,7,8-Pentachlorodibenzofuran				1.9 E+1	6.5 E+4		
1,2,3,4,7,8-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,6,7,8-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,7,8,9-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
2,3,4,6,7,8-Hexachlorodibenzofuran				3.8 E+0	1.3 E+4		
1,2,3,4,6,7,8-Heptachlorodibenzofuran				3.8 E-1	1.3 E+3		
1,2,3,4,7,8,9-Heptachlorodibenzofuran				3.8 E-1	1.3 E+3		
1,2,3,4,5,6,7,8-Octachlorodibenzofuran				3.8 E-2	1.3 E+2		
Chlorinated paraffins		108171-26-2	RCHAS-E	2.5 E-5	8.9 E-2	NC	2B
Chloroform		67-66-3	TAC	5.3 E-6	1.9 E-2	B2	2B
4-Chloro-*o*-phenylenediamine		95-83-0	RCHAS-E	4.6 E-6	1.6 E-2	NC	2B
p-Chloro-*o*-toluidine		95-69-2	RCHAS-E	7.7 E-5	2.7 E-1	NC	2A
Chromium (hexavalent)	(inhalation)	18540-29-9	TAC	1.5 E-1	5.1 E+2	A	1
	(oral)		RCHAS-S		4.2 E-1		
Chrysene[BaP]	(inhalation)	218-01-9	TAC	1.1 E-5	3.9 E-2	B2	3
	(oral)				1.2 E-1		
Creosote		8001-58-9	ATES	*	*	B1	2A
p-Cresidine		120-71-8	RCHAS-E	4.3 E-5	1.5 E-1	NC	2B
Cupferron		135-20-6	RCHAS-E	6.3 E-5	2.2 E-1	NC	NC
2,4-Diaminoanisole		615-05-4	RCHAS-E	6.6 E-6	2.3 E-2	NC	2B
2,4-Diaminotoluene		95-80-7	RCHAS-E	1.1 E-3	4.0 E+0	NC	2B
Dibenz[*a*,*h*]acridine[BaP]	(inhalation)	226-36-8	TAC	1.1 E-4	3.9 E-1	NC	2B
	(oral)				1.2 E+0		
Dibenz[*a*,*j*]acridine[BaP]		224-42-0	TAC	1.1 E-4	3.9 E-1	NC	2B
					1.2 E+0		
Dibenz[*a*,*h*]anthracene[BaP]	(inhalation)	53-70-3	TAC	3.9 E-4	1.4 E+0	B2	2A
	(oral)		RCHAS-S		4.1 E+0		
Dibenzo[*a*,*e*]pyrene[BaP]	(inhalation)	192-65-4	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
Dibenzo[*a*,*h*]pyrene[BaP]	(inhalation)	189-64-0	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
Dibenzo[*a*,*i*]pyrene[BaP]	(inhalation)	189-55-9	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		

Footnotes

A see Appendix A
BaP see benzo[a]pyrene TAC document
C see Appendix C
NA not available
NC not classified
[100 PCM fibers/m3]-1 ; see Appendix D
* can be calculated using PEF factors contained in the benzo[a]pyrene TAC document
P1 For use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs
P2 For use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs

Source Key

TAC Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S Standard Proposition 65 document, OEHHA
IRIS Integrated Risk Information System, U.S. Environmental Protection Agency (US EPA)
RCHAS-E Expedited Proposition 65 document, OEHHA
ATES Air Toxicology and Epidemiology Section document, OEHHA
PETS Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
Dibenzo[*a,l*]pyrene[BaP]	(inhalation)	191-30-0	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
7H-Dibenzo[*c,g*]carbazole[BaP]	(inhalation)	194-59-2	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
1,2-Dibromo-3-chloropropane		96-12-8	RCHAS-S	2.0 E-3	7.0 E+0	NC	2B
1,4-Dichlorobenzene		106-46-7	RCHAS-S	1.1 E-5	4.0 E-2	NC	2B
3,3'-Dichlorobenzidine		91-94-1	RCHAS-S	3.4 E-4	1.2 E+0	B2	2B
1,1-Dichloroethane		75-34-3	RCHAS-E	1.6 E-6	5.7 E-3	C	NC
Diethylhexylphthalate		117-81-7	PETS	2.4 E-6	8.4 E-3	B2	2B
p-Dimethylaminoazobenzene		60-11-7	RCHAS-E	1.3 E-3	4.6 E+0	NC	2B
7,12-Dimethylbenz[*a*]anthracene[BaP]	(inhalation)	57-97-6	TAC	2.4 E-2	8.4 E+1	NC	NC
	(oral)		RCHAS-S		2.5 E+2		
1,6-Dinitropyrene[BaP]	(inhalation)	4239-76-48	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
1,8-Dinitropyrene[BaP]	(inhalation)	4239-76-59	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
2,4-Dinitrotoluene		121-14-2	RCHAS-S	8.9 E-5	3.1 E-1	NC	2B
1,4-Dioxane		123-91-1	RCHAS-S	7.7 E-6	2.7 E-2	B2	2B
Epichlorohydrin		106-89-8	RCHAS-S	2.3 E-5	8.0 E-2	B2	2A
Ethylene dibromide		106-93-4	TAC	7.1 E-5	2.5 E-1	B2	2A
Ethylene dichloride		107-06-2	TAC	2.2 E-5	7.0 E-2	B2	2B
Ethylene oxide		75-21-8	TAC	8.8 E-5	3.1 E-1	NC	1
Ethylene thiourea		96-45-7	RCHAS-E	1.3 E-5	4.5 E-2	UR	2B
Formaldehyde		50-00-0	TAC	6.0 E-6	2.1 E-2	B1	2A
Hexachlorobenzene		118-74-1	RCHAS-S	5.1 E-4	1.8 E+0	B2	2B
Hexachlorocyclohexanes (technical grade)		608-73-1	RCHAS-S	1.1 E-3	4.0 E+0	B2	2B
Hydrazine	(inhalation)	302-01-2	IRIS	4.9 E-3	1.7 E+1	B2	2B
	(oral)				3.0 E+0		
Indeno[1,2,3-*cd*]pyrene[BaP]	(inhalation)	193-39-5	TAC	1.1 E-4	3.9 E-1	B2	2B
	(oral)				1.2 E+0		
Lead and lead compounds	(inhalation)	7439-92-1	TAC	1.2 E-5	4.2 E-2	B2	2B
	(oral)				8.5 E-3		
Lindane		58-89-9	RCHAS-S	3.1 E-4	1.1 E+0	NC	2B
3-Methylcholanthrene[BaP]	(inhalation)	56-49-5	TAC	2.1 E-3	7.4 E+0	NC	NC
	(oral)		RCHAS-S		2.2 E+1		
5-Methylchrysene[BaP]	(inhalation)	3697-24-3	TAC	1.1 E-3	3.9 E+0	NC	2B
	(oral)				1.2 E+1		
4, 4'-Methylene bis(2-chloroaniline) (MOCA)		101-14-4	RCHAS-E	4.3 E-4	1.5 E+0	NC	2A

Footnotes

A see Appendix A
BaP see benzo[a]pyrene TAC document
C see Appendix C
NA not available
NC not classified
[100 PCM fibers/m3]-1 ; see Appendix D
* can be calculated using PEF factors contained in the benzo[a]pyrene TAC document
P1 For use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs
P2 For use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs

Source Key

TAC Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S Standard Proposition 65 document, OEHHA
IRIS Integrated Risk Information System, U.S. Environmental Protection Agency (US EPA)
RCHAS-E Expedited Proposition 65 document, OEHHA
ATES Air Toxicology and Epidemiology Section document, OEHHA
PETS Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
Methylene chloride	(inhalation)	75-09-2	TAC	1.0 E-6	3.5 E-3	B2	2B
	(oral)		RCHAS-S		1.4 E-2		
4,4'-Methylenedianiline		101-77-9	RCHAS-E	4.6 E-4	1.6 E+0	NC	2B
Michler's ketone		90-94-8	RCHAS-E	2.5 E-4	8.6 E-1	NC	NC
Nickel compounds		7440-02-0	TAC	2.6 E-4	9.1 E-1	A	1
5-Nitroacenaphthene[BaP]	(inhalation)	602-87-9	TAC	1.1 E-5	3.9 E-2	NC	2B
	(oral)		RCHAS-S		1.3 E-1		
6-Nitrochrysene[BaP]	(inhalation)	7496-02-8	TAC	1.1 E-2	3.9 E+1	NC	2B
	(oral)				1.2 E+2		
2-Nitrofluorene[BaP]	(inhalation)	607-57-8	TAC	1.1 E-5	3.9 E-2	NC	2B
	(oral)				1.3 E-1		
1-Nitropyrene[BaP]	(inhalation)	5522-43-0	TAC	1.1 E-4	3.9 E-1	NC	2B
	(oral)				1.2 E+0		
4-Nitropyrene[BaP]	(inhalation)	57835-92-4	TAC	1.1 E-4	3.9 E-1	NC	2B
	(oral)				1.2 E+0		
N-Nitroso-n-dibutylamine		924-16-3	RCHAS-S	1.1 E-1	3.1 E-3	B2	2B
N-Nitroso-N-methylethylamine		10595-95-6	IRIS	6.3 E -3	3.7 E+0	B2	2B
N-Nitrosodi-*n*-propylamine		621-64-7	IRIS	2.0 E-3	7.0 E+0	B2	2B
N-Nitrosodiethylamine		55-18-5	RCHAS-S	1.0 E-2	3.6 E+1	B2	2A
N-Nitrosodimethylamine		62-75-9	RCHAS-S	4.6 E-3	1.6 E+1	B2	2A
N-Nitrosodiphenylamine		86-30-6	RCHAS-S	2.6 E-6	9.0 E-3	B2	3
p-Nitrosodiphenylamine		156-10-5	RCHAS-E	6.3 E-6	2.2 E-2	NC	3
N-Nitrosomorpholine		59-89-2	RCHAS-E	1.9 E-3	6.7 E+0	NC	2B
N-Nitrosopiperidine		100-75-4	RCHAS-E	2.7 E-3	9.4 E+0	NC	2B
N-Nitrosopyrrolidine		930-55-2	IRIS	6.0 E-4	2.1 E+0	B2	2B
Pentachlorophenol		87-86-5	RCHAS-S	5.1 E-6	1.8 E-2	B2	2B
Perchloroethylene	(inhalation)	127-18-4	TAC	5.9 E-6	2.1 E-2	NC	2A
	(oral)		RCHAS-S		5.1 E-2		
Polychlorinated biphenyls (PCBs)	(high risk)[P1]	1336-36-3	IRIS	5.7 E-4	2.0 E+0	B2	2A
	(low risk)[P2]			2.0 E-5	7.0 E-2		
Potassium bromate		7758-01-2	RCHAS-E	1.4 E-4	4.9 E-1	NC	2B
1,3-Propane sultone		1120-71-4	RCHAS-E	6.9 E-4	2.4 E+0	NC	2B
Propylene oxide	(inhalation)	75-56-9	IRIS	3.7 E-6	1.3 E-2	B2	2B
	(oral)				2.4 E-1		
1,1,2,2-Tetrachloroethane		79-34-5	IRIS	5.8 E-5	2.0 E-1	C	3
Thioacetamide		62-55-5	RCHAS-E	1.7 E-3	6.1 E+1	NC	2B
2,4-Toluene diisocyanate		584-84-9	RCHAS-E	1.1 E-5	3.9 E-2	NC	2B
2,6-Toluene diisocyanate		91-08-7	RCHAS-E	1.1 E-5	3.9 E-2	NC	2B

Footnotes

A	see Appendix A
BaP	see benzo[a]pyrene TAC document
C	see Appendix C
NA	not available
NC	not classified
#	[100 PCM fibers/m3]-1 ; see Appendix D
*	can be calculated using PEF factors contained in the benzo[a]pyrene TAC document
P1	For use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs
P2	For use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs

Source Key

TAC	Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S	Standard Proposition 65 document, OEHHA
IRIS	Integrated Risk Information System, U.S. Environmental Protection Agency (US EPA)
RCHAS-E	Expedited Proposition 65 document, OEHHA
ATES	Air Toxicology and Epidemiology Section document, OEHHA
PETS	Pesticide and Environmental Toxicology Section document, OEHHA

Hot Spots Unit Risk and Cancer Potency Values

Chemical		Chemical Abstract Service (CAS) Number	Source	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg\text{-}day)^{-1}$	US EPA Class[C]	IARC Class[C]
1,1,2-Trichloroethane (vinyl trichloride)		79-00-5	IRIS	1.6 E-5	5.7 E-2	C	3
Trichloroethylene	(inhalation)	79-01-6	TAC	2.0 E-6	1.0 E-2	NC	2A
	(oral)		RCHAS-S		1.5 E-2		
2,4,6-Trichlorophenol		88-06-2	RCHAS-S	2.0 E-5	7.0 E-2	B2	2B
Urethane		51-79-6	RCHAS-S	2.9 E-4	1.0 E+0	NC	2B
Vinyl chloride		75-01-4	TAC	7.8 E-5	2.7 E-1	NC	1

Footnotes

A	see Appendix A
BaP	see benzo[a]pyrene TAC document
C	see Appendix C
NA	not available
NC	not classified
#	[100 PCM fibers/m3]-1 ; see Appendix D
*	can be calculated using PEF factors contained in the benzo[a]pyrene TAC document
P1	For use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs
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RCHAS-E	Expedited Proposition 65 document, OEHHA
ATES	Air Toxicology and Epidemiology Section document, OEHHA
PETS	Pesticide and Environmental Toxicology Section document, OEHHA

Selection of Cancer Potency Values

In some instances, several governmental organizations have calculated cancer potency values for the same chemical. The sources for unit risk and cancer potency values included in the Technical Support Document (TSD) for Describing Available Cancer Potency Factors were generally chosen in the following hierarchical order for the reasons described below:

1. Toxic Air Contaminant documents (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency (Cal/EPA))

2. Standard Proposition 65 documents (Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

3. Integrated Risk Information System (IRIS) documents (Office of Health and Environmental Assessment, U.S. Environmental Protection Agency)

4. Expedited Proposition 65 documents (Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

5. Air Toxicology and Epidemiology Section (ATES) documents (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

6. Pesticides and Environmental Toxicology Section (PETS) documents (Pesticides and Environmental Toxicology Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency)

All the cancer potency value sources listed above generally follow the recommendations of the National Research Council on cancer risk assessment (NRC, 1983, 1994). The hierarchy of choice listed here gives preference to sources which include external peer review and public comment procedures for publishing cancer potency values. Additional weight of consideration was given to the most recent derivations using the latest data sets and scientific methodology. The publication procedure for Toxic Air Contaminant documents includes a public comment period and review by the Air Resources Board's Scientific Review Panel (SRP) before adoption by the Air Resources Board of the California Environmental Protection Agency (Cal/EPA). Furthermore, a petition procedure is available to initiate TAC document review and revision if required because of new or previously unconsidered toxicity data. The standard Proposition 65 document adoption procedure included a public comment and external peer review by the Proposition 65 Scientific Advisory Panel. The expedited Proposition 65 document adoption procedure includes a public comment period. IRIS documents do not receive public comment or external peer review, but do undergo extensive intraagency review at US EPA and must be approved by the Carcinogen Risk Assessment Verification Endeavor Work Group (CRAVE).

Additional ATES and PETS documents have not received public comment or external peer review, but have undergone extensive Cal/EPA intraagency review.

Cancer Risk Assessment Methodologies

This section describes in general the methodologies used to derive the cancer unit risk and potency factors listed in this document. As noted in the Preface section of this document, no new cancer unit risks or potency factors were developed for this document; all such values contained here were previously developed in documents by Cal/EPA or US EPA. US EPA released for public comment in 1995 the "Proposed and Interim Guidelines for Carcinogen Risk Assessment", indicating that US EPA will revise their cancer risk assessment methodologies. However, US EPA has also stated that cancer potency values listed in IRIS will not be revisited solely for the purpose of incorporating changes in cancer potency value calculation methods contained in the draft revised cancer risk assessment guidelines.

United States Environmental Protection Agency (US EPA)

US EPA carcinogen risk assessment procedures are generally described in Anderson *et al*. (1983) and "Guidelines for Carcinogen Risk Assessment" (US EPA, 1986), and are used in the calculation of cancer potency values listed on the Integrated Risk Information System (IRIS) (Office of Health and Environmental Assessment). US EPA states that cancer risk estimates based on adequate human epidemiologic data are preferred if available over estimates based on animal data.

US EPA Calculation of Carcinogenic Potency Based on Animal Data

The procedures used to extrapolate low-dose human cancer risk from animal carcinogenicity data generally assume that most agents that cause cancer also damage DNA, and that the quantal type of biological response characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. US EPA states that the risk assessments made with this model should be regarded as conservative, representing the most plausible upper limit for the risk. The mathematical expression used by US EPA to describe the linear non-threshold dose-response relationship at low doses is the linearized multistage procedure developed by Crump (1980). This model is capable of fitting almost any monotonically increasing dose-response data, and incorporates a procedure for estimating the largest possible linear slope at low extrapolated doses that is consistent with the data at all experimental dose levels.

The linearized multistage procedure has the form

$P(d) = 1 - \exp[- (q_0 + q_1 d + q_2 d^2 + \cdots + q_k d^k)]$, where $P(d)$ = lifetime risk (probability) of cancer at dose d, $q_i > 0$, and $i = 0, 1, 2, ..., k$

Equivalently, $A(d) = 1 - \exp [- (q_1 d + q_2 d^2 + \cdots + q_k d^k)]$, where $A(d) = \dfrac{P(d) - P(0)}{1 - P(0)}$ is the extra risk over background at dose d. The point estimate of the coefficients q_i; $i = 0, 1,2, ..., k$;

and therefore the extra risk function A(d) at any given dose d is calculated by maximizing the likelihood function of the data.

US EPA uses an updated version (GLOBAL86, Howe *et al*., 1986) of the computer program GLOBAL79 developed by Crump and Watson (1979) to calculate the point estimate and the 95% upper confidence limit of the extra risk $A(d)$. Upper 95% upper confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit q_1^* on a parameter q_1. When $q_1 \neq 0$, at low doses the extra risk $A(d)$ has approximately the form $A(d) = q_1^* * d$. This term is a 95% upper confidence limit on the extra risk and R / q_1^* is an approximate 95% lower confidence limit on the dose producing an extra risk of R. The upper limit of q_1^* is calculated by increasing q_1 to a value q_1^* such that when the log-likelihood is remaximized subject to this fixed value q^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation $2(L_0 - L_1) = 2.70554$, where L_0 is the maximum value of the log-likelihood function and 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, corresponding to a 95% upper limit (one-sided). This method of calculating the upper confidence limit for the extra risk $A(d)$ is a modification of the Crump (1980) model. The upper confidence limit for the extra risk calculated at very low doses is always linear with dose. The slope q_1^* is taken as an upper bound of the potency of the chemical in inducing cancer at low doses.

In fitting the dose-response model, the number of terms in the polynomial is chosen equal to k (where $1 \leq k \leq 6$). The algorithm for selecting the number of stages in the model selects the value of k that minimizes q_1^*, while providing an adequate model fit ($p \geq 0.01$). If the model does not sufficiently fit the data, data from the highest dose are deleted and the model is refitted to the remaining data. This process is continued until an acceptable fit to the remaining data is accomplished. For purposes of determining if a fit is acceptable, the chi-square

$$x^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1 - P_i)}$$

is calculated, where N_i is the number of animals in the ith dose group, x_i is the number of animals in the ith dose group with a tumor response, P_i is the probability of a response in the ith dose group estimated by fitting the multistage procedure to the data, and h is the number of remaining groups. The fit is unacceptable when chi-square (X^2) is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f is the number of dose groups minus the number of non-zero multistage coefficients.

US EPA separates tumor incidence data according to organ sites or tumor types. The incidence of benign and malignant tumors is combined whenever scientifically defensible. US EPA considers this incidence combination scientifically defensible unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin. The primary comparison in carcinogenicity evaluation is tumor response in dosed animals as compared to contemporary matched control animals. However, US EPA states that historical control data could be used along with concurrent control data in the evaluation of carcinogenic responses, and notes that for the evaluation of rare tumors, even small tumor

responses may be significant compared to historical data. If several data sets (dose and tumor incidence) are available (different animal species, strains, sexes, exposure levels, exposure routes) for a particular chemical, the data set used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set generating the highest lifetime cancer risk estimate (q_1^*) is chosen where appropriate. An example of an inappropriate data set would be a set which generates an artifactually high risk estimate because of a very small number of animals used. If there are 2 or more data sets of comparable size for a particular chemical that are identical with respect to species, strain, sex and tumor sites, the geometric mean of q_1^* estimated from each of those data sets is used for risk estimation. The geometric mean of numbers $A_1, A_2, \ldots, A_m$ is defined as $A_1 * A_2 * \ldots * A_m)^{1/m}$. US EPA assumes that mg/surface area/day is an equivalent dose between species. Surface area is further assumed to be proportional to the 2/3 power of the weight of the animal in question. Equivalent dose is therefore computed using the following relationship:

$$\mathrm{d} = \frac{1_e * m}{L_e * W^{2/3}}$$

where L_e = experimental duration, l_e = exposure duration, m = average dose (mg/day) and W = average animal weight. Default average body weights for humans, rats and mice are 70, 0.35 and 0.03 kg, respectively.

Exposure data expressed as ppm in the diet are generally converted to mg/day using the relationship $m = \text{ppm} * F * r$, where ppm is parts per million of the chemical in the diet, F is the weight of the food consumed per day in kg, and r is the absorption fraction (assumed to be 1 in the absence of data indicating otherwise). A proportionality exists between the weight of food consumed, calories required, animal surface area, and the 2/3 power of the animal weight, so that:

$$m \propto \text{ppm} * W^{2/3} * r, \text{ or } \quad \frac{m}{rW^{2/3}} \propto \text{ppm}$$

The relationship could lead to the assumption that dietary ppm is an equivalent exposure between species. However, US EPA believes that this assumption is not justified, since the calories/kg food consumed by humans is significantly different from that consumed by laboratory animals (primarily due to differences in moisture content). US EPA uses an empirically derived food factor, $f = F/W$, which is the fraction of a species' body weight consumed per day as food. The f values for humans, rats and mice used by US EPA are 0.028, 0.05 and 0.13, respectively. Dietary exposures expressed as concentrations in ppm are converted to mg/surface area using the following relationship:

$$\frac{m}{r * W^{2/3}} = \frac{\text{ppm} * F}{W^{2/3}} = \frac{\text{ppm} * f * W}{W^{2/3}} = \text{ppm} * f * W^{2/3}$$

Exposures expressed as mg/kg/day ($m/Wr = s$) are converted to mg/surface area using the relationship:

$$\frac{m}{rW^{2/3}} = s * W^{2/3}$$

The calculation of dose when exposure is via inhalation can be performed for cases where 1) the chemical is either a completely water-soluble gas or aerosol and is absorbed proportionally to the amount of inspired air, or 2) where the chemical is a partly water-soluble gas which reaches an equilibrium between the inspired air and body compartments. After equilibrium is attained, the rate of absorption is proportional to metabolic rate, which is proportional to the rate of oxygen consumption, which is related to surface area.

Exposure expressed as mg/day to completely water-soluble gas or aerosols can be calculated using the expression $m = I * v * r$, where I is the inspiration rate/day in m^3, v is the concentration of the chemical in air (mg/m^3), and r is the absorption fraction (assumed to be the same for all species in the absence of data to the contrary; usually 1). For humans, the default inspiration rate of 20 m^3 has been adopted. Inspiration rates for 113 g rats and 25 g mice have been reported to be 105 and 34.5 liters/day, respectively. Surface area proportionality can be used to determine inspiration rate for rats and mice of other weights; for mice, $I = 0.0345\ (W / 0.025)^{2/3}\ m^3$/day; for rats, $I = 0.105\ (W / 0.113)^{2/3}\ m^3$/day. The empirical factors for air intake/kg/day (i) for humans, rats and mice are 0.29, 0.64 and 1.3, respectively. Equivalent exposures in mg/surface area can be calculated using the relationship:

$$\frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

Exposure expressed as mg/day to partly water-soluble gases is proportional to surface area and to the solubility of the gas in body fluids (expressed as an absorption coefficient r for that gas). Equivalent exposures in mg/surface area can be calculated using the relationships $m = kW^{2/3} * v * r$, and $d = m/W^{2/3} = kvr$. The further assumption is made that in the case of route-to-route extrapolations (e.g., where animal exposure is via the oral route, and human exposure is via inhalation, or vice versa), unless pharmacokinetic data to the contrary exist, absorption is equal by either exposure route.

Adjustments are made for experimental exposure durations which are less than the lifetime of the test animal; the slope q_1^* is increased by the factor $(L/L_e)^3$, where L is the normal lifespan of the experimental animal and L_e is the duration of the experiment. This assumes that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. US EPA states that age-specific rates for humans increase by at least the 2nd power of the age, and often by a considerably higher power (Doll, 1971), leading to an expectation of an increase in the cumulative tumor rate, and therefore q_1^*, to increase by at least the 3rd power of age. If the slope q_1^* is calculated at age L_e, it would be expected that if the experiment was continued for the full lifespan L at the same average dose, the slope q_1^* would have been increased by at least $(L/L_e)^3$.

US EPA Calculation of Carcinogenic Potency Based on Human Data

US EPA states that existing human epidemiologic studies with sufficiently valid exposure characterization are always used in evaluating the cancer potency of a chemical. If they show a carcinogenic effect, the data are analyzed to provide an estimate of the linear dependence of cancer rates on lifetime cancer dose (equivalent to the factor q_1^*). If no carcinogenic effect is demonstrated and carcinogenicity has been demonstrated in animals, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study. An upper limit of cancer incidence is calculated assuming that the true incidence is just below the level of detection in the cohort studied, which is largely determined by the cohort size. Whenever possible, human data are used in preference to animal data. In human epidemiologic studies, the response is measured as the relative risk of the exposed cohort of individuals compared to the control group. The excess risk ($R(X)$ - 1, where $R(X)$ is relative risk) is assumed to be proportional to the lifetime average exposure X, and to be the same for all ages. The carcinogenic potency is equal to $[R(X) - 1]/X$ multiplied by the lifetime risk at that site in the general population. The confidence limit for the excess risk is not usually calculated due to the difficulty in accounting for inherent uncertainty in the data (exposure and cancer response).

Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency

Office of Environmental Health Hazard Assessment cancer risk assessment procedures are outlined in "Guidelines for Chemical Carcinogen Risk Assessments and their Scientific Rationale" (referred to below as the Guidelines) (CDHS, 1985). These procedures are generally used in generating Toxic Air Contaminant (TAC) cancer potency values (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment), standard Proposition 65 cancer potency values (Reproductive and Cancer Hazard Assessment Section (RCHAS), Office of Environmental Health Hazard Assessment) and ATES cancer potency values (Air Toxicology and Epidemiology Section, Office of Environmental Health Hazard Assessment). Expedited Proposition 65 cancer potency values (Reproductive and Cancer Hazard Assessment Section (RCHAS), Office of Environmental Health Hazard Assessment) depart somewhat from those procedures and are discussed separately below.

OEHHA cancer risk assessment methodology (CDHS, 1985) generally resembles that used by US EPA (Anderson *et al*., 1983; US EPA, 1986). The Guidelines state that both animal and human data, when available, should be part of the dose-response assessment.

OEHHA Calculation of Carcinogenic Potency Based on Animal Data

The procedures used to extrapolate low-dose human cancer risk from animal carcinogenicity data assume that a carcinogenic change induced in a cell is transmitted to successive generations of cells descended from that cell, and that the initial change in the cell is an alteration (e.g. mutation, rearrangement, etc.) in the cellular DNA. Non-threshold models are used to extrapolate to low-dose human cancer risk from animal carcinogenicity data.

Several models proposed for extrapolating low-dose human cancer risk from animal carcinogenicity data are described in the Guidelines; these models include the Mantel-Bryan method (log-probit model), the one-hit model, the linearized multistage procedure, the gamma multihit model, and a number of time-to-tumor models. The Guidelines state that time-to-tumor models (i.e., a Weibull model) should be used for low-dose extrapolation in all cases where supporting data are available and particularly when survival is poor due to competing toxicity. However, the Guidelines also note the difficulty of determining the actual response times in an experiment; internal tumors are generally difficult to detect in live animals and their presence is usually detected only at necropsy. Additionally, use of these models often requires making the determination of whether a tumor was the cause of death, or was found only coincidentally at necropsy when death was due to other causes. Further, competing causes of death, such as chemical toxicity, may decrease the observed time-to-tumor for nonlethal cancers by allowing earlier necropsy of animals in higher dose groups. The linearized multistage procedure is noted as being an appropriate method for dose extrapolation in most cases, with the primary exception being a situation in which sufficient empirical data are available to indicate a dose-response curve of a "quasi-threshold" type (e.g., flat for two or three dose levels, then curving sharply upwards). In this case, the linearized multistage procedure may underestimate the number of stages and overestimate the low-dose risks. In this case, the gamma multihit model is suggested as being a potential alternative. The Mantel-Bryan model is described as having little biological basis as applied to carcinogenesis, and being likely to underestimate risks at low doses. The Guidelines state that this model should not be used for low dose extrapolation.

The Guidelines state that both animal and human data, when available, should be part of the dose-response assessment. Low-dose extrapolation of human cancer risk from animal carcinogenicity data is generally based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the data set in question is not appropriate for use. Where both benign and malignant tumors are induced at the same site and the malignant tumors are significantly increased, the data on both types of tumors may be combined to form the basis for risk assessment. Pharmacokinetic data on chemical metabolism, effective dose at target site, or species differences between laboratory test animals and humans are considered in dose-response assessments when they are available. In performing exposure scaling from animals to humans, the "surface area" correction (correcting by the 2/3 power of body weight) is used unless specific data indicates that this should not be done. The Guidelines assume that in the absence of evidence to the contrary, chemicals that cause cancer after exposure by ingestion will also cause cancer after exposure by inhalation, and vice versa. Unit risk factors $(\mu g/m^3)^{-1}$ are calculated from cancer potency factors $(mg/kg\text{-}day)^{-1}$ using the following relationship:

$$UR = \frac{CPF * 20\ m^3}{70\ kg\ *\ CV}$$

where UR is the unit risk, CPF is the cancer potency factor, 70 kg is the reference human body weight, 20 m^3 is the reference human inspiration rate/day, and CV is the conversion factor from mg to µg (= 1000). The Guidelines recommend the use of the linearized 95% upper confidence interval of risk as a dose-response assessment guideline.

OEHHA Calculation of Carcinogenic Potency Based on Human Data

Human epidemiologic studies with adequate exposure characterization are used to evaluate the cancer potency of a chemical. If they show a carcinogenic effect, the data are analyzed to provide an estimate of the linear dependence of cancer rates on lifetime cancer dose. The Guidelines state that with continuous exposure, age-specific incidence continues to increase as a power function (e.g., t^4) of the elapsed time since initial exposure. Lifetime risks can be estimated by applying this power function to the observed data and extrapolating beyond the actual followup period. The specific approaches used in OEHHA risk assessments based on human epidemiologic studies vary on a case by case basis; examples of the methods used can be observed in the Toxic Air Contaminant documents (these documents are referenced in Appendix B).

Reproductive And Cancer Hazard Assessment Section (RCHAS), Office of Environmental Health Hazard Evaluation (OEHHA), California Environmental Protection Agency (Cal/EPA): Expedited Proposition 65 Cancer Risk Assessment Methodology

Expedited cancer potency values developed for several agents listed as carcinogens under Proposition 65 (California Health and Safety Code 25249.5 et seq.) by RCHAS were derived from selected data sets of the Carcinogenic Potency Database (CPDB) of Gold *et al.* (1984, 1986, 1987, 1989, 1990) using default procedures specified in the administrative regulations for Proposition 65 (Title 22 California Code of Regulations [CCR] 12703). OEHHA hazard assessments usually describe all relevant data on the carcinogenicity (including dose-response characteristics) of the chemical under examination, followed by an evaluation of any pharmacokinetic and mechanistic (e.g. genotoxicity) data. An evaluation of the data set for the chemical may indicate that adjustments in target dose estimates or use of a dose response model different from the default are appropriate. The procedure used by RCHAS to derive expedited Proposition 65 cancer potency values differs from the usual methodology in two ways. First, it relies on cancer dose response data evaluated and extracted from the original literature by Gold *et al.*. Second, the choice of a linearized multistage procedure for generating cancer potency values is automatic, and pharmacokinetic adjustments are not performed. The methods used by RCHAS to develop expedited cancer potency values incorporate the following assumptions:

1. The dose response relationship for carcinogenic effects in the most sensitive species tested is representative of that in humans.

2. Observed experimental results can be extrapolated across species by use of the interspecies factor based on "surface area scaling."

3. The dose to the tissue giving rise to a tumor is assumed to be proportional to the administered dose.

4. The linearized multistage polynomial procedure can be used to extrapolate potency outside the range of experimental observations to yield estimates of "low" dose potency.

5. Cancer hazard increases with the third power of age.

The Carcinogenic Potency Database of Gold *et al.* (1984, 1986, 1987, 1989, 1990) contains the results of more than 4000 chronic laboratory animal experiments on 1050 chemicals by combining published literature with the results of Federal chemical testing programs (Technical Reports from the Carcinogenesis Bioassay Program of the National Cancer Institute (NCI)/National Toxicology Program (NTP) published prior to June 1987). The published literature was searched (Gold *et* al., 1984) through the period December 1986 for carcinogenicity bioassays; the search included the Public Health Service publication "Survey of Compounds Which Have Been Tested for Carcinogenic Activity" (1948-1973 and 1978), monographs on chemical carcinogens prepared by the International Agency for Research on Cancer (IARC) and Current Contents. Also searched were Carcinogenesis Abstracts and the following journals: British Journal of Cancer, Cancer Letters, Cancer Research, Carcinogenesis, Chemosphere, Environmental Health Perspectives, European Journal of Cancer, Food and Cosmetics Toxicology, Gann, International Journal of Cancer, Journal of Cancer Research and Clinical Oncology (formerly Zeitschrift fur Krebsforschung und Klinische Onkologie), Journal of Environmental Pathology and Toxicology, Journal of Toxicology and Environmental Health, Journal of the National Cancer Institute, and Toxicology and Applied Pharmacology. Studies were included in the database if they met the following conditions:

1. The test animals were mammals.

2. Chemical exposure was started early in life (100 days of age or less for hamsters, mice and rats).

3. Route of administration was via the diet, drinking water, gavage, inhalation, intravenous injection or intraperitoneal injection.

4. The test chemical was administered alone (not in combination with other chemicals).

5. Chemical exposure was chronic, with not more than 7 days between exposures.

6. The experiment duration was at least half the standard lifespan for the species used.

7. The study design included a control group and at least 5 animals/exposure group.

8. No surgical interventions were performed.

9. Pathology data were reported for the number of animals with tumors (not total number of tumors).

10. All results reported were original data (not analysis of data reported by other authors).

Included in their data set tabulations are estimates of average doses used in the bioassay, resulting tumor incidences for each of the dose levels employed for sites where significant responses were observed, dosing period, length of study and histopathology. Average daily dose levels were calculated assuming 100% absorption. Dose calculations follow procedures similar to those of Cal/EPA and US EPA; details on methods used and standard values for animal lifespans, body weights, and diet, water and air intake are listed in Gold *et al.* (1984). RCHAS (1992) reviewed the quality assurance, literature review, and control procedures used in compiling the data and found them to be sufficient for use in an expedited procedure. Cancer potency estimates were derived by applying the mathematical approach described in the section below to dose response data in the Gold *et al.* database. The following criteria were used for data selection:

1. Data sets with statistically significant increases in cancer incidence with dose ($p \leq 0.05$) were used. (If the authors of the bioassay report considered a statistically significant result to be unrelated to the exposure to the carcinogen, the associated data set was not used.)

2. Data sets were not selected if the endpoint was specified as "all tumor-bearing animals" or results were from a combination of unrelated tissues and tumors.

3. When several studies were available, and one study stood out as being of higher quality due to numbers of dose groups, magnitude of the dose applied, duration of study, or other factors, the higher quality study was chosen as the basis for potency calculation if study results were consistent with those of the other bioassays listed.

4. When there were multiple studies of similar quality in the sensitive species, the geometric mean of potencies derived from these studies was taken. If the same experimentalists tested two sexes of the same species/strain under the same laboratory conditions, and no other adequate studies were available for that species, the data set for the more sensitive sex was selected.

5. Potency was derived from data sets that tabulate malignant tumors, combined malignant and benign tumors, or tumors that would have likely progressed to malignancy.

Cancer potency was defined as the slope of the dose response curve at low doses. Following the default approach, this slope was estimated from the dose response data collected at high doses and assumed to hold at very low doses. The Crump linearized multistage polynomial (Crump *et al.*, 1977) was fit to animal bioassay data:

$$\text{Probability of cancer} = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots)]$$

Cancer potency was estimated from the upper 95 % confidence bound on the linear coefficient q_1, which is termed q_1^*.

For a given chemical, the model was fit to a number of data sets. As discussed in the section above, the default was to select the data for the most sensitive target organ in the most sensitive species and sex, unless data indicated that this was inappropriate. Deviations from this default

occur, for example, when there are several bioassays or large differences exist between potency values calculated from available data sets.

Carcinogenicity bioassays using mice and/or rats will often use an exposure duration of approximately two years. For standard risk assessments, this is the assumed lifespan for these species. Animals in experiments of shorter duration are at a lower risk of developing tumors than those in the standard bioassay; thus potency is underestimated unless an adjustment for experimental duration is made. In estimating potency, short duration of an experiment was taken into account by multiplying q_1^* by a correction factor equal to the cube of the ratio of the assumed standard lifespan of the animal to the duration of the experiment (T_e). This assumes that the cancer hazard would have increased with the third power of the age of the animals had they lived longer:

$$q_{animal} = q_1^* * (104 \text{ weeks}/T_e)^3$$

In some cases excess mortality may occur during a bioassay, and the number of initial animals subject to late occurring tumors may be significantly reduced. In such situations, the above described procedure can, at times, significantly underestimate potency. A time-dependent model fit to individual animal data (i.e., the data set with the tumor status and time of death for each animal under study) may provide better potency estimates. When Gold *et al.* indicated that survival was poor for a selected data set, a time-dependent analysis was attempted if the required data were available in the Tox Risk (Crump *et al.*, 1991) data base. The Weibull multistage model (Weibull-in-time; multistage-in-dose) was fit to the individual animal data.

To estimate human cancer potency, q_{animal} values derived from bioassay data were multiplied by an interspecies scaling factor (K; the ratio of human body weight (bw_h) to test animal body weight (bw_a), taken to the 1/3 power (Anderson *et al.*, 1983)):

$$K = (bw_h/bw_a)^{1/3}$$

Thus, cancer potency = $q_{human} = K * q_{animal}$

Chemical-specific Descriptions of Cancer Potency Value Derivations

Information summaries for chemicals whose cancer potency values were obtained from standard or expedited Proposition 65 documents, Integrated Risk Information System (IRIS) documents, Health Effects Assessment Summary Table (HEAST) entries, Air Toxicology and Epidemiology (ATES) documents and Pesticides and Environmental Toxicology (PETS) documents follow this section. Complete information summaries for chemicals with cancer potency values obtained from Toxic Air Contaminant documents are contained in those documents and are not included below. These documents have all undergone public comment and review by the SRP, and are available from the California Air Resources Board (these documents are referenced in Appendix B).

How the Technical Support Document for Describing Available Cancer Potency Values (TSD) Addresses the RAAC Committee Recommendations

The Technical Support Document for Describing Available Cancer Potency Values (TSD), which was drafted concurrently with the release of the Risk Assessment Advisory Committee (RAAC) draft final report, follows the RAAC report recommendations quite closely. The table below lists the applicable RAAC report recommendations and the ways in which the TSD adheres to those recommendations.

RAAC recommendation	TSD implementation
An internal Cal/EPA working group should be established whose specific charge is to insure agency-wide consistency and harmonization.	Cal/EPA-generated cancer potency values contained in the TSD have been reviewed by the Standards and Criteria Work Group, an internal Cal/EPA working group, for consistency and harmonization. The cancer potency factors in the TSD are the same as those in the Standards and Criteria Workgroup's document entitled "Criteria for Carcinogens".
Cal/EPA should develop a formalized program for peer review.	The TSD will be peer reviewed by an advisory committee of scientists from outside State government (the Air Resources Board's Scientific Review Panel) using a formalized process.
Cal/EPA should seek early input into the risk assessment process from risk managers and from external stakeholders. The Agency should identify effective and efficient mechanisms for participation by the general public and interested stakeholders and apply these throughout the Agency.	The TSD has been reviewed by Cal/EPA risk assessors and the Air Quality Management and Air Pollution Control Districts and will be distributed to interested parties, including external stakeholders, for public comment. The Cal/EPA cancer potency factors have already undergone stakeholder, public and peer review in their respective programs prior to their inclusion in this document.
The Committee recommends that Cal/EPA consider an approach in conducting chemical risk assessments that balances the level of effort and resources with the importance of the risk assessment.	The TSD has optimized use of OEHHA resources by developing a decision hierarchy which permits utilization of previously developed Cal/EPA and US EPA cancer potency factors.
"Cal/EPA should endeavor to develop future risk assessments in concert with US EPA, especially for high volume and/or high risk compounds. Before Cal/EPA conducts an independent risk assessment for a substance, it should first review any existing US EPA risk assessment."	The TSD has incorporated US EPA cancer potency factors listed in IRIS (as shown in the Unit Risk and Cancer Potency Factors Table of the TSD) where appropriate. In other cases California-developed information has been used if it supersedes US EPA information, or addresses compounds still awaiting consideration by US EPA.

Appendix E of the TSD provides US EPA IRIS unit risk and cancer potency values for all chemicals listed in the TSD. Appendix F presents the ratios of the California-developed unit risk values used in the Unit Risk and Cancer Potency Factors Table of the TSD with the corresponding unit risk values (where available) listed in IRIS.

Comparison of Hot Spots Cancer Unit Risk Values Which Differ From Corresponding US EPA IRIS Cancer Unit Risk Values

Chemical	OEHHA RA performed considering US EPA RA information	OEHHA RA based on newer study compared to the corresponding US EPA RA	OEHHA RA received external peer review	OEHHA RA received public comment	Are OEHHA and US EPA unit risk values essentially similar?[A]	Resolution of the differences between the OEHHA and US EPA RAs will require additional research[C]
Acetaldehyde	yes	no	yes	yes	yes	no
Acrylonitrile	yes	no	yes	yes	no	no
Arsenic (inorganic, inhalation)	yes	yes	yes	yes	yes	no
Asbestos	no[B]	no	yes	yes	no	no
Benzene	yes	no	yes	yes	no	no
Benzidine	yes	no	yes	yes	no	no
Bis(2-chloroethyl) ether	yes	no	yes	yes	no	no
Bis(chloromethyl)ether	yes	no	yes	yes	no	no
1,3-Butadiene	yes	yes	yes	yes	yes	no
Cadmium (and compounds)	yes	no	yes	yes	no	no
Carbon tetrachloride	yes	no	yes	yes	no	no
Chloroform	yes	yes	yes	yes	no	no
Chromium (hexavalent)	yes	no	yes	yes	no	yes
3,3'-Dichlorobenzidine	yes	no	yes	yes	no	no
1,4-Dioxane	yes	no	yes	yes	no	no
Epichlorohydrin	yes	no	yes	yes	no	no
Ethylene dibromide	yes	no	yes	yes	no	no
Ethylene dichloride	yes	no	yes	yes	yes	no
Formaldehyde	yes	yes	yes	yes	yes	no
Hexachlorobenzene	yes	yes	yes	yes	yes	no
Hexachlorocyclohexanes (technical grade)	yes	no	yes	yes	no	no
Methylene chloride	yes	no	yes	yes	no	yes
Nickel compounds	yes	yes	yes	yes	yes	no
N-Nitroso-n-dibutylamine	yes	no	yes	yes	no	no
N-Nitrosodiethylamine	yes	no	yes	yes	no	no
N-Nitrosodimethylamine	yes	no	yes	yes	no	no
N-Nitrosodiphenylamine	yes	no	yes	yes	yes	no

Comparison of Hot Spots Cancer Unit Risk Values Which Differ From Corresponding US EPA IRIS Cancer Unit Risk Values (continued)

Chemical	OEHHA RA performed considering US EPA RA information	OEHHA RA based on newer study compared to the corresponding US EPA RA	OEHHA RA received external peer review	OEHHA RA received public comment	Are OEHHA and US EPA unit risk values essentially similar?[A]	Resolution of the differences between the OEHHA and US EPA RAs will require additional research[C]
Pentachlorophenol	yes	no	yes	yes	no	yes
2,4,6-Trichlorophenol	yes	no	yes	yes	no	yes

Abbreviations
RA: risk assessment CDHS: California Department of Health Services

Footnotes
A: Chemicals having a Hot Spots/IRIS unit risk ratio of greater than 0.5 but less than 2.
B: Both the CDHS RA and the US EPA RA were published in the same year.
C: This indicates instances where differences in scientific judgment on how to address data gaps in the information used in the risk assessment for that chemical exist between Cal/EPA and US EPA; additional studies could potentially eliminate those differences.

The above table describes differences between OEHHA and US EPA risk assessments in cases where US EPA IRIS unit risk values exist for chemicals that have an OEHHA unit risk value listed in the TSD Unit Risk And Cancer Potency Value Table. In addition to the chemicals listed above, the Unit Risk and Cancer Potency Table proposes OEHHA adoption of 12 US EPA IRIS cancer unit risk values. OEHHA/IRIS unit risk value ratios are listed in Appendix F.

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ACETAMIDE

CAS No: 60-35-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	59.07
Boiling point	222 °C
Melting point	81 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 2.416 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 7.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Male Fischer 344 rat liver tumor data (Fleischman *et* al., 1980), contained in Gold *et al.* database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of acetamide on humans are known to exist.

Animal Studies

Dessau and Jackson (1955) exposed 5 Rockland albino rats to acetamide by gavage (4 g/kg body weight/day in distilled water) for 205 days. One animal developed an hepatocellular adenoma.

Male Wistar rats (25/group) were fed diet containing 0, 1.25, 2.5 or 5% acetamide for 1 year (Jackson and Dessau, 1961). One rat/group was sacrificed at monthly intervals; the remaining animals were sacrificed at 1 year. Liver tumors (described as trabecular carcinomas or adenocarcinomas) were seen in 0/25, 4/24, 6/22 and 1/18 animals from the control, low, medium and high dose groups. In the same study, a group of 50 male Wistar rats were fed a diet containing 5% acetamide for 1 year. One animal was killed weekly for 26 weeks, after which 1 animal was killed every other week. Liver tumors (trabecular carcinomas or adenocarcinomas) were observed in 4/48 animals treated for 38-42 weeks, compared to 0/43 in controls.

Male Wistar rats were fed control diet (15 animals), or diets containing 2.5% acetamide (40 animals), 2.5% acetamide + 5.6% L-arginine L-glutamate (40 animals), or 5.6% L-arginine L-glutamate (15 animals) for 1 year. Hepatomas were observed in 2/8 animals fed acetamide alone and killed after 1 year; 7/16 animals fed acetamide alone for 1 year followed by control diet for 3 months also developed liver tumors. In contrast, 1/11 animals fed diet containing acetamide + L-

arginine L-glutamate for 1 year developed hepatomas, and 1/19 animals fed diet containing acetamide + L-arginine L-glutamate for 1 year followed by control diet for 3 months developed hyperplastic liver nodules, but not tumors. No liver tumors were noted in either the control or 5.6% L-arginine L-glutamate treatment groups (Weisburger *et al*., 1969).

Fleischman *et al*.(1980) fed male and female C57BL/6 mice (50/sex/group) and Fischer 344 rats (50/sex/group) a diet containing 1.18% (mice) or 2.36% (mice, rats) acetamide for 365 consecutive days; animals were then fed a control diet for an additional 4 months. Male mice demonstrated a treatment-related increase in hematopoietic tumors, primarily malignant lymphomas; tumor incidence was 7/50 and 7/46 for the low and high dose groups, respectively, compared to 0/95 for the pooled (male and female) control group. Neoplastic nodules and hepatocellular carcinomas were observed in both male and female rats. However, the incidence, speed of onset and frequency of metastases were greater in males (Fleischman *et al*., 1980). No liver tumors were noted in control animals. Incidence data for hepatocellular carcinomas in F344 rats, the most sensitive species tested, are given in Table 1.

Table 1: Incidence of hepatocellular carcinomas in F344 rats treated with acetamide by dietary administration (Fleischman *et al*., 1980).

Dietary Concentration (%)	Average Dose[1] (mg/kg-day)	Tumor Incidence[2]	
		Male	Female
0	0	0/50	0/49
2.36	710	41/47	33/48

1. Doses as reported by Gold *et al*. (1984).

2. Decreased survival of treatment group according to Gold *et al*. (1990) (56% survival at study termination compared to 86% for controls); potency may be an underestimate (Cal/EPA, 1992).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The carcinogenicity bioassay by Fleischman *et al*. (1980) indicated that acetamide causes hematopoietic tumors in male C57BL/6 mice, and hepatocellular carcinomas in male and female Fischer 344 rats. Rats were more sensitive than mice, and male rats were more sensitive than female rats in this study; therefore, the male Fischer 344 rat liver tumor data was used as the basis of a cancer potency factor.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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ACRYLAMIDE

CAS No: 79-06-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	71.08
Boiling point	125°C at 25 mm Hg
Melting point	84.5
Vapor pressure	0.007 mm Hg at 25°C
Air concentration conversion	1 ppm = 2.91 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-3 (µg/m^3)$^{-1}$
Slope Factor: 4.5 E+0 (mg/kg-day)$^{-1}$
[Calculated by US EPA/IRIS (1988, 1993) from female Fischer 344 rat tumor data (central nervous system, mammary and thyroid glands, uterus, oral cavity) (Johnson *et al*., 1986) using a linearized multistage procedure, extra risk; adopted by CDHS/RCHAS (1990).]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1993) reviewed a study of cancer mortality in workers exposed to acrylamide by Collins (1984). Data from a long duration exposure group (10 individuals) and a short duration/intermittent exposure group (52 individuals) was analyzed using a standardized proportional mortality ratio (SPMR) procedure. No excess mortality for all types of cancer combined was noted in either group. Mortality from lung and central nervous system cancer appeared to be slightly elevated. However, the SPMRs were not significantly different from expected values, due to small group size. US EPA (1993) also noted additional study limitations including underrepresentation of the potential at-risk worker population, incomplete cause of death ascertainment, and incomplete exposure data.

Sobel *et al*. (1986) studied the mortality experience of 371 workers (365 white males, 6 white females) employed in acrylamide monomer production and polymerization operations at the Michigan Division of the Dow Chemical Company from 1955 through 1979. Vital status followup was performed from the date of the first potential exposure to December 31, 1982. Mortality comparisons were made between the cohort and United States white male mortality rates; comparisons were made with a subcohort of workers previously exposed to organic dyes both included and excluded. Slight excesses of mortality from all cancers (11 observed/7.9 expected), digestive tract cancer (4 observed/1.9 expected) and respiratory tract cancer (4 observed/2.9 expected) were observed in the total cohort; these excesses were not observed when the organic dye exposure subcohort was excluded. The authors concluded that the study did not

support a relationship between acrylamide exposure and general or specific cancer mortality. However, US EPA (1988) considers this study insufficient to assess the carcinogenicity of acrylamide in humans because of small cohort size, multiple chemical exposures, limited followup, and short exposure duration (167 cohort members had < 1 year of employment; 109 had 1-4 years of employment).

Animal Studies

Bull *et al*. (1984a) exposed female Sencar mice and male and female A/J mice to acrylamide. Female Sencar mice (40/treatment group) were exposed to 0, 12.5, 25.0 or 50.0 mg/kg body weight acrylamide by gavage, intraperitoneal injection or dermal application. Doses were administered 6 times over a 2 week period; total doses were 0, 75, 150 and 300 mg/kg. Acrylamide was dissolved in distilled water for gavage and intraperitoneal injection administration, and in ethanol for dermal application. Two weeks after the cessation of acrylamide exposure, 1.0 µg 12-*O*-tetradecanoyl-phenol-13-acetate (TPA) dissolved in 0.2 ml acetone was applied to the shaved back of each animal 3 times/week for 20 weeks. A promotion control group was included which received 300 mg/kg acrylamide followed by dermal applications of 0.2 ml acetone on the same treatment schedule and duration as the animals receiving TPA. All animals were sacrificed at 52 weeks, and were evaluated for the presence of skin tumors. Male and female A/J mouse (40/sex/treatment group) acrylamide exposures were conducted at laboratories of the US EPA (Cincinnati, OH) and the Medical College of Ohio (Toledo, OH) (MCO) . Animals exposed at US EPA received acrylamide dissolved in distilled water by gavage 3 times/week for 8 weeks at doses of 0, 6.25, 12.5 or 25 mg/kg. Animals exposed at MCO initially received acrylamide by intraperitoneal injection 3 times/week for 8 weeks at doses of 0, 1, 3, 10, 30 or 60 mg/kg; however, peripheral neuropathy and decreased survival forced treatment termination on the 60 mg/kg group after the 11th injection. An untreated control group was also included. Animals were sacrificed after either 7 months (US EPA) or 6 months (MCO) and examined for lung adenomas. Acrylamide induced skin tumors (squamous cell papillomas and carcinomas) in TPA-promoted female Sencar mice in a dose-dependent manner when administered by gavage, intraperitoneal injection or dermal application. Acrylamide did not induce skin tumors by any route of administration in animals not receiving TPA. Tumor incidence data from female Sencar mice exposed to acrylamide are listed in Table 1.

The incidence of lung adenomas in both male and female A/J mice exposed to acrylamide by either gavage or intraperitoneal injection was significantly increased in a dose-related manner (Bull *et al*., 1984a). Tumor incidence data for animals treated by intraperitoneal injection is listed in Table 2; numerical tumor incidence data for animals exposed to acrylamide by gavage was not listed.

Acrylamide dissolved in water was administered by gavage (0, 75, 150 or 200 mg/kg body weight, divided into 6 equal portions) to female ICR-Swiss mice (40 animals/treatment group) over a 2 week period (Bull *et al*., 1984b). Two weeks after the last acrylamide exposure, the animals were exposed 3 times/week to dermal applications of 2.5 µg TPA for 20 weeks. Another group of 20 animals were exposed to a total dose of 300 mg/kg acrylamide, but received dermal

applications of acetone alone. All animals were sacrificed after 52 weeks. Acrylamide caused a significant dose-related increase in the incidence of skin tumors (papillomas and carcinomas combined). The incidence in animals also receiving TPA was 0/35, 4/34, 4/32 and 13/32 (number of animals with tumors/number of animals examined) for the control, low, mid and high dose groups, respectively; the skin tumor incidence in animals receiving 300 mg/kg acrylamide but not TPA was 10/36. Acrylamide-treated animals also demonstrated a significant dose-related increase in the incidence of lung tumors (alveolar and bronchiolar adenomas and carcinomas). The incidence in animals also receiving TPA was 4/36, 8/34, 6/36 and 11/34 for the control, low, mid and high dose groups, respectively; the lung tumor incidence in animals receiving 300 mg/kg acrylamide but not TPA was 14/36.

Table 1. Skin tumor (squamous cell papillomas and carcinomas) incidence in female Sencar mice exposed to acrylamide (Bull *et al*., 1984a)

Total administered dose[1] (mg/kg body weight)	Route of administration	TPA[2]	Tumor incidence
0	gavage	+	2/40
75		+	12/40
100		+	23/40
300		+	30/40
300		-	0/20
0	intraperitoneal injection	+	0/40
75		+	10/40
100		+	13/40
300		+	21/40
300		-	0/20
0	dermal	+	7/40
75		+	4/40
100		+	11/40
300		+	18/40
300		-	0/20

1. The exposure duration was less than lifetime (2 weeks); the total administered dose listed was not adjusted to reflect a less-than-lifetime exposure.
2. TPA = 12-*O*-tetradecanoyl-phenol-13-acetate

Table 2. Lung adenoma incidence in male and female A/J mice exposed to acrylamide by intraperitoneal injection (Bull *et al*., 1984a)

Dose level[1] (mg/kg body weight)	Percent of animals with tumors	
	males	females
0	13	8
1	50	35
3	38	53
10	59	79
30	93	93

1. The exposure duration was less than lifetime (8 weeks); the dose level listed was not adjusted to reflect a less-than-lifetime exposure.

Robinson *et al*. (1986) exposed female SENCAR, BALB/c, A/J and ICR-Swiss mice (60 mice/strain/treatment group) to a single 50 mg/kg body weight dose of acrylamide by intraperitoneal injection; 2 days later 40 of the 60 mice in each treatment group received 1.0 µg (SENCAR), 2.5 µg (A/J and ICR-Swiss) or 5.0 µg (BALB/c) TPA in 0.2 ml acetone applied dermally 3 times/week for 20 weeks. The remaining 20 mice/strain/treatment group received acetone alone for the same treatment schedule and duration. All animals were sacrificed at 40 weeks, and were only examined for the number of skin papillomas and lung adenomas/animal. Acrylamide induced a significant increase in the number of skin papillomas and lung adenomas per animal in SENCAR mice receiving TPA treatment. The total number of animals bearing tumors was not listed. No significant increase in either tumor type was noted in the other mouse strains tested; tumor data for the animals receiving acrylamide but not TPA was not reported.

Male and female Fischer 344 rats (90/sex/treatment group) were exposed to acrylamide in drinking water for 2 years (Johnson *et al*., 1986). Acrylamide water concentrations were adjusted to provide dosages of 0, 0.01, 0.1, 0.5 or 2 mg/kg body weight/day. Interim sacrifices (10 animals/sex/treatment group) were performed at 6, 12 and 18 months. A maximum tolerated dose (MTD) was achieved based on decreased weight gain, increased mortality during the last 4 months of the study and the appearance of several toxic effects (including peripheral nerve degeneration) in the 2 mg/kg/day group. Increases in the incidences of a number of tumor types were observed in the 2.0 mg/kg/day exposure group animals. An increased incidence of thyroid gland-follicular epithelium tumors was observed in both males and females. In females, increased tumor incidences were noted in the mammary glands, central nervous system, oral tissues, uterus and clitoral gland. An increased incidence of scrotal mesothelioma was noted in males, in both the 2.0 and 0.5 mg/kg/day exposure group; additionally, although not statistically significant, the incidence of scrotal mesothelioma in the 0.1 mg/kg/day group was greater than either the control group or historical control incidences. Male rats in the 2.0 mg/kg/day exposure group also had a significant increase in adrenal pheochromocytomas, and an increased incidence of central nervous system tumors when compared to historical controls but not when compared to concurrent controls. Tumor incidence data is listed in Table 3.

Table 3. Acrylamide-induced tumor incidences in male and female Fischer 344 rats (Johnson *et al*., 1986)

Administered dose (mg/kg/day)	Human equivalent dose[1] (mg/kg/day)	Tumor type	Tumor incidence	
			males	females
0	0	combined central nervous system (CNS), mammary gland, oral cavity, thyroid gland, uterus[2]	NA	13/60
0.01	0.001		NA	18/60
0.1	0.015		NA	14/60
0.5	0.076		NA	21/60
2.0	0.305		NA	46/60
0	0	adrenal pheochromacytomas[3]	3/60	NA
0.01	0.001		7/60	NA
0.1	0.015		7/60	NA
0.5	0.076		5/60	NA
2.0	0.305		10/60	NA
0	0	central nervous system[4]	5/60	1/60
0.01	0.001		2/60	2/60
0.1	0.015		0/60	1/60
0.5	0.076		3/60	1/60
2.0	0.305		8/60	9/60
0	0	oral cavity[5]	6/60	0/60
0.01	0.001		7/60	3/60
0.1	0.015		1/60	2/60
0.5	0.076		5/60	3/60
2.0	0.305		6/60	8/60
0	0	mammary gland[6]	NA	2/60
0.01	0.001		NA	2/60
0.1	0.015		NA	1/60
0.5	0.076		NA	5/58
2.0	0.305		NA	8/61
0	0	scrotal mesotheliomia	3/60	NA
0.01	0.001		0/60	NA
0.1	0.015		7/60	NA
0.5	0.076		11/60	NA
2.0	0.305		10/60	NA
0	0	thyroid[7]	1/60	1/58
0.01	0.001		0/58	0/59
0.1	0.015		2/59	1/59
0.5	0.076		1/59	1/58
2.0	0.305		7/59	5/60
0	0	uterine adenocarcinomas	NA	1/60
0.01	0.001		NA	2/60
0.1	0.015		NA	1/60
0.5	0.076		NA	0/59
2.0	0.305		NA	5/60

1, 2. As calculated by US EPA (1988).

Table 3 (continued). Acrylamide-induced tumor incidences in male and female Fischer 344 rats (Johnson *et al*., 1986)

3. Benign and malignant.
4. Tumors of glial origin or glial proliferation suggestive of early tumor.
5. Squamous cell papillomas and carcinomas.
6. Adenomas and adenocarcinomas.
7. Males: follicular adenomas; females: follicular adenomas and adenocarcinomas.

NA not available

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Bull *et al*. (1984a, 1984b), Robinson *et al*. (1986) and Johnson *et al*. (1986) indicate that acrylamide is capable of acting as both an initiator and a complete carcinogen in animals. However, only the Johnson *et al*. (1986) study contained a data set suitable for generating a cancer potency factor. Female Sencar mice developing tumors after exposure to acrylamide in the study by Bull *et al*. (1984a) were also additionally exposed to TPA; animals not exposed to TPA did not develop skin tumors. Female A/J mice exposed in that study to acrylamide by either gavage or intraperitoneal injection developed an increased incidence of lung adenomas without requiring TPA exposure. However, the animals were not evaluated for tumor types other than lung adenomas, and numerical tumor incidence data for animals exposed to acrylamide by gavage was not listed. Also, the exposure and observation durations for animals exposed by gavage (8 weeks and 7 months, respectively) and by intraperitoneal injection (8 weeks and 6 months, respectively) were short. Female ICR-Swiss mice exposed to acrylamide by gavage in the study by Bull *et al*. (1984b) were generally also exposed to TPA; only one exposure group was included which received acrylamide (300 mg/kg) but not TPA. Additionally, the exposure duration was only 2 weeks and the exposure duration was less than lifetime (52 weeks). In the study by Robinson *et al*. (1986), all animals for which tumor incidence data was reported were exposed to TPA as well as acrylamide. Animals in the Johnson *et al*. (1986) study were exposed to acrylamide alone for the lifetime of the animals, and were comprehensively examined for tumors. For these reasons, tumor incidence data from the Johnson *et al*. (1986) study was used to derive a cancer potency factor for acrylamide.

Methodology

As recommended in the US EPA Guidelines for Carcinogen Risk Assessment (1986), US EPA (1988) pooled tumor incidence data from different tumor sites, under the consideration that risk numbers derived from site-specific tumor incidence data potentially may not be predictive of, and may in fact underestimate, “whole-body” risks that are determined using the pooled individual animal data. The dose-response curves for each sex based on the pooled tumor incidence (benign and malignant) constituted the data sets of choice for risk assessment. Tumors at a particular site were added into the pool only when the tumor site had statistically significantly increased incidence at least at the high dose level (treated vs. control). The female rat was considered to be

the more sensitive sex, as there were significantly increased tumor incidences at a greater number of sites than in the males; the female rat tumor data was therefore used as the basis of a risk estimate. A linearized multistage procedure (GLOBAL 83) was used to calculate a cancer potency factor (q_1^*) from the female rat tumor incidence data. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Body weight values used for humans and rats were 70 kg and 0.2 kg, respectively. No exposure route adjustment was made to the risk estimates because data exists which indicates that the pharmacokinetics and tissue distribution of acrylamide were not significantly affected by the dose administered or the route of administration (Dearfield *et al*., 1988). US EPA calculated a cancer potency value (q_{human}) of 4.5 E+0 $(mg/kg\text{-}day)^{-1}$. A unit risk factor was then calculated from the cancer potency factor by OEHHA/ATES using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day. The unit risk should not be used if the air concentration exceeds 8 $\mu g/m^3$, as above this concentration the unit risk may not be appropriate.

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ACRYLONITRILE

CAS No: 107-13-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	53.06
Boiling point	77.3°C
Melting point	-82°C
Vapor pressure	100 mm Hg at 23°C
Air concentration conversion	1 ppm = 2.2 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.9 E-4 (µg/m^3)$^{-1}$
Slope Factor: 1.0 E+0 (mg/kg-day)$^{-1}$
[Human respiratory tract cancer incidence data (O'Berg, 1980), relative risk model (US EPA, 1983), reevaluated by CDHS/RCHAS (1988).]

III. CARCINOGENIC EFFECTS

Human Studies

Cancer incidence and mortality in a cohort of 1345 male workers exposed to acrylonitrile at a E.I. du Pont de Nemours and Co., Inc. textile plant in Camden SC was studied by O'Berg (1980). The study cohort was identified as having had potential exposure to acrylonitrile in the period between plant startup in 1950 and 1966. The 1966 cutoff date allowed for a 10-year follow-up through the end of 1976. Worker exposure levels were assessed qualitatively by the author and a committee of six DuPont employees with long-term experience in the acrylonitrile exposure area; plant environmental monitoring data was not available for the 1950-1966 period. High, moderate and low exposure categories were established. The U.S. Environmental Protection Agency (US EPA) (1983) noted that DuPont representatives agreed that 5, 10 and 20 ppm might be used to represent the low medium and high exposure classification levels. Expected numbers of cancer cases and deaths were calculated from both DuPont corporate data and from the 1969-1971 National Cancer Institute survey data set. However, the author only listed the results of cancer incidence and mortality calculations using the DuPont "control" data set as the source of the expected numbers of cancer cases and mortality; US EPA (1983) stated that the presentation of results based on this control cohort only would ignore the possible effects of other chemicals on the company control cohort. Exposed workers demonstrated 25 cases of all types of cancer, with 20.5 expected. Of these cases, 8 were lung cancer versus 4.4 expected. For workers employed during plant startup (1950-1952) and exposed for at least 6 months, 8 cases of lung cancer were noted vs. 2.6 expected ($p < 0.01$). Most of this excess occurred during the latest followup period (1970-1976) (6 cases of lung cancer vs. 1.5 expected, $p < 0.01$). Total cancer cases in this period were also significantly increased (17 observed, 5.6 expected, $p < 0.01$). Also, a trend was observed correlating increased cancer risk with increased severity of exposure.

Workers in the moderate exposure group with a probable latent period of at least 15 years exhibited 13 cases of cancer of all types vs. 5.5 expected, and 5 cases of lung cancer vs. 1.4 expected ($p < 0.05$).

One potential confounding factor in this study is the lack of controls for tobacco smoking. US EPA (1983) investigated the possible impact of smoking on lung cancer incidence in the O'Berg (1980) study. DuPont provided additional data on 32 of 36 cancer cases reported on in the plant under study (some cases were not in the study cohort) and on smoking data for a matched group of non-cancer cases. Of the 32 cancer cases for which smoking data was available, 22 were cancer types other than lung, and 16 of the non-lung cancer cases (73%) were smokers. Of the matched noncancer controls, 25 (69%) were smokers. US EPA estimated that 70% of the plant population were smokers and 30% nonsmokers, and of the smoker population, 50% were "moderate" smokers and 20% were "heavy" smokers. Based on the assumption that the relative risk of lung cancer for nonsmokers, moderate, and heavy smokers is 1, 10 and 20, respectively, US EPA adjusted the number of expected lung cancer cases in the study cohort to reflect the smoking prevalence data. The number of expected lung cancer cases after adjustment for smoking is 1.61 cases. This is about 15% higher than the 1.4 cases expected without considering smoking differences; however, this adjustment did not substantially alter the significance of the increased prevalence of lung cancer in the workers exposed to acrylonitrile. US EPA (1983) concluded that the observations by O'Berg (1980) of a statistically significant excess of lung cancer in acrylonitrile-exposed workers constitutes significant evidence that acrylonitrile is likely to be a human carcinogen.

A followup to the O'Berg (1980) study was conducted by O'Berg *et al*. (1985). Observations of cancer incidence and mortality for the study cohort of 1345 DuPont workers exposed to acrylonitrile was extended through 1981 for mortality and through 1983 for cancer incidence. Exposed workers demonstrated 43 cases of all types of cancer, with 37.1 expected. Of these cases, 10 were lung cancer versus 4.4 expected. These rates were in excess but were not statistically significant. Additionally, prostate cancer rates were significantly elevated, with 6 cases observed compared to 1.8 cases expected ($p < 0.05$).

Theiss *et al*. (1980) (reviewed by US EPA, 1983) conducted a cohort mortality study of 1469 workers from 12 factories owned by the BASF company in the Federal Republic of Germany (FRG). BASF purchased acrylonitrile during the study period in order to produce styrene-acrylonitrile and acrylonitrile-butadiene-styrene polymers in addition to organic intermediate products. Processing methods differed between factories, and worker exposure data was not available. The study population was defined as all workers employed for over 6 months in acrylonitrile processing from the time of first use of acrylonitrile (approximately 1956) to the study cut-off date of May 15, 1978. The cohort included 1081 German workers and 338 workers of other nationalities. Followup was 98% complete on the German workers, but only 56% complete on the foreign workers. Expected deaths were calculated from mortality rates for the city of Ludwigshafen, the state of Rheinhessen-Pfalz, and the FRG as a whole. An elevated risk of cancer (all types) mortality was noted in the study cohort (27 observed, 20.5 expected based on FRG mortality rates). The study cohort also demonstrated a significantly elevated risk of lung cancer (11 observed, 5.65 expected based on FRG rates, $p < 0.05$; 5.92 expected based on

Rheinhessen-Pfalz rates, $p < 0.05$). An excess significant risk of lung cancer remained after 78 cohort members from one factory who reported "contact with other substances since proven to be carcinogenic" were removed from the calculations (9 observed, 4.37 expected based on FRG mortality rates, $p < 0.05$); additionally, a significant excess risk of lymphatic cancer was seen (4 observed, 1.38 expected based on FRG mortality rates, $p < 0.05$).

US EPA (1983) noted that the members of the study cohort were exposed to a number of other carcinogens, including vinyl chloride, and distillation residues including polycyclic aromatic hydrocarbons, cadmium, ß-napthylamine, dimethyl sulfate and epichlorohydrin. Additionally, tobacco smoking was a potential confounding factor; all lung cancer cases were smokers. However, US EPA also noted that the lung cancer risk associated with exposure to acrylonitrile estimated from this study could actually be an underestimate of the actual risk because 1) combining workers from 12 factories between which acrylonitrile exposure levels varied could have lend to an underestimate of risk due to the inclusion of unexposed or minimally exposed workers; 2) the "healthy worker" effect could have resulted in an underestimate of risk; 3) followup on the relatively youthful cohort was insufficient, and did not allow sufficient latency in the cohort segments most at risk - only 447.1 person-years were accumulated in members over 64 years of age and 4) underascertainment of vital status (12% of the study cohort were lost to followup) may have resulted in an undercount of observed deaths. US EPA concluded that it was possible that exposure to acrylonitrile might be related to the excess risk of lung cancer demonstrated by the study cohort of Theiss *et al*. (1980).

Werner and Carter (1981) studied the mortality of 1111 men who worked in acrylonitrile polymerization and acrylic fiber production (6 plants, located in England, Northern Ireland, Scotland and Wales) from 1950 to 1968; surveillance was continued to the end of 1978. An excess of total cancer deaths was noted (21 observed, 18.6 expected) but was not statistically significant. Expected deaths were calculated from mortality rates from England and Wales combined. Only 68 deaths from all causes had occurred as of the end of 1978; 72.4 were expected. An excess of deaths from all types of cancer combined was noted (21 observed, 18.6 expected), but this excess was not statistically significant. Significant increases in deaths due to stomach cancer were noted in all age groups combined (5 observed, 1.9 expected, $p < 0.05$), with deaths in the 55-64 age group comprising the largest portion of those deaths (3 observed, 0.7 expected, $p < 0.05$). A statistically significant elevated risk of lung cancer was also noted in the 15-44 age group (3 observed, 0.7 expected, $p < 0.05$), but not in other age groups or in all age groups combined. The authors note the lack of acrylonitrile exposure data, including potential differences in exposure levels between the 6 plants surveyed. US EPA (1983) also notes the relatively short followup in the cohort subgroup which would be expected to have incurred the greatest risk, the 158 men having the earliest exposure (during the 1950-1958 period). US EPA (1983) concluded that because of the relative youth of the cohort resulting in a small number of expected deaths, the lack of followup, and the lack of control for smoking, the findings of this study are only suggestive.

A cohort mortality study of 327 white male workers employed for 2 or more years between January 1, 1940 and July 1, 1971 at a rubber manufacturing plant in Akron OH who were potentially exposed to acrylonitrile was conducted by Delzell and Monson (1982). Acrylonitrile

exposure levels were not reported. Cause-specific expected deaths were calculated based on both U.S. age and calendar specific white male mortality and mortality rates for other rubber workers from the same city; however, most results reported in this study used expected deaths calculated using U.S. white male mortality rates. An excess risk of lung cancer mortality was observed when either U.S. mortality rates (9 observed, 5.9 expected) or Akron rubber industry mortality rates (9 observed, 4.7 expected) were used to calculate expected lung cancer deaths. Workers employed for 5-15 years and followed for at least 15 years demonstrated a significantly increased risk of lung cancer (4 observed, 0.8 expected, $p < 0.01$). Cohort members could potentially have been exposed to other chemicals used in the same area (butadiene, styrene, vinyl pyridine). Also, smoking controls were not included. However, US EPA (1983) commented that the possibility that the excess risk of lung cancer demonstrated in this study was due to acrylonitrile exposure could not be dismissed.

Chen *et al*. (1987) examined cancer incidence and mortality in a cohort of 1083 male employees at a E.I. du Pont de Nemours and Co., Inc. textile plant in Waynesboro, VA who were potentially exposed to acrylonitrile in the period 1944-1970. Worker exposure levels were assessed by an Exposure Classification Committee consisting of seven DuPont employees with long-term experience in the acrylonitrile exposure area; plant environmental monitoring data was not available for the 1944-1970 period. High, moderate and low exposure categories were established. Expected numbers of deaths were calculated from both U.S. and DuPont mortality rates; however, the authors only listed the results of cancer incidence and mortality calculations using the DuPont "control" data set as the source of the expected numbers of cancer cases and mortality. No significant increase in incidence was noted for either all types of cancer (37 observed, 36.5 expected) or lung cancer (5 observed, 6.9 expected). However, a significant increase in the incidence of prostate cancer (5 observed, 1.9 expected) was noted; of these, 4 occurred in the 1975-1983 period (0.9 expected).

US EPA (1983) also reviewed several unpublished studies of cancer mortality and/or morbidity potentially caused by acrylonitrile (Kiesselbach *et al*., 1980; Zack, 1980; Gaffey and Strauss, 1981; Herman, 1981; Stallard, 1982). These studies indicated no cancer increase in workers potentially exposed to acrylonitrile. However, US EPA concluded that due to design and methodological deficiencies including short followup, small cohort size and young cohort age, "none of these studies can be cited as adequate evidence that acrylonitrile is not carcinogenic".

Animal Studies

Maltoni *et al*. (1977) (reviewed by US EPA, 1983) exposed male and female Sprague-Dawley rats (30/sex/exposure group) to 0, 5, 10, 20 or 40 ppm acrylonitrile by inhalation for 4 hours/day, 5 days/week for 12 months. The animals were then maintained for the remainder of their lifetime. Slight increases in the incidence of the following tumor types were noted: mammary gland tumors in males and females, nonglandular forestomach tumors in males and skin tumors in females. Tumor incidence data are listed in Table 1.

Table 1. Tumor incidence in male and female Sprague-Dawley rats exposed to acrylonitrile by inhalation (Maltoni *et al*., 1977)

Tumor type	Tumor incidence Acrylonitrile concentration (ppm)				
	0	5	10	20	40
mammary tumors (females)	5/30	10/30	7/30	10/30	7/30
mammary tumors (males)	1/30	0/30	1/30	4/30	4/30
nonglandular forestomach papillomas (males)	0/30	1/30	2/30	0/30	3/30
skin carcinomas (females)	0/30	4/30	1/30	1/30	1/30

The authors claimed that these results indicated a "border-line carcinogenic effect". US EPA (1983) noted that low sensitivity of this study due to the low concentrations of acrylonitrile used and the short duration of acrylonitrile exposure (12 months). Additionally, male and female Sprague-Dawley rats (40/sex/group) were exposed to 0 or 5 mg/kg body weight acrylonitrile by gavage 3 times/week for 52 weeks. On spontaneous death, a moderate increase in the incidence of female rat mammary gland tumors and nonglandular forestomach tumors was noted. US EPA (1983) commented that although the observation period was relatively short (52 weeks) and only a single dose level was used, this study provides additional evidence for the carcinogenicity of acrylonitrile.

A three-generation reproductive study on the effect of acrylonitrile exposure in male and female Charles River rats [CRL:COBS CD (SD) BR] was conducted by Litton-Bionetics, Inc. for the Chemical Manufacturers Association (Beliles *et al*., 1980; reviewed by US EPA, 1983). The rats and their offspring were exposed to drinking water containing 0, 100 or 500 ppm acrylonitrile starting 15 days post-weaning and were mated after 100 days. After delivery of two litters, the animals were exposed to acrylonitrile for approximately 45 weeks. After exposure, all animals in generations F_0, F_1b and F_2b were sacrificed and examined histologically. Second-generation rats in the 500 ppm exposure group demonstrated a significant increase in the incidence of astrocytomas and Zymbal gland tumors. Tumor incidence data are listed in Table 2.

Table 2. Tumor incidence data in Charles River rats during a three-generation reproductive study (Beliles *et al*., 1980)

Tumor type	Generation	Tumor incidence Acrylonitrile dose (ppm)		
		0	100	500
astrocytomas	F_0	0/19	1/20	2/25
	F_1b	0/20	1/19	4/17
	F_2b	0/20	1/20	1/20
Zymbal gland	F_0	0/19	0/20	1/25
	F_1b	0/20	2/19	4/17
	F_2b	0/20	0/20	3/20

Bio/Dynamics Inc. conducted a study on the toxicity and carcinogenicity of acrylonitrile in Sprague-Dawley rats (Bio/Dynamics, 1980a) for the Monsanto Company (St. Louis, MO); the results of this study were subsequently submitted to the US EPA by the Monsanto Company on June 30, 1980. Male and female Sprague-Dawley rats (100/sex/treatment group) were exposed to acrylonitrile in drinking water at concentrations of 0,1, and 100 ppm. Interim sacrifices (10/sex/treatment group) were conducted at 6, 12 and 18 months. The study was terminated at less than 2 years because of low survival rates; males were sacrificed at 22 months and females were sacrificed at 19 months. Statistically significant increases were noted in the incidence of astrocytomas of the brain and spinal cord, adenomas and carcinomas of the Zymbal gland, and nonglandular forestomach squamous cell papillomas and carcinomas in males and females of the 100 ppm group. Tumor incidence data are listed in Table 3.

Table 3. Tumor incidences in male and female Sprague-Dawley rats exposed to acrylonitrile in drinking water (Bio/Dynamics, 1980a)

Tumor type	Dose level (ppm)	Tumor incidence	
		males	females
brain astrocytomas	0	2/98	0/99
	1	3/95	1/100
	100	23/97	32/97
spinal cord astrocytomas	0	NA	0/96
	1	NA	0/99
	100	NA	7/98
Zymbal gland carcinomas	0	1/100	0/99
	1	0/91	0/95
	100	14/93	7/98
nonglandular forestomach papillomas/carcinomas	0	3/98	1/100
	1	3/98	4/99
	100	12/97	7/99

NA - not analyzed

A similar study was conducted by Bio/Dynamics Inc. on the toxicity and carcinogenicity of acrylonitrile in Fischer 344 rats (Bio/Dynamics, 1980b) for the Monsanto Company (St. Louis, MO); the results of this study were subsequently submitted to the US EPA by the Monsanto Company on December 12, 1980. Male and female Fischer 344 rats (100/sex/acrylonitrile treatment group; 200/sex/control group) were exposed to acrylonitrile in the drinking water at concentrations of 0,1, 3, 10, 30 and 100 ppm. Interim sacrifices (10/sex/acrylonitrile treatment group; 20/sex/control group) were conducted at 6, 12 and 18 months. The study was designed to be 24 months in duration; however, because of poor survival, all females were sacrificed at 23 months. Males were continued on study until 26 months, when survival rates comparable to females were achieved. Statistically significant increases were noted in the incidence of astrocytomas of the brain and spinal cord in males (30 and 100 ppm groups) and females (10, 30 and 100 ppm group), adenomas and carcinomas of the Zymbal gland in males (30 and 100 ppm groups) and females (10, 30 and 100 ppm groups), and nonglandular forestomach squamous cell

papillomas and carcinomas in males (3, 10 and 30 ppm groups) and females (30 ppm group). Tumor incidence data are listed in Table 4.

Table 4. Tumor incidences in male and female Fischer 344 rats exposed to acrylonitrile in drinking water (Bio/Dynamics, 1980b)

Tumor type	Dose level (ppm)	Tumor incidence	
		males	females
brain astrocytoma	0	2/200	1/199
	1	2/100	1/100
	3	1/100	2/101
	10	2/100	4/95*
	30	10/99*	6/100*
	100	21/99*	23/98*
spinal cord astrocytoma	0	1/196	1/197
	1	0/99	0/97
	3	0/92	0/99
	10	0/98	1/92*
	30	0/99	0/96
	100	4/93*	1/91
Zymbal gland[1]	0	2/189	0/193
	1	1/97	0/94
	3	0/93	2/92
	10	2/88	4/90*
	30	7/94*	5/94*
	100	16/93*	10/86*
nonglandular forestomach[2]	0	0/199	1/199
	1	1/100	1/100
	3	4/97*	2/100
	10	4/100*	2/97
	30	4/100*	4/100*
	100	1/100	2/97

* Statistically significant at $p < 0.05$

Male and female Sprague-Dawley rats (Spartan strain) (100/sex/group) were exposed to acrylonitrile by gavage at dose levels of 0, 0.1 and 10 mg/kg-day, 5 days/week in a study conducted by Bio/Dynamics Inc. for the Monsanto Company (St. Louis, MO) (Bio/Dynamics, 1980c). Study termination was originally planned for 24 months; however, because only 10 and 13 high dose males and females, respectively, were still alive at 20 months, all surviving animals in all groups were killed during the 20th month to ensure that at least 10 animals/sex/group were available for histopathological examination. Interim sacrifices were performed at 6, 12 and 18 months (10 animals/sex/group). Statistically significant increases in tumor incidence were noted in the following tumor types: brain astrocytomas and Zymbal gland squamous cell carcinomas (high dose males and females), stomach papillomas and carcinomas and intestinal tumors (high

dose males), and mammary gland tumors (high dose females). Tumor incidence data are listed in Table 5.

Table 5. Tumor incidence in male and female Sprague-Dawley rats (Spartan strain) exposed to acrylonitrile by gavage (Bio/Dynamics, 1980c)

Tumor type	Sex	Tumor incidence Dose level (mg/kg-day)		
		0	0.10	10.0
brain astrocytoma	male	2/100	0/97	16/98
	female	1/99	2/100	17/100
spinal cord astrocytoma	male	0/94	0/93	1/97
	female	0/100	0/95	1/99
Zymbal gland squamous cell carcinomas	male	1/96	0/93	10/96
	female	0/85	0/94	9/94
stomach papillomas/carcinomas	male	2/99	6/97	40/99
	female	2/99	4/99	17/99
intestine	male	0/100	1/100	6/100
	female	NA	NA	NA
mammary gland	male	NA	NA	NA
	female	7/101	6/100	22/101

Dow Chemical Company (Midland, MI) performed a study in which male and female Sprague-Dawley rats (48 animals/sex/acrylonitrile exposure group; 80 animals/sex/control group) were exposed to acrylonitrile in drinking water for 2 years (Quast *et al*., 1980a). For the first 21 days of the study, the concentrations used were 0, 35, 85 and 210 ppm; the two higher concentrations were subsequently raised to 100 and 300 ppm. Animals at the highest 2 concentrations demonstrated treatment-related toxicity after 9 months. The mean administered doses of acrylonitrile were calculated to be 0, 3.42, 8.53 and 21.18 mg/kg-day for males and 4.36, 10.76 and 24.97 mg/kg-day for females for the 35, 100 and 300 ppm exposure groups, respectively. All surviving animals were sacrificed at 24 months. Statistically significant increases in tumor incidence were noted for the following tumor types: central nervous system tumors (astrocytomas, gliomas) in males and females (all treatment groups), Zymbal gland adenomas and carcinomas in females (all treatment groups) and males (300 ppm group), nonglandular forestomach squamous cell papillomas and carcinomas in males (all treatment groups) and females (100, 300 ppm groups), tongue squamous cell papillomas and carcinomas in males (all treatment groups) and females (100, 300 ppm groups), mammary gland tumors (benign and malignant) in females (35, 100 ppm groups), and small intestine cystadenocarcinomas in females (100, 300 ppm). Tumor incidence data are listed in Tables 6 and 7.

Table 6. Tumor incidence in male Sprague-Dawley rats exposed to acrylonitrile in drinking water (Quast *et al*., 1980a)

Tumor type	Tumor incidence Acrylonitrile dose level (ppm)			
	0	35	100	300
brain and/or spinal cord[1]	1/80	12/47	22/48	30/48
nonglandular forestomach[2]	0/80	3/46	23/48	39/47
tongue[2]	1/75	2/7	4/9	5/40
Zymbal gland carcinomas	3/80	4/47	3/48	15/48

1. Benign and/or malignant
2. Squamous cell papillomas and/or carcinomas

Table 7. Tumor incidence in female Sprague-Dawley rats exposed to acrylonitrile in drinking water (Quast *et al*., 1980a)

Tumor type	Tumor incidence Acrylonitrile dose level (ppm)			
	0	35	100	300
brain and/or spinal cord[1]	0/80	17/48	22/48	24/48
mammary gland[1]	57/80	42/48	42/48	35/48
nonglandular forestomach[2]	1/80	1/47	12/48	30/48
small intestine[3]	0/80	1/7	4/11	4/48
tongue[2]	0/78	1/5	2/3	12/45
Zymbal gland carcinomas[4]	1/80	5/48	8/48	18/48

1. Benign and/or malignant
2. Squamous cell papillomas and/or carcinomas
3. Mucinous cystadenocarcinomas
4. Adenomas and carcinomas

Male and female Sprague-Dawley rats (Spartan substrain; 100 animals/sex/exposure group) were exposed to acrylonitrile by inhalation in a study conducted by Dow Chemical Company for the Chemical Manufacturers Association (Quast *et al*., 1980b). Study animals were exposed to 0, 20 or 80 ppm of acrylonitrile for 6 hours/day, 5 days/week for 2 years. Statistically significant increases in tumor incidence were noted for the following tumor types: brain and spinal cord glial cell tumors (males and females), mammary gland adenocarcinomas (females), small intestine tumors (benign and malignant) (males), tongue squamous cell papillomas and carcinomas (males) and Zymbal gland tumors (males and females). All tumor incidence increases were noted at the highest concentration tested, 80 ppm, except for brain and spinal cord glial cell tumors in females, which were also noted in the 20 ppm group. Tumor incidence data are listed in Table 8.

Table 8. Tumor incidence in male and female Sprague-Dawley rats exposed to acrylonitrile by inhalation (Quast *et al*., 1980b)

Tumor type	Sex	Tumor incidence Acrylonitrile concentration (ppm)		
		0	20	80
Brain and/or spinal cord glial cell tumors[1]	male	0/100	4/99	22/99
	female	0/100	8/100	21/100
mammary gland adenocarcinomas	female	9/100	8/100	20/100
small intestine[1]	male	2/99	2/20	15/98
Zymbal gland tumors[1]	male	2/100	4/100	11/100
	female	0/100	1/100	11/100

1. Benign and/or malignant

Bigner *et al*. (1987) exposed male and female Fischer 344 rats to acrylonitrile in drinking water. Exposure groups were as follows: 147 males and 153 females exposed to 500 ppm acrylonitrile; 50 males and 50 females exposed to 500 ppm acrylonitrile; 50 males and 50 females exposed to 100 ppm acrylonitrile and 51 males and 49 female control animals. The study was not complete at the time of the report (18 months of exposure); however, they reported 49 primary brain tumors in 215 animals examined from the high dose treatment groups.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Acrylonitrile has been demonstrated to cause cancer in humans (O'Berg, 1980; Werner and Carter, 1981; Delzell and Monson, 1982) and rats; routes of administration for rats include gavage (Bio/Dynamics, 1980c), oral exposure (Beliles *et al*., 1980; Bio/Dynamics, 1980a; Bio/Dynamics, 1980b; Quast *et al*., 1980a; Bigner *et al*. 1987) and inhalation (Maltoni *et al*., 1977; Quast *et al*., 1980b). US EPA (1991) chose to use the O'Berg acrylonitrile occupational exposure study as the basis of derivation of a cancer potency factor for acrylonitrile. This study demonstrated the carcinogenicity of acrylonitrile in a cohort which was sufficiently large and which was followed for an adequate time period. Exposure levels were estimated by representatives of the company employing the study cohort, and a dose-response relationship was observed for the increased cancer risk. This increased risk remained after adjusting for smoking. US EPA (1983) noted that the cancer potency values for acrylonitrile derived from human exposure (O'Berg, 1980) was within one order of magnitude of the cancer potencies derived from rat oral exposure (Bio/Dynamics, 1980a; Bio/Dynamics, 1980b; Quast *et al*., 1980a) and inhalation exposure (Quast *et al*., 1980b) studies.

Methodology

A unit risk (UR) for acrylonitrile was calculated by US EPA (1991) from a relative risk model adjusted for smoking and based on a continuous lifetime equivalent of occupational exposure using the relationship

$$UR = PO\ (R-1) / X = 1.5E\text{-}4/ppb * 0.45\ ppb/\mu g/m^3 = 6.8E\text{-}5\ (\mu g/m^3)^{-1}$$

where: PO = 0.036 = background lifetime probability of death from respiratory cancer
R = 5.0/1.6 = 3.1 = relative risk of respiratory cancer adjusted for smoking (O'Berg, 1980)
X = 500 ppb = continuous equivalent lifetime exposure when 9 years = estimated average exposure duration, and 60 years = estimated maximum possible age at the end of the observation period.

CDHS (1988) reestimated the unit risk factor for acrylonitrile, using the standard lifespan typically assumed by CDHS in risk assessments (70 years) and taking into account the uncertainty in the relative risk estimate. The unit risk was corrected using the following relationship:

$$B^* = B(95) * (70/60)^3$$

where B^* is the unit risk and B(95) is the upper 95% bound on B. This bound was estimated directly by substituting R(95), the upper 95% confidence bound on R, which was found to be 6.6; the second factor $[(70/60)^3]$ was used to extrapolate from a 60 year observation period to a 70 year observation period. The resulting unit risk factor derived was 2.9E-4 $(\mu g/m^3)^{-1}$.

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ALLYL CHLORIDE

CAS No: 107-05-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	76.5
Boiling point	44.96°C
Freezing point	-134.5°C
Vapor pressure	295.5 mm Hg at 20°C
Air concentration conversion	1 ppm = 3.13 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-6 (µg/m^3)$^{-1}$
Slope Factor: 2.1 E-2 (mg/kg-day)$^{-1}$
[Linearized multistage procedure (GLOBAL82) (US EPA, 1986) fitted to NCI (1977) female mouse forestomach tumor data, body weight scaling, adopted by RCHAS/OEHHA (1994), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

A retrospective cohort mortality study of 1,064 male workers potentially exposed to epichlorohydrin and allyl chloride was conducted by Olsen *et al*. (1994). Study subjects had a minimum of 1 month work experience between 1957-1986 in the production or use of epichlorohydrin and allyl chloride and 1 year total employment duration at Dow Chemical's Texas Operations (Freeport, TX). Job exposure categorization was used to quantify individual exposure based on an evaluation of work practices, production processes and available environmental monitoring data. Vital status follow-up occured through 1989; 66 total deaths were recorded. Standardized mortality ratios (SMR) for all malignant neoplasms or lung cancer were not significantly increased when compared to external (U.S.) or internal (Texas Operations) populations. The authors noted that the study results are limited by the cohort's size, duration of follow-up, relatively few number of observed and expected deaths, and the level of potential epichlorohydrin and allyl chloride exposure.

Animal Studies

Several studies exist on the potential carcinogenicity of allyl chloride in animals; these studies have been reviewed by IARC (1985) and U.S. EPA (1986, 1991).

Male and female B6C3F$_1$ mice and Osborne-Mendel rats (50/group) were exposed to allyl chloride (technical grade; 98% pure) by gavage daily 5 days/week for 78 weeks (NCI, 1977).

Exposure groups for mice were initially 172 or 199 mg/kg body weight for males and 129 or 258 mg/kg for females. Exposure groups for rats were initially 70 or 140 mg/kg body weight for males and 55 or 110 mg/kg for females. Due to toxicity, the initial doses were reduced as the study progressed. Final time-weighted average doses for the 78 week dosing period were 172 and 199 mg/kg/day for male mice; 129 and 258 mg/kg/day for female mice; 57 and 77 mg/kg/day for male rats and 55 and 73 mg/kg/day for female rats. Mice and rats were observed for an additional 13 and 30-33 weeks after the end of the dosing period, respectively. Excessive mortality (50% after 14-38 weeks) was noted in the high-dose rats (both sexes) and male mice. The number of surviving animals in all low-dose groups and high-dose female mice were adequate to evaluate late-developing tumor risk.

No significant increases in tumor incidence were noted in rats. Proliferative nonneoplastic lesions of the stomach were noted in mice of both sexes. In male mice, squamous cell carcinomas of the stomach were found in 0/29 controls (17 vehicle and 12 untreated), 2/36 low-dose animals, and 0/10 high-dose animals (only 10 survived past 52 weeks). In female mice, squamous cell papillomas and carcinomas of the forestomach were found in 0/39 controls (19 vehicle and 20 untreated), 3/47 low-dose animals (2 carcinomas) and 3/45 high-dose animals (no carcinomas). Tumor incidence was not significantly increased compared to controls for either dose group of either sex. However, the combined tumor incidence in females and the carcinoma incidence in low-dose males was significantly increased at both doses compared to historical vehicle controls (1/180 female mice with squamous cell papilloma or carcinoma of the forestomach; 1/180 male mice with squamous cell carcinoma of the forestomach). The authors considered the findings to be strongly suggestive of carcinogenicity in mice because of the rarity of the tumor type involved and because the proliferative lesions demonstrated could be preneoplastic.

Female Ha:ICR Swiss mice (30/group) were exposed to allyl chloride by topical application (31 or 94 mg allyl chloride in 0.2 ml acetone) 3 times/week for 63-85 weeks (Van Duuren *et al*., 1979). Skin tumors were not induced. Lung and stomach papillomas were induced in both the low dose group (3 stomach, 14 lung papillomas) and the high dose group (3 stomach, 12 lung papillomas, 1 glandular stomach adenocarcinoma). Tumor incidences were not significantly increased compared to vehicle or untreated controls (control incidence not reported).

Female Ha:ICR Swiss mice (30/group) received a single dermal application of 94 mg technical grade allyl chloride in 0.2 ml acetone followed 2 weeks later by dermal applications of 5 µg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) 3 times/week for life (median survival 61-82 weeks) (Van Duuren *et al*., 1979). Skin papilloma incidence was significantly increased (7/30 treated animals compared to 6/90 TPA control animals, $p < 0.025$) and time to tumor was decreased (first tumor in treated animals at day 197 compared to day 449 in TPA controls) in allyl chloride -treated animals.

Male and female A/St mice (10/group) received intraperitoneal injections of allyl chloride in tricaprylin 3 times/week for 8 weeks; total doses were 1.2, 2.9 and 5.9 g/kg body weight (Theiss *et al*., 1979). Animals were killed 24 weeks after exposure initiation. The only pathological endpoint examined was the induction of lung tumors as determined by gross examination. The

average number of adenomas/mouse (20 animals/group, both sexes combined) was 0.19 ± 0.1, 0.60 ± 0.2, 0.50 ± 0.27 and 0.60 ± 0.15 in the control, low, medium and high-dose groups, respectively. The incidence of lung adenomas in the high-dose group was significantly increased ($p < 0.05$ by Student's T-test or chi-square test).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI (1978) carcinogenicity bioassay demonstrated a statistically significant increased incidence of squamous cell papillomas and carcinomas of the forestomach in low-dose male mice (2/46, $p < 0.029$) and low-dose (3/47; $p < 0.003$) and high-dose (3/45; $p < 0.003$) female mice when compared to tumor incidences in male (1/180) and female (1/180) historical controls. The female mouse tumor incidence data from this study was chosen as the basis of a cancer potency factor because it demonstrated induction of a rare tumor type by allyl chloride in the most sensitive sex of a sensitive species.

Methodology

Transformed doses were calculated as follows:

transformed dose = experimental dose x (5 days/7 days) x (78 weeks/92 weeks)

Animals were dosed 5 days/week, and the duration of exposure and of the experiment were 78 and 92 weeks, respectively. Experimental doses were 129 and 258 mg/kg/day; transformed doses were 78 and 156 mg/kg/day. A linearized multistage procedure (GLOBAL82) was then applied to the tumor incidence data; the resulting unadjusted cancer potency factor (q_1^*) was 1.01 E-3 $(mg/kg/day)^{-1}$. A q_1^* for humans was calculated from the unadjusted q_1^* as follows:

$$\text{human } q_1^* = \text{unadjusted } q_1^* \times (70 \text{ kg}/0.025 \text{ kg})^{1/3} \times (104 \text{ weeks}/92 \text{ weeks})^3$$
$$= 2.1 \text{ E-2 } (mg/kg/day)^{-1}$$

The reference human body weight and the average female mouse weight were 70 kg and 0.025 kg, respectively, and the experiment length and the mouse lifespan were 92 weeks and 104 weeks, respectively. A unit risk factor of 6.0 E-6 $(\mu g/m^3)^{-1}$ was derived from the human q_1^* by OEHHA/ATES using an inspiration rate of 20 m^3/day.

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2-AMINOANTHRAQUINONE

CAS No: 117-79-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994) except where noted)

Molecular weight	223.24
Boiling point	sublimes (IARC, 1982)
Melting point	302 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 9.131 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 9.4 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 3.3 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat liver tumor data (NCI, 1978), contained in Gold *et al*. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 2-aminoanthraquinone (2-AA) on humans are known to exist.

Animal Studies

Results from the National Cancer Institute (NCI) (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are tabulated in Gold *et al*. (1984). 2-Aminoanthraquinone (technical grade, unspecified impurities) was administered in feed to groups of 50 male and 50 female animals of each species. Matched control groups were included for each mouse dose group (50 animals/sex/species). Control groups of 50 male and 25 female rats were also included; these animals were observed for 107-109 weeks. Diet fed to mice contained 5000 or 10000 mg/kg 2-AA; diet fed to female rats contained 2000 mg/kg 2-AA. Diet fed to male rats contained 10000 or 20000 mg/kg 2-AA for the first 10 weeks; this was reduced to 2500 or 5000 mg/kg for the remaining 68 weeks. For rats, NCI reported the time-weighted average dietary concentrations to be 0.69% and 0.35% for high and low dose males, and 0.2% for treated females over a 78-week period. An additional observation period of 28-32 weeks was included after treatment ended. High and low dose mice of both sexes were administered time-weighted average dietary concentrations of 1.0% (over 80 weeks) and 0.5% (over 78 weeks) respectively, and were observed for an additional 15-16 weeks after treatment ended.

At study termination, 82, 78, 94 and 86% of male mice and 78, 76, 88 and 76% of female mice were still alive in the low-dose control, high-dose control, low-dose and high-dose groups,

respectively. In male rats, 54% of the controls, 64% of low-dose and 70% of high-dose animals were alive at the end of the study. Insufficient numbers of female rats survived to the latter portion of the experimental period to permit analysis of late-developing tumors.

High-dose male and female mice demonstrated a significantly increased incidence of hepatocellular carcinomas. Tumor incidence in male mice was 12/46 in low-dose controls, 6/48 in high-dose controls, 20/47 in low-dose animals, and 36/49 ($p < 0.001$) in high-dose animals; in female mice, the frequencies were 4/46, 1/50, 5/47 and 12/47 ($p < 0.001$) (NCI, 1978; Murthy *et* al., 1979). A dose-dependent increase in hepatic neoplastic nodules and hepatocellular carcinomas ($p < 0.001$) was noted in 18/41 low-dose and 18/45 high dose males; tumors were observed in 0/36 control male rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI carcinogenicity bioassay of 2-AA indicated that 2-AA induced tumor formation in both rats and mice. The cancer potency value derived is based on the dose-response data for hepatic tumors in the more sensitive sex and species, the male rat (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. The average dose administered to the male rat high-dose group as calculated by Gold *et al*. (1984) was 102 mg/kg/day. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a p-value of ≤ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ANILINE

CAS No: 62-53-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	93.12
Boiling point	184-186°C
Melting point	-6.3°C
Vapor pressure	0.67 mm Hg at 25°C
Air concentration conversion	1 ppm = 3.82 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-6 (µg/m^3)$^{-1}$
Slope Factor: 5.7 E-3 (mg/kg-day)$^{-1}$
[Derived from a cancer potency factor calculated by US EPA/IRIS (1990, 1994) from male rat primary splenic sarcoma incidence data (CIIT, 1982) using a linearized multistage procedure, extra risk; adopted by CDHS/RCHAS (1990)]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1994) reviewed a study that examined the occurrence of bladder tumors in British workers in the chemical dye industry (Case *et al.*, 1954). A group of 4622 men employed for more than 6 months in the United Kingdom chemical industry during the period 1910-1952 were studied. In a subgroup of 1233 men exposed solely to aniline, one death from bladder cancer was observed compared to 0.83 expected from English/Welsh male mortality data. Among the entire group (who had generally been exposed to a number of aromatic amines including napthylamine, benzidine, auramine and aniline; no detailed exposure information was available), 127 deaths from bladder cancer were observed compared to 4.1 expected. The authors concluded that the data provided insufficient evidence to suggest that aniline itself causes bladder tumors.

Animal Studies

Forty-three male and female Osborne-Mendel rats were fed diets containing 330 mg/kg aniline hydrochloride for up to 1032 days (White *et al*., 1948). Hepatomas and splenic sarcomas were noted in 4 and 3 animals, respectively. No control group was included in the study; however, the authors claimed that liver and spleen tumors were rare in the rat strain used in the study.

IARC (1982) reviewed a study by Druckrey (1950) in which rats (random bred, sex unspecified) were exposed to aniline hydrochloride in drinking water (22 mg/rat/day) over their lifetime. Mortality was quite high; 50% mortality occurred at day 450 and 100% mortality at day 750. No tumors were observed in the treated animals; however, only the bladder, liver, spleen and kidney were evaluated for tumors.

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing aniline hydrochloride for 103 weeks (NCI, 1978). Rats were fed diets containing 0, 3000 or 6000 mg/kg diet aniline hydrochloride; mice were fed diets containing 0, 6000 or 12000 mg/kg diet aniline hydrochloride. Group sizes were 50/sex/group, except for high dose female mice (n = 49), and control rats (25/sex). Surviving rats and mice were sacrificed at 107-108 and 107 weeks, respectively. No significantly increased treatment-related tumor incidences were noted in treated mice. Male rats demonstrated significantly elevated incidences of hemangiosarcomas in the spleen, as well as fibrosarcomas and sarcomas (not otherwise specified) in multiple organs of the body cavity and spleen. There were also significant dose-related trends in the incidence of hemangiosarcomas, sarcomas or fibrosarcomas and malignant pheochromocytomas. For female rats, a dose-related trend was observed in the incidence of fibrosarcomas and sarcomas in the spleen and in multiple organs of the body cavity. No fibrosarcomas, or sarcomas of the spleen or multiple organs of the body cavity were observed in pooled (249 female and 250 male) control animals. Tumor incidence data is listed in Table 1.

Table 1. Aniline hydrochloride-induced tumor incidence data in male and female Fischer 344 rats (NCI, 1978)

Tumor type	Sex	Tumor incidence aniline hydrochloride dietary concentration (mg/kg diet)		
		0	3000	6000
spleen hemangiosarcoma	male	0/25	19/50	20/46
spleen fibrosarcoma/sarcoma NOS	male	0/25	7/50	9/46
multiple organ fibrosarcoma/sarcoma NOS	male	0/25	2/50	9/48
	female	0/24	1/50	7/50
adrenal pheochromocytomas	male	2/24	6/50	12/44

NOS = not otherwise specified

Hagiwara *et al.* (1980) administered aniline in the diet at a concentration of 300 mg/kg diet to 28 male Wistar rats over a period of 80 weeks. An untreated control group of 28 rats was also included. No significant increase in tumor incidences were observed as a result of aniline exposure. However, the treatment group sizes used were relatively small, and the exposure was relatively low and less than lifetime.

Male and female CD-F rats (130/sex/exposure group) were exposed to aniline hydrochloride in the diet for 2 years at exposure levels of 0, 10, 30 and 100 mg/kg body weight/day (CIIT, 1982). An increased incidence of primary splenic sarcomas was noted in the male 100 mg/kg exposure group (high dose group); stromal hyperplasia and fibrosis of the splenic red pulp, a potential sarcoma precursor lesion, was also observed in high dose males, and to a lesser degree, in high dose females. No fibrosarcomas, stromal sarcomas, capsular sarcomas or hemangiosarcomas were noted in female rats. Tumor incidence data is listed in Table 2.

Table 2: Incidence of splenic tumors in male CD-F rats fed diets containing aniline hydrochloride (CIIT, 1982)

Dietary aniline hydrochloride concentration (approximate) (ppm)	Aniline hydrochloride exposure level (mg/kg body weight/day)	Human equivalent dose[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0	0/64
200	10	1.23	0/90
600	30	3.69	1/90
2000	100	12.29	31/90

1. Calculation of the doses included a correction for the difference in molecular weight of aniline and aniline hydrochloride (compound administered) (US EPA, 1992).
2. Tumor incidence includes fibrosarcomas, stromal sarcomas, capsular sarcomas, and hemangiosarcomas as reported by US EPA (1992).

Syrian golden hamsters (15 male and 15 female) received subcutaneous injections of aniline (521 mg/kg body weight; total dose 9219 mg/kg) for 52 weeks (Hecht *et al*., 1983). Although mean survival was reduced in the aniline-treated groups, no increase in tumor incidence was observed. However, the experimental exposure was less than lifetime, and the number of exposed animals was small.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). Male rat spleen tumor data (CIIT, 1982) was used to generate a cancer potency factor for aniline. Male rats in the high-dose group showed a marked increase in the incidence of splenic tumors (see Table 2). US EPA (1994) also noted the presence of stromal hyperplasia and fibrosis of the splenic red pulp in high-dose males and, to a lesser degree, in females; this may represent a precursor lesion of sarcoma.

Methodology

A linearized multistage procedure (US EPA,1980) was used to calculate a slope factor of 5.7 E-3 $(mg/kg\text{-}day)^{-1}$ from the CIIT (1982) male splenic tumor incidence data. Calculation of the transformed doses for aniline included a correction for the difference in molecular weights of aniline and aniline hydrochloride, the form in which the compound was administered in the NCI and CIIT bioassays. Calculation of the unit risk by OEHHA/ATES from the US EPA slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ARSENIC (inorganic)

CAS No. 7440-38-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	74.92
Boiling point	615 °C (sublimes)
Melting point	817°C at 28 atm.
Vapor pressure	10 mm Hg at 437°C
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit risk factor: 3.3 E-3 $(\mu g/m^3)^{-1}$
[Human lung cancer data (CDHS, 1990)]
Oral slope factor: 1.5 E+0 $(mg/kg\text{-}day)^{-1}$
[Human skin cancer data (Tseng *et al*., 1968, 1977; US EPA, 1995).]

III. CARCINOGENIC EFFECTS

Human Studies

Inhalation

Several studies have demonstrated that exposure to arsenic by inhalation results in an increased incidence of lung cancer in humans. These studies and the derivation of the inhalation risk factor are described in the Toxic Air Contaminant (TAC) document for inorganic arsenic (CDHS, 1990).

Oral

Chronic exposure to high levels of arsenic in drinking water has been identified as increasing skin cancer incidence in humans (US EPA, 1988, 1995).

In a region on the southwest coast of Taiwan, artesian well water with high arsenic concentrations ranging from 0.01-1.82 ppm had been in use for more than 45 years (Tseng *et al*., 1968, 1977). 40,421 inhabitants of 37 villages of the regions were examined for skin lesions, peripheral vascular disorders and cancers. The study identified 7,418 cases of hyperpigmentation, 2,868 of keratosis (Type A/benign), 428 of skin cancer (squamous cell carcinoma, basal cell carcinoma, *in situ* squamous cell carcinoma, and Type B keratoses/intraepidermal carcinomas) and 360 cases of Blackfoot disease. The incidence rates for keratosis and skin cancer were 183.5 and 10.6/1000, respectively. A control population of 7,500 people did not exhibit any of the above disorders.

The above exposed population was divided into "low", "mid" and "high" exposure groups based upon the well-water arsenic concentration in each village (<0.3, 0.3-0.6, and >0.6 ppm, respectively). A dose-response relationship was identified for the prevalence of skin cancer and Blackfoot disease (no dose-response data was presented for hyperpigmentation and keratosis). The prevalence of both disease was also found to increase with age. Males were found to have higher prevalence rates than females (male to female ratios for skin cancer and Blackfoot disease were 2.9 and 1.3, respectively).

Additional studies of chronic human arsenic exposure resulting in increased skin cancer or internal organ cancer incidence have been identified and reviewed (Fierz, 1965; Borgono and Greiber, 1972; Cebrian *et al*., 1983; Yue-Zhen *et al*., 1985; Chen *et al*., 1985, 1986; reviewed by US EPA, 1988).

Animal Studies

CDHS (1990) has determined that arsenic is a human carcinogen for which carcinogenicity has not been conclusively demonstrated in animals. CDHS (1990) reviewed studies in which animals were exposed to arsenic by inhalation, intratracheal instillation, subcutaneous injection, gavage, or in drinking water. The studies reviewed were generally either negative, or were not conclusive due to methodology or reporting deficiencies.

IV. DERIVATION OF ORAL CANCER POTENCY

Basis for Cancer Potency

US EPA (1995) conducted a review of the available literature and identified the studies by Tseng *et al*. (1968, 1977) as the key references for quantifying ingested arsenic cancer potency. US EPA stated that these studies demonstrate a causal association between arsenic ingestion and an elevated risk of skin cancer. These data were considered reliable for the following reasons: 1) the study and control populations (40,421 and 7,500, respectively) were large enough to provide reliable estimates of the skin cancer incidence rates; 2) a statistically significant elevation in skin cancer incidence in the exposed population compared to the control population was observed many years after first exposure; 3) a pronounced skin cancer dose-response by exposure level was demonstrated; 4) the exposed and control populations were similar in occupational and socioeconomic status, with ingestion of arsenic-contaminated drinking water the only apparent difference between the two groups, and 5) over 70% of the observed skin cancer cases were pathologically confirmed.

Methodology

A generalized multistage model with both linear and quadratic dose assumptions was used to predict the prevalence of skin cancer as a function of arsenic concentration in drinking water (d) and age (t), assuming exposure to a constant dose rate since birth. F(t,d) represents the probability of developing skin cancer by age t after lifetime exposure to arsenic concentration d. The model used is expressed as follows: $F(t,d) = 1 - \exp[-g(d)\, H(t)]$, where g(d) is a polynomial in dose with non-negative coefficients, and H(t) is $(t-w)^k$, where k is any positive real number, and $t > w$ for induction time w. The cancer potency calculation was based on skin cancer incidence data for Taiwanese males (Tseng *et al*., 1968) because their skin cancer prevalence rates were higher than the females studied. The calculation was also based on several assumptions listed below.

1. The mortality rate was equal for both diseased (skin cancer) and nondiseased persons.

2. The population composition (with respect to skin cancer risk factors) remained constant over time, implying that there was no cohort effect.

3. Skin cancers were not surgically removed from diseased persons.

The population at risk was classified into 4 age groups (0-19, 20-39, 40-59 and ≥ 60 years of age) and three dose groups (0 - 0.3, 0.3 - 0.6 and > 0.6 ppm drinking water arsenic concentration) for males and females separately from the reported prevalence rates (Tseng *et al*., 1968, 1977) as percentages. The assumption was made that the Taiwanese persons had a constant arsenic exposure from birth, and that males and females consumed 3.5 L and 2 L drinking water/day, respectively. The multistage procedure was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic. Both linear and quadratic model fitting of the data were conducted. The maximum likelihood estimate (MLE) of skin cancer risk for a 70 kg person drinking 2 L of water/day, adjusted for U.S. population survivorship by life-table analysis, ranged from 1 E-3 to 2 E-3 for an arsenic intake of 1 µg/kg/day. Expressed as a single value, the cancer unit risk for drinking water is 5 E-5 $(\mu g/L)^{-1}$; the corresponding cancer potency value is 1.5 E-0 $(mg/kg/day)^{-1}$.

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BENZIDINE

CAS No: 92-87-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	184.2
Boiling point	402°C
Melting point	115-120°C
Vapor pressure	0.0005 mm Hg
Air concentration conversion	1 ppm = 7.53 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-1 (µg/m^3)$^{-1}$
Slope Factor: 5.0 E+2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Case *et al.* (1954) examined mortality among British chemical workers exposed to benzidine. Among the population examined (total number not specified), ten deaths were certified as due to bladder cancer. The death rate from bladder cancer in the male Welsh and English population predicts 0.72 deaths from this cause, giving a standard mortality ratio of 13.9 (10/0.72, $p < 0.001$). Non-fatal bladder cancers were also noted among the exposed population.

Mancuso and El-Atar (1967) examined the incidence of urinary tract cancer among 639 male employees of an Ohio plant where benzidine and β-naphthylamine were made, with potential exposure occurring between 1938 and 1939. Six cases of bladder cancer occurred among white workers, giving a population incidence of 204 per 10^5. The expected incidence of bladder cancer among Ohio white males is 4.4 per 10^5. The authors do not present the significance of the change in incidence because of exposure of workers to other compounds.

Zavon *et al.* (1973) conducted a prospective study of workers exposed to benzidine during its manufacture. The authors report on the health surveillance of all 25 employees of a chemical plant who were exposed to benzidine from 3 to 28 years (1930-1958). During the 13 year follow-up period (1957-1970), 11 cases of transitional cell bladder cancer and 2 cases of benign bladder tumors developed. Among the workers with bladder cancers, two also developed kidney carcinomas and one a benign tumor of the kidney. No background tumor incidences were reported. The average exposure duration for workers with tumors was 13.6 years, whereas the

average exposure duration for those without tumors was 8.9 years. Levels of urinary benzidine were measured at the beginning of the follow-up period of the study, with samples taken at the beginning and end of the work day and at the before the work week began. Mean levels were reported to be ~0.01 mg/l before shift, ~0.04 mg/l after shift, and ~0.004 mg/l Monday morning. Quantitative estimates of exposure have been based on these levels. Exposure conditions at the time of the sampling were reported to be representative of conditions in the previous years of plant operation. Air sampling at different locations in the chemical plant showed benzidine concentrations ranged from <0.007 to 17.6 mg/m^3. Potential confounding variables in the study include smoking and exposure to other carcinogens in the work environment such as β-naphthylamine, o-toluidine, and dichlorobenzidine.

Tsuchiya *et al.*(1975) report on the incidence of bladder cancer among 1303 Japanese workers employed in benzidine production or use. Among workers involved in the manufacture of benzidine 61/542 developed bladder cancer. Among workers involved in benzidine use, 11/761 developed bladder cancer. Exposure levels to benzidine and population background incidence of bladder cancer in the Japanese population were not provided in the study. A statistically significant difference in bladder cancer incidence was observed between workers involved in benzidine production versus those involved in benzidine use ($p<10^{-10}$, Fisher's exact test).

Meigs *et al.* (1986) conducted a 30-year follow-up study of 597 male workers at a benzidine manufacturing plant in Connecticut. Workers were categorized based upon time of employment, but benzidine levels were not quantitated. Among workers in the high exposure category (> 2 years of employment) 6/105 developed bladder cancer. Among workers in the medium (6 mo.-2 yrs.) and low (1 day-6 mo.) exposure categories, 1/147 and 0/345 developed bladder cancer, respectively. Connecticut cancer statistics predict 1.77 cases of bladder cancer in an unexposed population of 597 people. A significant difference in incidence between high exposure workers and unexposed populations was found ($p<0.003$).

Animal Studies

Saffioti *et al.*(1967) exposed Syrian Golden hamsters (30/sex/group) for life to 0 or 1000 ppm benzidine or benzidine dihydrochloride in feed, and examined them for evidence of liver tumors. Among animals treated with benzidine, 19/22 males and 6/26 females developed cholangiomatous liver tumors (none in controls). Among animals treated with benzidine dihydrochloride, 10/20 males and 12/27 females developed cholangiomatous liver tumors (none in controls). Liver tumor incidence was found to be significantly elevated in exposed animals in each group ($p<0.001$, Fisher's exact test).

Griswold *et al* .(1968) treated female Sprague-Dawley rats with benzidine by oral gavage. Animals received 1.2 or 2.5 mg/dose (10 animals/group) or 3.5 or 5 mg/dose (20 animals/group) every 3 days, with a total of 10 administrations. After 9 months, surviving animals were examined for tumors. Increased incidence of mammary carcinoma was found in benzidine treated groups, with 5/10, 7/9, and 4/5 showing tumors in the 1.2, 2.5, and 5 mg dose groups, respectively, versus 3/127 in control animals. There were no survivors among the animals receiving 3.5 mg benzidine.

Miakawa and Yoshida (1975) fed female dd strain mice (50/group) diet containing either 0 or 0.2% benzidine for 280 days. Hepatocellular carcinomas were identified in 11 of 32 mice surviving 140 days or more, whereas no hepatocellular carcinomas were reported among control mice. The significance level of the difference in incidence was $p<0.001$ by Fisher's exact test.

Littlefield *et al.*(1984) exposed male and female F_1 generation mice (BALB/c males × C57BL females) to benzidine in drinking water for life (~33 months). Mice from a cross of F_1 generation males and females were also exposed as above . Exposure levels and incidence of hepatocellular carcinomas are presented in Table 1. Significant differences in the incidence of hepatocellular carcinoma were observed in all exposed groups ($p<0.05$, Fisher's exact test). Frith *et al.* (1980) also exposed F_1 and F_2 generation mice (BALB/c males × C57BL/6 females) to 30-400 ppm benzidine dihydrochloride in drinking water for 40, 60, or 80 weeks at which time animals were sacrificed. As in the Littlefield *et al*. (1984) study, animals showed a dose-dependent increase in hepatocellular carcinoma incidence. This effect was also shown to be dependent upon duration of exposure.

Table 1. Incidence of hepatocellular carcinoma in F_1 and F_2 generation mice (BALB/c × C57BL) exposed to benzidine in drinking water (Littlefield *et al*., 1984).

hepatocellular carinoma incidence					
males			females		
exposure level (ppm)	F_1	F_2	exposure level (ppm)	F_1	F_2
0	14/125	17/123	0	3/124	10/125
30	24/119	20/118	20	51/120	54/119
40	30/96	20/95	30	52/95	43/95
60	32/71	23/72	40	45/72	31/71
80	35/71	24/71	60	55/71	37/72
120	61/71	37/71	80	60/69	51/69
160	49/71	32/71	120	64/72	56/72

Vesselinovitch *et al.* (1975) treated male $B6C3F_1$ mice with feed containing 150 ppm benzidine dihydrochloride from weeks 6 to 45 of life. Groups of 50 mice thus treated were sacrificed at 45, 60, 75, or 90 weeks and examined for liver tumors. Hepatoma incidence was reported to be 8/50, 20/50, 31/50, and 35/50, respectively, at successive sacrifice times, while only one hepatoma was found among 98 control animals sacrificed at 90 weeks ($p<0.001$; Fisher's exact test). Among the animals with hepatomas, the incidence of hepatocellular carcinoma was 2/50, 5/50, 14/50, and 24/50, respectively, at the successive sacrifice times.

Two other feeding studies have been conducted. Boyland *et al.* (1954) found cases of hepatocellular carcinoma in rats fed diet containing 0.017% benzidine or benzidine plus tryptophan for life. Inadequate study size, data on controls and poor survival, however, limit the usefulness of this study. Marhold *et al.* (1968) found no tumors in lifetime benzidine feeding study, but poor survival also limits the study's value.

Zabezhinski (1970) exposed 48 albino rats (male and female numbers not specified) to 10-20 mg/m^3 benzidine aerosol for 4 hours/day, 5 days/week for 20 months. Among animals surviving at 13 months, 5/28 developed leukemia (0/21 untreated; p=0.052)

Tumors have also been observed in animals injected subcutaneously with benzidine. They include hepatocellular carcinomas, Zymbal gland tumors and injection-site tumors (Spitz *et al*., 1950; Bonser *et al*, 1956; Pliss, 1964; Prokofjeva, 1971). Intraperitoneal injection of benzidine resulted in the induction of mammary tumors in a single study (Morton *et al*, 1981).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The data presented by Zavon *et al.* (1973) are the only human cancer data appropriate for the development of a cancer potency value for benzidine. The US EPA (1986, 1987, 1988), Allen *et al.* (1987), and CDHS (1988) have each provided estimates of cancer potency based on human data. However, different assumptions made in the calculation of exposure levels has resulted in different estimates of the cancer potency. Potencies derived in these studies assume that cancer risk is proportional to cumulative exposure. Previously, IARC (1982) had suggested that benzidine cancer risk be based on the assumption that the empirical distribution of cumulative incidence rate is a function of the duration of continual exposure. Derivations of cancer potencies from the human data using these different methodologies and exposure assessments are described in the *Methodology* section below.

Cancer potency values have also been derived from animal studies, in particular those of Griswold *et al*. (1968), Miakawa and Yoshida (1975), Saffioti *et al* (1967), and Littlefield *et al*. (1984). Resulting potency estimates were well below those derived from the human data, suggesting humans may be more sensitive to the carcinogenic effects of benzidine, and therefore animal data are not appropriate for use in the establishing a cancer potency value. CDHS has based its benzidine cancer potency value on the human data of Zavon *et al*. (1973) using exposure level assessment modifications of Allen *et al.* (1987) and the methodology of US EPA (1986, 1987, 1988).

Methodology

US EPA (1986, 1987, 1988) made exposure estimates from the Zavon *et al.* study (1973) based upon reported mean urinary concentrations of 0.04 mg/l. Assuming that average body weight is 70 kg, average urinary output is 1.2 l/day, and 1.45% of absorbed benzidine is excreted in the urine, US EPA calculated the average daily dose to be 0.047 mg/kg-day. Adjusting this value for work time exposure, with 11.46 years the average time exposed, 56.5 years the average age of the cohort, and 240 work days per year, final lifetime exposure levels were calculated to be 0.0063 mg/kg-day.

US EPA (1986,1987, 1988) based estimates of cancer potency on the following relationship where p(t) is the probability of developing a tumor in a study of cohort of average age t at the end of the follow-up period (56.5 years) and an average lifespan t_L (71.3 years), exposed to dose level d (0.0063 mg/kg-day), and assuming that background tumor incidence is negligible:

$$\text{cancer potency} = \frac{-\ln(1-p(t))}{(d)(\frac{t}{t_L})^3}$$

With this model, US EPA used total tumor incidence (13/25, both benign and malignant) in its calculation, giving a final potency value of 234 $(\text{mg/kg-day})^{-1}$ (See Table 2). Using the upper 95% confidence bound on the tumor incidence (0.68 vs. 0.52) resulted in a cancer potency value of 363 $(\text{mg/kg-day})^{-1}$.

Using mean urine benzidine concentrations reported at the beginning (0.01 mg/l) and end (0.04 mg/l) of the work day, Allen *et al.* (1987) adjusted benzidine exposure estimates on the assumption of linear increases in urine concentration during the workday and first-order decay during non-work hours. The resulting average urine concentration during workdays was 0.023 mg/l. Based on assumptions that 1.5% of the inhaled benzidine is present in the urine (100% absorption), urinary output is 1.5 l/day, breathing rate is 10 m^3/8-hour work day, and average exposure time of the cohort is 11.24 years, Allen *et al.* (1987) estimated average cumulative dose to be 2.59 mg-yrs/m^3.

Allen *et al.* (1987) calculated potency using this dose value and the malignant tumor incidence only [p(t) = 11/25 = 0.44] with a background tumor incidence factor (α = 0.002; NIH, 1981) and without using a time adjustment factor. That is:

$$\text{cancer potency} = \frac{-\ln[1-p(t)] + \alpha}{d}$$

The resulting estimate of cancer potency from work place exposure was 0.22 $(\text{mg}\cdot\text{yrs/m}^3)^{-1}$. with upper and lower 90% confidence bounds of 0.81 and 0.045 $(\text{mg}\cdot\text{yrs/m}^3)^{-1}$. Cancer potency from continuous lifetime exposure was calculated by assuming 240 workdays of a 365 day year and 10 of 20 m^3/day total air breathed during the workday. Potencies thus expressed are 0.67 $(\text{mg-yr/m}^3)^{-1}$ with upper and lower confidence bounds of 2.5 and 0.14 $(\text{mg-yr/m}^3)^{-1}$. Assumptions of 70 kg body weight, 70 yr lifespan, and 20 m^3/day breathing rate (CDHS, 1988) result in a cancer potency of 160 $(\text{mg/kg-day})^{-1}$ with upper and lower 90% confidence bounds of 600 and 30 $(\text{mg/kg-day})^{-1}$.

An estimate of cancer potency was also made based on a description of cumulative risk described by IARC (1982) (CDHS, 1988). IARC (1982) describe risk based on the assumption that the risk varies linearly with the duration of exposure. IARC (1982) report the data from Zavon *et al.* (1973) show a cumulative bladder tumor incidence of 25% among workers exposed to benzidine for 15 years. Under such an assumption, cancer potency (B) from lifetime (t_L = 70 yrs) exposure

can be based on the following relationship, where $C(t_1)$ is the experimentally derived cumulative tumor incidence (25%) and $d(t_1)$ is the average daily dose at time t_1 (15 years):

$$B = [C(t_1)/d(t_1)] \times [(t_L/t_1)^k]$$

The factor k describes the relationship of time of exposure to potency, in this case k=1 because of the assumption of linear proportionality. From this relationship, CDHS (1988) derived a cancer potency value. Using the average daily dosing derived by Allen *et al.* (0.023 mg/kg-day) and the cumulative incidence data described by IARC (1982), the calculated cancer potency was 50 $(mg/kg\text{-}day)^{-1}$ with upper and lower 95% confidence bounds of 130 and 16 $(mg/kg\text{-}day)^{-1}$ derived from the confidence bounds of the dose.

CDHS (1988) considers the Allen *et al* .(1987) estimation of daily urine concentration of 0.023 mg/l to be the most useful for establishing exposure levels. Assuming 1.5 ℓ/day urinary output, 70 kg body weight, 240 work days per year, and average duration of exposure 11.46 yrs in a cohort of 56.5 yrs average age, lifetime average exposure is 0.0044 mg/kg-day. Using the US EPA (1986, 1987, 1988) methodology and the upper 95% confidence bound on incidence [p(t) = 0.68], the cancer potency is 5.0 E+2 $(mg/kg\text{-}day)^{-1}$.

A unit risk factor of 0.14 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES assuming a breathing rate of 20 m^3/day, 70 kg body weight, and 100% fractional absorption of inhaled benzidine.

Table 2. Benzidine cancer potencies derived from Zavon *et al.* (1973).

Source of methodology	Potency $[(mg/kg\text{-}day)^{-1}]$	Upper 95% confidence bound $[(mg/kg\text{-}day)^{-1}]$
US EPA (1986, 1987, 1988)	234	363
Allen *et al*.(1987)	160	600
IARC (1982)*	50	130
CDHS (1988)		500

*Estimate based on IARC methodology using the dosage estimation of Allen *et al.* (1987).

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BENZYL CHLORIDE

CAS No: 100-44-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994))

Molecular weight	126.58
Boiling point	179°C
Melting point	-43 to -48°C
Vapor pressure	1 mm Hg at 22°C
Air concentration conversion	1 ppm = 5.26 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.9 E-5 (µg/m^3)$^{-1}$
Slope Factor: 1.7 E-1 (mg/kg-day)$^{-1}$
[Cancer potency factor derived by US EPA/IRIS (1989) from female rat C-cell thyroid tumor incidence data (Lijinsky, 1986) using a linearized multistage procedure, extra risk; adopted by RCHAS/CDHS (1991).]

III. CARCINOGENIC EFFECTS

Human Studies

Several studies report on cancer mortality in workers occupationally exposed to benzyl chloride.

Sakabe *et al*. (1976) studied cancer incidences among 41 workers exposed to chemicals including benzyl chloride over 18 years (ending in 1972) in a plant producing benzoyl chloride in Japan. Four cases of cancer were reported among the workers: two fatal cases of lung cancer, one fatal maxillary malignant lymphoma, and one squamous cell carcinoma of the lung (still surviving in 1973). The range of employment duration among the workers with cancer was 6 to 14 years. Both cases of lung cancer were in smokers. The expected number of lung cancer deaths among 41 Japanese males was 0.06. In addition to smoking, another potential confounding factor is the reporting of exposure to other compounds in the work environment including benzotrichloride, benzoyl chloride, toluene, chlorine gas, hydrogen chloride, benzal chloride, and other chlorinated toluenes and polymers. Exposure levels were not quantitated.

Sakabe and Fukuda (1977) also reported on cancer deaths among workers exposed to chemicals including benzyl chloride in another plant involved with the production of benzoyl peroxide and benzoyl chloride between 1952 and 1963. Two lung cancer deaths (one a smoker) were reported. Expected number of deaths and exposure levels were not reported, and workers were also exposed to other chemicals as listed in the description of the study by Sakabe *et al*. (1976).

Sorahan *et al*. (1983) studied cancer mortality among British workers occupationally exposed to a number of compounds including toluene, benzotrichloride, benzoyl chloride, benzyl chloride,

and benzal chloride during the course of producing chlorinated toluenes. Five digestive system cancers and 5 respiratory system cancers were reported among 163 male workers employed more than 6 months between 1961 and 1970. Expected mortality rates from these tumors in England and Wales were 1.24 and 1.78, respectively, and the mortality ratio was significantly elevated. Smoking rates were not reported among the workers. Cumulative exposure and death from any cancer among workers employed before 1951 was shown to be significantly correlated by survival analysis using the Cox Proportional Hazard Model, although this was not the case when entry cohorts were combined.

Wong and Morgan (1984) studied cancer mortality among a cohort of 697 workers employed from 1 to more than 35 years in a chlorination plant in Tennessee. Workers were exposed to benzyl chloride, benzoyl chloride, and benzotrichloride. Deaths from respiratory cancers were reported for 7 workers, 5 of whom were exposed for more than 15 years. Expected mortality for U.S. males in a group of this size was 2.84 deaths (1.32 deaths for the subgroup exposed > 15 years). No data on smoking was reported.

Animal Studies

Lijinsky (1986) treated F344 rats (52/sex/dose) and $B6C3F_1$ mice (52/sex/dose) with benzyl chloride in corn oil by gavage. The rats were dosed with 0, 15, and 30 mg/kg/day benzyl chloride and mice with 0, 50 and 100 mg/kg/day benzyl chloride, with treatments 3 days/week for 2 years. Animals were histopathologically examined 3-4 weeks after the end of the treatment using the NCI bioassay protocol. Survival in both species was not significantly affected by treatment. The incidence of C-cell adenoma/carcinoma of the thyroid was significantly increased in female rats in the high-dose group compared to control animals (14/52 treated vs. 4/52 control; $p < 0.01$ by Fisher's exact test). In male mice in the high-dose group, significantly increased incidences were found for hemangioma/hemangiocarcinoma (5/52 treated vs. 0/52 control), forestomach carcinoma (8/52 treated vs. 0/51 control) and forestomach carcinoma/papilloma (32/52 treated vs. 0/51 control). In male mice in the low-dose group only, an increased incidence of hepatic carcinoma/adenoma (28/52 treated vs. 17/52 control) was reported. In female mice in the low- and high-dose groups, an increased incidence of forestomach carcinoma/papilloma (5/50 low-dose, 19/51 high-dose vs. 0/52 control) was reported.

Injection-site sarcomas developed in 3 of 14 BD-strain rats administered benzyl chloride in peanut oil subcutaneously weekly for 51 weeks at 40 mg/kg-week and 6 of 8 rats administered 80 mg/kg-week (Druckrey *et al*., 1970). Mean induction time was 500 days.

Poirier *et al*. (1975) treated A/H mice (20/dose) 3 times weekly over 24 weeks intraperitoneally with a total dose of 0.6, 1.5 or 2 g benzyl chloride/kg body weight in tricaprylin. Surviving animals were sacrificed at 24 weeks. Among the survivors, lung tumors were found in 4/15, 7/16, and 2/8 animals, respectively. Animals treated with tricaprylin alone had an average of 0.22 lung tumors/mouse and animals receiving no treatment had 0.21 lung tumors/mouse. The incidence of lung tumors in treated animals was not found to be statistically significant from control animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Human studies do not provide adequate data for the development of a cancer potency value because of the presence of confounding factors in the studies (multiple compound exposures, no data on smoking status) and no reporting of exposure levels. The animal study by Lijinsky (1986) showing development of thyroid tumors in female rats, and forestomach papillomas and carcinomas in male and female mice provides data from which cancer potency values can be derived.

Methodology

Cancer potency values were derived by US EPA (1989) from the tumor incidence data presented in the study by Lijinsky (1986). The experimentally administered doses (15 and 30 mg/kg) were converted to time-weighted dosage based on the dosing schedule (3 times/week) and the experimental duration (107.5 weeks). The human equivalent dose (HED) was calculated based on an assumed experimental animal body weight (bw_a) of 0.35 kg and human body weight (bw_h) of 70 kg using the following relationship:

$$\text{HED} = \text{time-weighted dose} \times (bw_a/bw_h)^{1/3}$$

The calculated human equivalent doses in the Lijinsky (1986) study were 1.06 and 2.12 mg/kg-day. A linearized multistage procedure (CDHS, 1985) was applied to the tumor incidence data for thyroid tumors in female rats (4/52 controls, 8/51 low-dose, 14/52 high-dose), forestomach tumors in male mice (0/51 controls, 5/50 low-dose, 32/52 high-dose) and forestomach tumors in female mice (0/52 controls, 5/50 low-dose, 19/51 high-dose). This resulted in estimations of the upper 95% confidence bound of cancer potency (q_1^*) of 0.17, 0.056, and 0.12 $(\text{mg/kg-day})^{-1}$, respectively. Selection of the cancer potency value is made in the most sensitive species and site; therefore, the cancer potency value [0.17 $(\text{mg/kg-day})^{-1}$] derived from the female rat C-cell thyroid tumor data was chosen.

A unit risk value of 4.9 E-5 $(\mu g/m^3)^{-1}$ was derived by ATES/OEHHA assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

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BERYLLIUM

CAS No: 7440-41-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	9.012
Boiling point	2970°C
Melting point	1287°C
Vapor pressure	10 mm Hg @ 1860°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.4 E-3 $(\mu g/m^3)^{-1}$
[Calculated by US EPA (1992) from the human inhalation exposure data of Wagoner *et al.* (1980).]

Oral Cancer Potency Factor: 4.3 E+0 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1995) from male and female rat tumor data (Schroeder and Mitchner *et al*., 1975, using a linearized multistage procedure, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

US EPA (1992) reviewed several studies that found increased incidences of lung cancer in beryllium processing workers. A cohort mortality study of 3055 white males employed at a single beryllium processing plant in Pennsylvania with a median duration of employment of 7.2 months demonstrated a statistically significant increased incidence of mortality due to lung cancer in the entire cohort, as well as in the 2068 cohort members followed for 25 years or more since initial employment (Wagoner *et al.*, 1980). Recalculation of the number of expected deaths using 1968-1975 lung cancer mortality data indicated that the increased incidence was significant only among workers followed for 25 years or more (Bayliss, 1980; MacMahon, 1977, 1978), and was not significant when the number of expected deaths was adjusted for smoking (US EPA, 1986).

Earlier studies of workers from the same beryllium processing plant alone or combined with workers from other beryllium plants reported a statistically significant increase in lung cancer mortality (Bayliss and Wagoner, 1977; Mancuso, 1970, 1979, 1980). These studies made no adjustment for smoking and had methodological constraints and deficiencies that precluded their use to establish a causal relationship between beryllium exposure and lung cancer.

Animal Studies

Slight, non-statistically significant increases in cancer incidence (all tumor types) were observed in male Long-Evans rats (52/sex/group) following lifetime exposure to 5 ppm beryllium sulfate administered in the drinking water (Schroeder and Mitchener, 1975a). Tumors were observed in 9/33 treated and 4/26 control rats. High mortality during the study resulting from a pneumonia epidemic at 20 months greatly reduced the power of this study to detect any potential carcinogenic effect of beryllium exposure. A non-statistically significant increase in combined lymphoma and leukemia incidence was observed in female Swiss mice administered 5 ppm beryllium sulfate in drinking water for life (9/52 exposed, 3/47 controls) (Schroeder and Mitchener 1975b).

Male and female Wistar-derived rats were exposed to diet containing beryllium sulfate at concentrations of 0, 5, 50, or 500 ppm for life (Morgareidge *et al*., 1977). Reticulum cell carcinomas of the lung were observed in 10/49 male control animals, 17/35 low dose animals, 16/40 intermediate dose animals, and 12/39 high dose animals, respectively. Since the results were published only as an abstract, and since no response was seen at the highest dose, these results are considered to be only suggestive for the induction of cancer via this route.

Beryllium and beryllium compounds have been shown to cause statistically significant tumor increases in male and female rhesus monkeys and several strains of rats via inhalation and intratracheal installation, and the induction of osteosarcomas in rabbits by intravenous or intramedullary injection. Studies describing the induction of lung tumors (adenomas, adenocarcinomas) by beryllium via inhalation during exposure periods of up to 72 weeks are listed in Table 1. Intratracheal instillation of beryllium also resulted in the induction of lung tumors and extrapulmonary lymphosarcomas and fibrosarcomas in rats (Groth *et al*., 1980; Ishinishi *et al*., 1980).

Table 1. Induction of lung tumors in animals exposed to beryllium via inhalation

Study	Species/strain	Compound
Reeves *et al*., 1967	male, female Sprague-Dawley rats	beryllium sulfate
Schepers, 1961	male, female Sherman and Wistar rats	beryllium phosphate, beryllium fluoride, zinc beryllium silicate
Wagner *et al*., 1969	male Charles River CR-CD rats	beryl ore
Vorwald, 1968	male, female rhesus monkeys	beryllium sulfate

Beryllium compounds were shown to induce osteogenic sarcomas in rabbits by intravenous injection in 12 studies and by intramedullary injection in 4 studies (US EPA, 1991)

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

Wagoner *et al*. (1980) studied a cohort of 3055 white males employed at a single beryllium processing plant in Pennsylvania (exposed to beryllium metal, oxide or hydroxide) sometime between January 1, 1942 and December 31, 1967 with a median duration of employment of 7.2 months. A significantly increased incidence of mortality due to lung cancer was observed in the entire cohort (47 observed versus 34.29 expected, $p < 0.05$), as well as in the 2068 cohort members followed for 25 years or more since initial employment (20 observed versus 10.79 expected, $p < 0.01$). When the number of expected deaths was recalculated using 1968-1975 lung cancer mortality data, significance was lost for the cohort overall (38.2 expected), but not for the subgroup followed for 25 years or more (13.36 expected, $p \approx 0.05$) (Bayliss, 1980; MacMahon, 1977, 1978). However, significance was lost for the subgroup when the number of expected deaths was adjusted for smoking (14.67 expected) (US EPA, 1986).

The data of Wagoner *et al*. (1980) was used for the quantitation of cancer potency due to inhalation exposure despite study limitations. Human inhalation exposure is usually to beryllium oxide rather than other beryllium salts. Animal studies utilizing beryllium oxide have used intratracheal instillation instead of inhalation exposure. The use of the available human data therefore avoids uncertainties due to cross-species extrapolation, and uses the most relevant route of administration and beryllium species.

Oral

The data of Schroeder and Mitchener (1975a) was used to caculate an oral cancer potency factor for beryllium. Slight, non-statistically significant increases in tumors were observed in male Long-Evans rats administered 5 ppm (0.54 mg/kg/day) beryllium sulfate in drinking water for the duration of their natural lifetime. While this study is limited but the use of only one non-zero dose group, the occurrence of high mortality and unspecified type of and site of the tumors, it was used as the basis of the quantitative estimate because exposure occurred via the most relevant route. Oral risk estimates derived by extrapolation from studies in other species/strains for the intravenous and inhalation routes (also highly uncertain) are within an order of magnitude.

Methodology

Inhalation

A risk assessment was performed based on the occupational exposure study of Wagoner *et al*. (1980). The narrowest range for median exposure that could be obtained on the basis of available information was 100 to 1000 $\mu g/m^3$. Effective dose was calculated by adjusting for the

duration of daily (8 of 24 hours) and annual (240 of 365 days) exposure, and the fraction of the lifetime at risk (time from start of employment to study termination). Smoking-adjusted expected lung cancer deaths were found to range from 13.91 to 14.67 (based on exposure range) compared to 20 observed. Relative risk estimates of 1.36 and 1.44 were calculated and the 95% confidence limits of these estimates used to calculate the lifetime cancer risk (Table 2). These estimates were based on one data set and a range of estimated exposure levels and times. To account for estimation uncertainties, unit risks were derived using two estimates each of concentration, fraction of lifetime exposed and relative risk. The listed unit risk factor [2.4 E-3 $(\mu g/m^3)^{-1}$] is the arithmetic mean of the 8 derived unit risks. US EPA has stated that this unit risk may not be appropriate if the air concentration exceeds 4 $\mu g/m^3$ and should not be used under those circumstances.

Table II. Effective dose, upper-bound estimate of relative risk and unit risk of carcinogenicity due to human beryllium exposure via inhalation (US EPA, 1992).

Beryllium concentration in workplace ($\mu g/m^3$)	Fraction of lifetime	Effective dose ($\mu g/m^3$)	95% upper-bound estimate of relative risk	Unit risk/ ($\mu g/m^3$)
100	1.00	21.92	1.98	1.61E-3
			2.09	1.79E-3
	0.25	5.48	1.98	6.44E-3
			2.09	7.16E-3
1000	1.00	219.18	1.98	1.61E-4
			2.09	1.79E-4
	0.25	54.79	1.98	6.44E-4
			2.09	7.16E-4

Oral

A cancer potency factor (q_1*) was derived by applying a linearized multistage procedure to the tumor incidence data presented in Schroeder and Mitchener (1975a). Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors. Assumed body weight values for humans and rats were 70 kg and 0.325 kg, respectively.

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BIS(2-CHLOROETHYL)ETHER

CAS No: 111-44-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	143.02
Boiling point	176-178.5°C
Melting point	-24.5°C
Vapor pressure	0.7 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.1 E-4 (µg/m^3)$^{-1}$
Slope Factor: 2.5 E+0 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for bis(2-chloroethyl)ether (BCEE).

Animal Studies

Two studies address the carcinogenicity of bis(2-chloroethyl)ether by the oral route of exposure. Innes *et al.* (1969) administered 100 mg/kg body weight bis(2-chloroethyl)ether by oral gavage to two F_1 generation strains of mice termed X (C57BL/6 × C3H/Anf) and Y (C57BL/6 × AKH) (18/sex/strain) from day 7 to 28 of life, without adjusting the initial dose to account for weight gain. After 28 days, BCEE was added to feed at a concentration of 300 ppm for 76 weeks. Surviving animals were sacrificed at 80 weeks. Ninety animals of each strain were included as controls. Tumor incidence in surviving animals is summarized in Table 1. A statistically significant increase in hepatomas ($p<0.05$) was noted in both males and females of strain X and in males of strain Y. No other tumor type showed significant increases in incidence.

Charles River CD rats (26/sex/group) were treated with 0, 25 or 50 mg/kg-day bis(2-chloroethyl)ether by gavage for 18 months by Weisburger *et al.* (1981). Animals were observed for 2 years. No carcinogenic effects were observed, although the authors report increased mortality among the high-dose females and reduction in mean weight among high-dose males and females.

Van Duuren *et al.* (1972) report on two experimental approaches to evaluate the carcinogenicity of bis(2-chloroethyl)ether; a subcutaneous injection study and an initiation study by dermal

application. ICR/Ha Swiss mice (30 females) were injected weekly with 1 mg BCEE for 685 days. No tumors remote from the injection site were observed. Two sarcomas were noted at the injection site (2/30) but were not found to be statistically different from controls (0/30) ($p>0.05$ by Fisher's Exact Test).

Van Duuren *et al.* (1972) also treated ICR/Ha Swiss mice (20 females/group) with a single dose of 1 mg BCEE applied to the skin followed by three applications/week of the tumor promoter phorbol myristate acetate (PMA) in acetone for life. Control groups included animals not treated with BCEE and animals treated with BCEE but without the promoter. Skin papillomas were noted among animals treated with both BCEE and PMA, but the incidence was not significantly higher than among control animals (3/20 treated, 2/20 controls; $p>0.05$ by Fisher's Exact Test). No tumors were observed among animals treated only with BCEE.

Theiss *et al.* (1977) injected A/St mice (20 males) intraperitoneally with 8, 20, or 40 mg/kg BCEE 3 times/week for 8 weeks. After 24 weeks all surviving mice were sacrificed and examined only for lung tumors. The incidence of tumors among treated animals was not found to be significantly higher than among controls.

Table 1. Incidence of tumors in rats treated with bis(2-chloroethyl)ether* (Innes *et al.*,1969).

		Tumor Incidence			
		Strain X		Strain Y	
Tumor Type/Treatment		female	male	female	male
hepatomas	treated	4/18**	14/16**	0/18	9/17**
	control	0/87	8/79	1/82	5/90
pulmonary tumors	treated	0/18	0/16	0/18	2/16
	control	3/83	5/79	3/92	10/90
lymphomas	treated	0/18	2/16	0/18	0/17
	control	4/87	5/79	4/82	1/90

* F_1 generation mice were administered 100 mg/kg body weight bis(2-chloroethyl)ether by oral gavage from day 7 to 28 of life and subsequently in feed at a concentration of 300 ppm for 76 weeks (calculated dose is 39 mg/kg-day). Surviving mice were sacrificed at 80 weeks.
** statistically significant increase in incidence ($p<0.001$ by Fisher's exact test)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

In the absence of studies in humans useful in evaluating the carcinogenicity of bis(2-chloroethyl)ether, a single animal study (Innes *et al.*, 1969) has been identified as appropriate for the development of a cancer potency value. The most sensitive endpoint from this study is the development of hepatomas in treated male strain X rats. Other studies either do not show development of tumors (Weisburger, 1981) or experimental duration/dosing limited the interpretation of negative data (Van Duuren, 1972; Theiss, 1977).

Methodology

Lifetime average dose estimates from the Innes *et al.* study (1969) have been calculated to be 39 mg/kg-day bis(2-chloroethyl)ether (US EPA, 1980). A linearized multistage procedure polynomial was applied to the tumor incidence data (CDHS, 1985; Anderson, 1983). The upper 95% confidence bound on the cancer potency estimate is termed q_1^*. Using the data presented in Table 1, the following cancer potencies were derived from groups showing significant increases in hepatoma incidence:

animal group	q_1^* (mg/kg-day)$^{-1}$
Strain X - males	0.086
Strain X - females	0.013
Strain Y - males	0.031

The selection of the cancer potency value has been based on the q_1^* value from the most sensitive sex and strain in this case, 0.086 (mg/kg-day)$^{-1}$ in Strain X males derived from Innes *et al.*(1969). Calculation of the cancer potency in animals (q_{animal}) can be made from the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (80 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} is 0.19 (mg/kg-day)$^{-1}$. Conversion to human cancer potency (q_{human}) is based on the following relationship, where bw_{animal} is the assumed body weight for the test species (0.03 kg - mice; US EPA, 1980) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The estimate of q_{human} based on this relationship is 2.5 (mg/kg-day)$^{-1}$. A unit risk value based upon air concentrations was derived by OEHHA/ATES asssuming the human breathing rate of 20 m^3/day, 100% fractional absorption, and average human body weight of 70 kg. The calculated unit risk value is 7.1 E-4 ($\mu g/m^3$)$^{-1}$.

V. REFERENCES

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BIS(CHLOROMETHYL)ETHER

CAS No: 542-88-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	114.96
Boiling point	106°C
Melting point	-41.5°C
Vapor pressure	30 mm Hg at 22°C
Air concentration conversion	1 ppm = 4.75 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-2 $(\mu g/m^3)^{-1}$
Slope Factor: 4.6 E+2 $(mg/kg\text{-}day)^{-1}$
[Calculated from potency value derived by RCHAS, cross-route extrapolation (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Increases in the incidence of lung cancer have been reported in a number of studies of workers exposed to both bis(chloromethyl)ether (BCME) and chloromethyl methyl ether (CMME). Some of these studies involve workers primarily exposed to CMME contaminated with 1-8 % BCME. Exposure to CMME, a known human carcinogen, is a confounding variable in these studies. However, there are several studies in which individuals were known to have been exposed to BCME, but exposure to CMME was not known to have occurred and appears unlikely.

Theiss *et al*. (1973) (reviewed by IARC, 1973) reported a retrospective study of a small group of BCME workers exposed between 1956 and 1962. Six cases of lung cancer were found in 18 men employed in a testing facility; 5 of the 6 men were smokers. Two additional lung cancer cases were found in a group of 50 production workers. Five of the 8 total cases were oat-cell carcinomas. Exposure periods were 6-9 years, and tumor latency was 8-16 years.

Sakabe (1973) reported on lung cancer cases occurring in 32 workers exposed to BCME in a Japanese dyestuff factory in the period 1955-1970. Five cases of lung cancer were reported compared to 0.024 expected cases ($p < 0.001$). One case was reported to be oat-cell carcinoma; the others were of mixed histological types. Duration of exposure to BCME ranged from 4 to 7 years; cancer mortality latency ranged from 8 to 14 years after initial exposure. It was noted that all the workers that developed lung cancer were also smokers, and that 4 of the 5 cases were also exposed to other industrial chemicals.

Lemen *et al*. (1976) conducted a retrospective cohort study of cancer incidence in a group of 115 white male anion-exchange resin manufacturing workers in San Mateo County, California. Worker tobacco smoking status was evaluated and used to adjust expected tumor incidence rates. Five cases of lung cancer were observed compared to 0.54 cases expected ($p < 0.01$), representing a nine-fold increased lung cancer risk. The histological type of lung cancer primarily observed was small cell-undifferentiated; exposure ranged from 7.6 to 14 years (mean of 10 years). The mean induction-latency period was 15 years. No quantitative worker exposure evaluation was performed.

The studies described above demonstrated a significant increase in lung cancer incidence, predominantly small-cell-undifferentiated carcinoma. This histologic type is not the one generally associated with smoking (squamous cell carcinoma).

Animal Studies

Male Sprague-Dawley rats and golden Syrian hamsters (50/exposure group) received 1, 3, 10 or 30 exposures (6 hours/exposure) to 1 ppm BCME by inhalation (Drew *et al*., 1975). After exposure, the animals were exposed for the remainder of their lifetime. Median survival time for hamsters receiving 0, 1, 3, 10 or 30 exposures was 675, 620, 471, 137 and 42 days, respectively. Median survival time for exposed rats was 467, 457, 168, 21 and 23 days, respectively. One rat in the 3 exposure group developed a squamous-cell carcinoma of the skin; additionally, one hamster in the 1 exposure group developed an undifferentiated nasal tumor. These tumor incidences were not statistically significant. However, the study treatment durations were short, and survival of the treated animals was poor.

Kuschner *et al*. (1975) exposed male Sprague-Dawley rats and golden Syrian hamsters to BCME by inhalation. Groups of 100 hamsters and 70 rats were exposed to 0.1 ppm BCME 6 hours/day, 5 days/week. Control group sizes were not stated. Exposure was generally for the life of the animals. After 80 exposures, 57/70 rats were still alive; 20 rats were then removed from the exposure schedule and observed for the remaining life of the animals. Mortality at 60 weeks was approximately 90% for rats (both animals exposed for their entire lifetime and animals receiving 80 exposures) and hamsters; corresponding control mortality at 60 weeks was approximately 40% and 15% for rats and hamsters, respectively. Two rats in the group receiving 80 exposures developed tumors; the tumor types were a nasal esthesioneuroepitheloma and a keratinizing squamous cell carcinoma of the lung. Additionally, one hamster developed an undifferentiated carcinoma of the lung. No corresponding tumors were reported in control rats or hamsters. Additional groups of rats were given 0, 10, 20, 40, 60, 80 or 100 6-hour exposures to 0.1 ppm BCME (group sizes 240, 50, 50, 20, 20, 30, and 30, respectively), then observed for the life of the animals. Mortality of the exposed animals in all exposure groups was equivalent to that of controls. Nasal and lung tumors were noted in the exposed animals. Nasal tumor types included esthesioneuroepithelomas, unclassified malignant olfactory tumors, squamous cell carcinomas involving the turbinates and gingiva, poorly differentiated epithelial tumors and adenocarcinomas of the nasal cavity. Lung tumors included squamous cell carcinomas and adenocarcinomas. Tumor incidence data for combined respiratory tract tumors is listed in Table 1.

Table 1. Bis(chloromethyl)ether-induced respiratory tract tumors in male Sprague-Dawley rats (Kuschner *et al*., 1975)

Number of exposures (6 hours, 0.1 ppm)	Human equivalent[1] $(mg/kg/day)^{-1}$	Tumor incidence[2]
0	0	0/240
10	0.00027	11/41
20	0.000541	3/46
40	0.00105	4/18
60	0.00184	4/18
80	0.00347	15/34
100	0.00373	12/20

1. Calculated by US EPA (1991)
2. Incidence of respiratory tract cancers in animals surviving beyond 210 days.

Male Sprague-Dawley rats (Spartan substrain) (120/group) and Ha/ICR mice (144-157/group) were exposed to 0, 1, 10 or 100 ppb BCME by inhalation for 6 hours/day, 5 days/week for 6 months (Leong *et al*., 1981). The animals were then observed for the duration of their lifespan. No significant increases in mortality were associated with BCME exposure, except for the 100 ppb exposure group; all animals in this group were dead by 19 months. Significant treatment-related increases in the incidence of respiratory tract tumors were noted. Tumor types included nasal esthesioneuroepithelomas and carcinomas, and pulmonary adenomas. Tumor incidence data is listed in Table 2.

Table 2. Bis(chloromethyl)ether-induced nasal tumors in male Sprague-Dawley rats (Leong *et al*., 1981)

Concentration[1] (ppb)	Tumor Incidence[2]
0	0/112
1	0/113
10	0/111
100	97/112

1. Animals were exposed to 0, 1, 10, 100 ppb BCME for 6 hours/day, 5 days/week for 6 months.
2. Incidence of nasal tumors as reported by CDHS (1988).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency factors for BCME were derived from male Sprague-Dawley rat respiratory tract tumor data (Kuschner *et al*., 1975; Leong *et al*., 1981). Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). The Kuschner *et al.* (1975) study used relatively high exposure levels of BCME. The exposure levels used in the Leong *et al*. (1981) study were lower, and the dose-response exhibited is highly non-linear. Therefore, a cancer potency estimated from the Leong *et al*. (1981) data set may be more representative of low-dose rate potency. For low dose exposures to BCME (below 1 ppb), the potency value was calculated from dose-response data published by Leong *et al*. (1981); for periodic high dose exposures (at or above 1 ppb BCME), the potency was derived from the study by Kuschner *et al*. (1975) (CDHS, 1988).

Methodology

Cancer potency factors (q_1^*) were derived using a linearized multistage procedure (CDHS, 1985) with the dose-response data for male Sprague-Dawley rat respiratory tract tumors (Kuschner *et al.*, 1975) and nasal tumors (Leong *et al*., 1981). Absorbed doses were calculated assuming complete absorption of inhaled BCME, using an inspiration rate of 0.29 m^3/day for Sprague-Dawley rats. The dose from a continuous exposure to 1 ppb BCME (4.7 µg/m^3) would therefore be 1.36 µg/day, or 2.6 µg/kg-day. The cancer potency factors (q_1^*) derived from the Leong *et al*. (1981) and Kuschner (1975) data sets were 8.9 $(mg/kg/day)^{-1}$ and 47 $(mg/kg/day)^{-1}$, respectively. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights, respectively. Body weight values used for humans and Sprague-Dawley rats were 70 kg and 0.52 kg, respectively. The human cancer potency factors (q_1^*) derived from the Leong *et al*. (1981) and Kuschner (1975) data sets were 45.6 $(mg/kg/day)^{-1}$ and 240 $(mg/kg/day)^{-1}$, respectively. The unit risk factor was derived by OEHHA/ATES from the low dose exposure cancer potency value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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CHLORINATED PARAFFINS (Average chain length C12, 60% chlorine by weight)

CAS No: 108171-26-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1994) except where noted)

Molecular weight	411 (average) [NTP, 1986]
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 17 mg/m^3 (approximate)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.5 E-5 (µg/m^3)$^{-1}$
Slope Factor: 8.9 E-2 (mg/kg-day)$^{-1}$
[NTP (1986) female mouse liver tumor data, contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (OEHHA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of chlorinated paraffins are known to exist.

Animal Studies

Male and female B6C3F$_1$ mice and Fischer 344N rats (50/sex/group) were treated by gavage with a commercial-grade chlorinated paraffin product dissolved in corn oil 5 days/week; treatment duration was 103 and 104 weeks for mice and rats, respectively (NTP, 1986). Exposure levels were 0, 125 and 250 mg/kg body weight for mice, and 0, 312 and 625 mg/kg for rats. Significant increases in the incidence of liver tumors were noted in male and female mice; the incidence of alveolar and bronchiolar carcinoma was significantly increased in male mice, as was the combined incidence of thyroid follicular-cell adenomas and carcinomas in female mice. Tumor incidences in mice are listed in Table 1.

Significant increases in liver tumor incidence were noted in male and female rats. Significant increases were also noted in the incidence of leukemia in male rats, and in the incidence of thyroid follicular-cell tumors in female rats. Tumor incidences in rats are listed in Table 2.

Table 1. Tumors induced in B6C3F$_1$ mice by gavage administration of chlorinated paraffins (NTP, 1986)

Dose (mg/kg bw)	Hepatocellular adenomas	Hepatocellular adenomas and carcinomas	Alveolar/bronchiolar carcinomas	Thyroid follicular-cell tumors
Males				
0	11/50	20/50	0/50	
125	20/50	34/50	3/50	
250	29/50	38/50	6/50	
Females				
0	0/50	3/50		8/50
125	18/50	22/50		12/49
250	22/50	28/50		13/49

Table 2. Tumors induced in Fischer 344 rats by gavage administration of chlorinated paraffins (NTP, 1986)

Dose (mg/kg bw)	Hepatocellular carcinomas	Hepatocellular adenomas and carcinomas	Mononuclear cell leukemia	Thyroid follicular-cell tumors
Males				
0	0/50	0/50	7/50	
312	10/50	13/50	12/50	
625	16/48	16/50	14/50	
Females				
0	0/50	0/50		0/50
312	4/50	5/50		6/50
625	7/50	7/50		6/50

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NTP (1986) gavage study of chlorinated paraffins in male and female B6C3F$_1$ mice and F344 rats are listed in Gold *et al*. (1990). Benign and malignant liver tumors were observed in both sexes and species; significant elevations in tumor incidences at other sites were also observed. Estimates of cancer potency are similar for male and female mice and male rats. Cancer potency is based on dose-response data for benign and malignant liver tumors in female mice (see Table 1) (OEHHA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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4-CHLORO-*o*-PHENYLENEDIAMINE

CAS No: 95-83-0

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	142.60
Boiling point	not available
Melting point	76 °C (NCI, 1978)
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.83 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 1.6 E-2 $(mg/kg\text{-}day)^{-1}$
[Male rat urinary bladder tumor data (NCI, 1978), contained in Gold *et al.* (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 4-chlor*o*-o-phenylenediamine in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and $B6C3F_1$ mice were fed diets containing 4-chloro-*o*-phenylenediamine (NCI, 1978). Dietary 4-chloro-*o*-phenylenediamine concentrations and treatment durations for rats and mice are listed in Table 1. Treatment group sizes were 50 animals/sex/species/group, except for low-dose male rats, where a group size of 49 was used.

At study termination, 84, 84 and 70% of male mice, and 72, 88 and 78% of female mice in the control, low-dose and high-dose groups, respectively, were still alive. Survival in treated rats was somewhat lower; 64, 80 and 56% of male rats and 72, 84 and 54% of female rats in the control, low-dose and high-dose groups, respectively, were still alive at study termination. Significantly increased treatment-related liver tumor (hepatocellular adenomas, carcinomas) incidences were noted in both male and female mice. These data are listed in Table 2. A significant dose-related trend was also noted in the increased incidence of urinary bladder carcinomas in male (transitional cell papillomas, carcinomas) and female (papillary or transitional cell carcinomas) rats (Table 2). Increases in the incidence of forestomach tumors also occurred in both male and female rats. The forestomach tumor increases were not statistically significant; however, these tumors are rare in F344 rats.

Table 1. Study design summary for NCI (1978) carcinogenicity bioassay of 4-chloro-*o*-phenylenediamine in Fischer 344 rats and B6C3F$_1$ mice.

Sex/species	Treatment group	4-chloro-*o*-phenylenediamine concentration (mg/kg diet)	Observation period		Time-weighted average concentration (mg/kg diet)
			Treated (weeks)	Untreated (weeks)	
Male rats	control	0		105	
	low-dose	5000	78		
				27	
	high-dose	10000	78		
				28	
Female rats	control	0		106	
	low-dose	5000	78		
				28	
	high-dose	10000	78		
				28	
Male mice	control	0		97	0
	low-dose	10000	33		7000
		5000	45		
		0		17	
	high-dose	20000	33		14000
		10000	45		
		0		18	
Female mice	control	0		97	0
	low-dose	10000	33		7000
		5000	45		
		0		18	
	high-dose	20000	33		14000
		10000	45		
		0		18	

Table 2. Tumor induction in F344 rats and B6C3F$_1$ mice fed diet containing 4-chloro-*o*-phenylenediamine (NCI, 1978)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
Male rats	control low-dose high-dose	0 149 294	urinary bladder tumors	0/50 15/49 25/50
Female rats	control low-dose high-dose	0 184 368	urinary bladder tumors	0/50 5/50 22/50
Male mice	control low-dose high-dose	0 701 1390	liver tumors	15/50 28/50 34/50
Female mice	control low-dose high-dose	0 752 1500	liver tumors	0/50 11/50 10/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984) list results of the NCI (1978) feeding study in male and female B6C3F$_1$ mice and F344 rats. Benign and malignant neoplasms of the liver were elevated in treated male and female mice. Forestomach tumors were also observed in treated rats; these tumors are relatively uncommon in this strain. In addition, substantial increases in the incidences of urinary bladder cancers were seen in rats of both sexes. Dose-response data are given in Table 2. Rats appear to be more sensitive than mice. Quantitative analysis of dose-response data for urinary bladder tumors indicate that male and female rats have nearly the same sensitivity. The upper confidence bound on potency for data on male rats is slightly higher, and this is the value used as a cancer potency for 4-chloro-*o*-phenylenediamine (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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National Cancer Institute (NCI) 1978. Bioassay of 4-Chloro-*o*-Phenylenediamine for Possible Carcinogenicity. CAS No. 95-83-0. Carcinogenesis Technical Report Series No. 165. NCI-CG-TR-63. DHEW Publication No. (NIH) 78-1313. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

p-CHLORO-*o*-TOLUIDINE

CAS No: 95-69-2

p-CHLORO-*o*-TOLUIDINE HYDROCHLORIDE

CAS No: 3165-93-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

***p*-Chloro-*o*-toluidine**

Molecular weight	141.61
Boiling point	241 °C
Melting point	30 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.79 mg/m^3

***p*-Chloro-*o*-toluidine hydrochloride**

Molecular weight	178.07
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 7.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 7.7 E-5 (µg/m^3)$^{-1}$
Slope Factor: 2.7 E-1 (mg/kg-day)$^{-1}$
[Male and female mouse hemangioma and hemangiosarcoma tumor data (Weisburger *et* al., 1978; NCI, 1979), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

IARC (1990) reviewed studies by Currie (1933) and Uebelin and Pletscher (1954) which investigated bladder tumor incidence in small groups of male workers exposed to *p*-chloro*o*-*o*-toluidine; one case of bladder carcinoma was discovered (Currie, 1933).

A cohort study by Ott and Langner (1983) investigated 342 male workers involved in the manufacture of organic dyes in the US between 1914 and 1958. One plant area involved 117 workers with potential exposure to *p*-chloro*o*-*o*-toluidine and other raw materials and intermediates, including *ortho*-toluidine. Followup of this subcohort from 1940 to 1975

indicated that a nonsignificant excess of total cancer deaths occurred (12 observed, 8 expected) and no bladder cancer was observed.

Two studies were conducted on a cohort of 355 male workers in *p*-chloro*-o*-toluidine manufacturing plants in the Federal Republic of Germany (FRG) who had been followed up for mortality from 1929 to 1982. No deaths due to bladder cancer were found in the first study (Stasik *et al*., 1985). The second study examined a subcohort of 116 workers exposed prior to 1970 (the implementation date of improved exposure controls) with presumed high *p*-chloro*-o*-toluidine exposure levels. Excluding 2 cases of urinary bladder carcinomas in the current work force, 6 cases of bladder carcinoma were found between January 1983 and June 1986 in hospital and other institution records. No cancer registry data was available for the area of the FRG where the plant was located; cancer registration rates for a different area of the FRG was therefore used as a basis of comparison. The expected number of tumors was 0.11 based on sex- and age-specific cancer rates. Two patients had hemorrhagic cystitis thought to be due to massive exposure to *p*-chloro*-o*-toluidine. Cigarette smoking was discounted as a confounding variable after reviewing patient smoking histories (3 patients were nonsmokers). Quantitative exposure data was unavailable, but the predominant chemical exposure was to *p*-chloro*-o*-toluidine; however, exposure to other amines could have occurred.

Animal Studies

Male and female random-bred CD-1 albino mice (derived from HaM/ICR mice) and male Charles River CD Sprague-Dawley-derived rats (25/sex/group) were fed diets containing *p*-chloro*-o*-toluidine hydrochloride (97-99% pure) as part of a larger carcinogenicity study of several compounds (Weisburger *et al*., 1978). Mouse exposure levels were 0, 750 or 1500 mg/kg diet and 0, 2000 or 4000 mg/kg diet for males and females, respectively; the mice were fed treated diet for 18 months, followed by an additional 3 month observation period. Rats were fed diet containing 2000 or 4000 mg/kg diet *p*-chloro*-o*-toluidine for 3 months; the doses were then reduced to 500 and 1000 mg/kg diet for 15 months. An untreated control group (25 males) was included. All rats were killed after 24 months. Tumor incidence differences between control and exposed rat groups were not statistically significant. Hemangiomas and hemangiosarcomas were observed in male and female mice; tumor incidence data is listed in Table 1. These tumor types were found in 5/99 male and 9/102 female pooled controls from the larger carcinogenicity study, but were not present in the simultaneous controls.

Diets containing *p*-chloro*-o*-toluidine hydrochloride (99% pure) were fed to groups of male and female $B6C3F_1$ mice and Fischer 344 (F344) rats (50 animals/sex/species/treatment group) (NCI, 1979). Exposure levels for mice were 3750 or 15000 and 1250 or 5000 mg/kg diet for males and females, respectively. Exposure levels for rats were 1250 or 5000 mg/kg diet. Untreated control groups (20 animals/sex/species) were included. Exposed animals were fed treated diet for the duration of the study. All surviving mice were killed at 99 weeks; however, all high-dose females had died by 92 weeks. All surviving rats were killed at 107 weeks.

Exposure to *p*-chloro-*o*-toluidine did not affect mortality of either male or female rats; a dose-related increase in mortality was noted for both male and female mice (NCI, 1979). However,

sufficient numbers of mice of each sex were at risk for tumor development for determination of tumor incidence significance. The percentage of mice surviving to study week 52 was at least 95% for all sexes and treatment groups. No significant tumor incidence increase was observed in male or female F344 rats as a result of *p*-chloro-*o*-toluidine exposure. Significant treatment-related increases ($p < 0.001$) were observed in the incidence of both hemangiosarcomas and hemangiomas and hemangiosarcomas combined in both male and female mice. Tumor incidence data is listed in Table 1.

Table 1: Incidence of vascular tumors (hemangiomas and hemangiosarcomas) in male and female mice treated with *p*-chloro*-o*-toluidine hydrochloride by dietary administration

Study	Sex/Strain	Dietary concentration (mg/kg diet)	Average Dose[1] (mg/kg-day)	Tumor Incidence
Weisburger *et al*. (1978)[2]	male CD-1	0 750 1500	0 90 180	0/14 12/20 13/20
Weisburger *et al*. (1978)[3]	female CD-1	0 2000	0 260	0/15 18/19
NCI (1979)[2]	male $B6C3F_1$	0 3750 15000	0 450 1800	0/20 6/50 41/50
NCI (1979)[3]	female $B6C3F_1$	0 1250	0 162	1/20 43/50

1. Doses as reported by Gold *et al*. (1984).

2. Decreased survival according to Gold *et al*.; a time-to-tumor analysis was performed using TOX_RISK (Crump *et al*., 1991; Cal/EPA, 1992).

3. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≤ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983; US EPA, 1986), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

On the basis of positive bioassay results, the hydrochloride salt of *p*-chloro*-o*-toluidine was classified as a compound with sufficient evidence of carcinogenicity in animals by IARC (1987). The results of feeding studies on by NCI (1979) using male and female $B6C3F_1$ mice and Fischer

344 rats and by Weisburger *et al.* (1978) using male and female CD-1 HaM/ICR mice and male Charles River CD rats are reported in Gold *et al*. (1984). In contrast to rats, mice are sensitive to *p*-chloro*-o*-toluidine hydrochloride-induced carcinogenicity. Vascular tumors (hemangiomas and hemangiosarcomas) were induced in treated mice of both strains and sexes tested.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. The cancer potency for *p*-chloro*-o*-toluidine is based on the bioassay results for the hydrochloride, adjusted for differences in molecular weight. An overall cancer potency was estimated by taking the geometric mean of the 4 values derived from dose-response data for vascular tumors from each of the mouse sex and strains tested (male and female CD-1 and $B6C3F_1$ mice) (Weisburger *et* al., 1978; NCI, 1979; see Table 1). Male $B6C3F_1$ mouse survival in the NCI (1979) study was poor; a cancer potency for that sex and strain was therefore derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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CREOSOTE (COAL TAR-DERIVED)

CAS No: 8001-58-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	complex mixture
Boiling point	194 - 400ºC
Melting point	not available
Vapor pressure	not available
Air concentration conversion	not available

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: Can be calculated using PEF factors contained in the benzo[a]pyrene Toxic Air Contaminant (TAC) document (OEHHA, 1993).

Slope Factor: Can be calculated using PEF factors contained in the benzo[a]pyrene TAC document (OEHHA, 1993).

III. CARCINOGENIC EFFECTS

Human Studies

Henry (1947) reviewed 3753 cases of cutaneous epitheliomata (epitheliomatous ulceration or cancer of the skin) reported to the British Medical Inspector of Factories from 1920 to 1945. Thirty five cases (12 of the scrotum) had creosote exposure. Henry (1946) also reported that the crude mortality rate for scrotal cancer during 1911-1938 for British brickmakers exposed to creosote oil was 29 per million men based on 9 verified cases as compared to a national average of 4.2 per million and rates of 1 per million or less for groups not exposed to suspected skin carcinogens.

A cohort study reported on 123 Swedish workers who treated wood with creosote and were exposed to both creosote and arsenic between 1950 and 1980 (Axelson and Kling, 1983; reviewed in IARC, 1985). Eight workers died of cancer compared to 6 expected. Three cancer deaths (leukemia, pancreas and stomach) were observed compared to 0.8 expected in a subgroup of 21 workers exposed only to creosote for five or more years.

A case-referent study of Swedish workers examined potential relationships between past occupational and radiation exposure and multiple myeloma (Flodin *et al*., 1987). Exposure assessment employed a mailed questionnaire that asked questions about occupational (including coal tar creosote) and radiation exposure. Data analysis using the Miettinen confounder score technique indicated that an increased prevalence of multiple myeloma was associated with occupational exposure to coal tar creosote (crude rate ratio = 6.0, p = 0.001). The rate ratio point estimate for creosote exposure increased to 9.0 after age stratification. The power of this study

was limited by differences between the case group and the referent group in the number of smokers and gender composition.

Creosote contains many of the same compounds present in other polycyclic aromatic hydrocarbon (PAH) mixtures (roofing tar pitch, coke oven emissions) known to be human carcinogens (US EPA, 1986; ATSDR, 1990).

Animal Studies

Female C57BL mice (10 animals/group) were exposed to blended creosote oil (a mixture of creosote, anthracene oils and naphthalene recovery residue oil) in toluene. One drop (8.7 - 9 µl) of a 20% or 80% solution was applied to the skin three times/week for the animals' lifetimes or until tumors developed (21 - 44 weeks and 18 - 35 weeks for the 20% and 80% solution exposure groups, respectively). All treated mice developed skin papillomas and 7 mice in each group developed epidermoid carcinomas, some of which metastasized to pulmonary or regional lymph nodes. None of the vehicle control animals developed skin tumors (Poel and Kammer, 1957).

Female Swiss mice (30/group) were treated twice weekly with one drop of a 2% solution of creosote in acetone applied dermally for 70 weeks. Skin tumors (including 16 carcinomas) were reported in 23 of 26 surviving mice. The average tumor latency period was 50 weeks. No vehicle control group was included; however, no animals in a control group of 50 mice receiving a single application of 1% 7,12-dimethylbenz[*a*]anthracene in mineral oil developed tumors after 80 weeks (Lijinsky *et al*., 1957).

Undiluted creosote applied topically twice weekly (25 µl) to 30 random-bred female mice for 28 weeks induced an average of 5.4 papillomas per animal; 82% of the mice had carcinomas. The average time to tumor for papillomas and carcinomas was 20 and 26 weeks, respectively. No vehicle control group was included in the study (Boutwell and Bosch, 1958). In a similar study, a group of 24 albino mice treated dermally with 25 µl creosote twice weekly for 5 months and housed in stainless steel cages exhibited 139 lung adenomas (5.8 tumors/mouse) after 8 months. A group of 29 mice born and housed in creosote-treated wood cages treated dermally with 25 µl creosote for 5 months demonstrated 315 lung adenomas (10.8 tumors/mouse) after 8 months. A control group (19 mice) housed in stainless steel cages demonstrated 9 lung adenomas (0.5 tumors/mouse) after 8 months (Roe *et al*., 1958).

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Creosote has been demonstrated to cause skin and lung tumors in mice after dermal exposure, and is predominantly composed of PAH; similar PAH-containing coal tar products (roofing tar pitch, coke oven emissions) have been shown to be human carcinogens (US EPA, 1986; ATSDR, 1990). Creosote has been given B1 and 2A classifications (probable human carcinogen) by US EPA (1987) and IARC (1985), respectively. No creosote carcinogenicity bioassay study suitable for quantitative risk assessment exists. However, a cancer unit risk factor for the PAH

benzo[*a*]pyrene (BaP) derived from an inhalation exposure study (Thyssen *et al*., 1981) has been developed, along with Potency Equivalency Factors (PEFs) for several related PAHs. (OEHHA, 1993).

Thyssen *et al*. (1981) exposed male Syrian golden hamsters (24/group) by inhalation to 0. 2.2, 9.5 or 46.5 mg BaP/m^3 in a sodium chloride aerosol (greater than 99% of the particle diameters were between 0.2 and 0.5 µm). The hamsters were exposed to BaP daily for 4.5 hours/day for the first 10 weeks of exposure; subsequent exposure was daily for 3 hours/day. Total treatment duration was 95 weeks. Animals dying in the first year of the study were replaced. The effective number of animals in the control, 2.2, 9.5 and 46.5 mg/m^3 exposure groups were 27, 27, 26 and 25, respectively. Survival time for the 46.5 mg/m^3 exposure group was significantly reduced (60 weeks) when compared to controls (96 weeks). Survival times for the other exposure groups were similar to controls. Respiratory tract (including nasal cavity, larynx and trachea) tumor incidence was significantly increased in a dose-dependent manner in the 9.5 and 46.5 mg/m^3 exposure groups (34.6% and 52%, respectively, compared to controls); those exposure groups also demonstrated an increase in upper digestive tract (including pharynx, esophagus and forestomach) tumor incidence (27% and 56%, respectively). This study was selected as the basis of a cancer potency factor for exposure to BaP by inhalation because it used the most sensitive species and sex demonstrating a dose response and using the most relevant exposure route.

Methodology

A linearized multistage procedure (GLOBAL86) (Howe and van Landingham, 1986) was used with the Syrian golden hamster respiratory tract tumor incidence data of Thyssen *et al*. (1981) to calculate a cancer potency factor. Data from the highest exposure group (46.5 mg/m^3) was not used due to the shortened lifespan of the hamsters in this group. Administered dose for the 2.2 and 9.5 mg/m^3 exposure groups based on an inspiration rate of 0.063 m^3/day and a body weight of 0.1 kg was 0.152 and 0.655 mg/kg/day, respectively. Surface area scaling was then used to extrapolate a human cancer potency factor and an inhalation unit risk factor (using assumptions of 70 kg body weight and 20 m^3/day inspiration rate). Creosote is approximately 91% PAH, nitro-PAH or hydroxy-PAH (Wright *et al*., 1985); a unit risk for creosote can be calculated using the unit risk value for BaP and the PEFs for related PAHs (OEHHA, 1993).

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p-CRESIDINE

CAS No: 120-71-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	137.20
Boiling point	235 °C
Melting point	51.5 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.611 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.3 E-5 (µg/m^3)$^{-1}$
Slope Factor: 1.5 E-1 (mg/kg-day)$^{-1}$
[Female mouse urinary bladder tumor data (NCI, 1979), contained in Gold *et* al. (1984), expedited Proposition 65 methodology, with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-cresidine in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice (50 animals/sex/species/group) were fed diets containing *p*-cresidine (NCI, 1979). The study design is outlined in Table 1. Dose levels for male and female mice were reduced after 21 weeks; the study report did not describe the rationale for the dose reduction.

Mortality in mice was dose-related and associated with the development of bladder tumors; mortality in rats was also dose-related and was related to development of urinary bladder and nasal cavity tumors. Survival percentages after 75 weeks of treatment are listed in Table 2. Significant incidence increases were seen for urinary bladder tumors in male and female rats (squamous-cell or transitional-cell carcinomas) and mice (transitional-cell carcinomas), for liver tumors in female mice (hepatocellular adenomas or carcinomas) and male rats (neoplastic liver nodules, hepatocellular carcinomas or cholangiocarcinomas), and for nasal cavity tumors (primarily nasal cavity tumors) in male and female rats. These data are listed in Table 2. Nonsignificant increases in nasal cavity tumors were also observed in male and female mice.

Table 1. Study design summary for NCI (1979) carcinogenicity bioassay of *p*-cresidine in Fischer 344 rats and $B6C3F_1$ mice.

Sex/species	Treatment group	*p*-cresidine dietary concentration (mg/kg diet)	Observation period	
			Treated (weeks)	Untreated (weeks)
Male rats	control	0		106
	low-dose	5000	104	1
	high-dose	10000	104	1
Female rats	control	0		106
	low-dose	5000	104	2
	high-dose	10000	104	2
Male mice	control	0		97
	low-dose	5000	21	
		1500	83	
		0		2
	high-dose	10000	21	
		3000	71[a]	
Female mice	control	0		97
	low-dose	5000	21	
		1500	83	
		0		2
	high-dose	10000	21	
		3000	83	
		0		2

a. All animals in this group were dead by the end of week 92.

Table 2. Mortality and tumor incidences associated with dietary exposure of Fischer 344 rats and $B6C3F_1$ mice to *p*-cresidine (NCI, 1979)

Sex/species	Treatment group	Average Dose[1] (mg/kg-day)	Survival after 75 weeks (%)	Tumor type	Tumor incidence[2]
male mice	controls	0	98	urinary bladder tumors	0/50
	low-dose	260	50		40/50
	high-dose	552	10		31/50
female mice	controls	0	90	urinary bladder tumors	0/50
	low-dose	281	78		42/50
	high-dose	563	28		45/50
	controls			liver tumors	0/50
	low-dose				14/50
	high-dose				6/50
male rats	controls	0	94	urinary bladder tumors	0/50
	low-dose	198	96		30/50
	high-dose	396	62		44/50
	controls			liver tumors	0/50
	low-dose				13/50
	high-dose				2/50
	controls			nasal cavity tumors	0/50
	low-dose				2/50
	high-dose				23/50
female rats	controls	0	96	urinary bladder tumors	0/50
	low-dose	245	98		31/50
	high-dose	491	76		43/50
	controls			nasal cavity tumors	0/50
	low-dose				0/50
	high-dose				11/50

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1979) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are listed in Gold *et al*. (1984). Urinary bladder tumors as well as tumors at other sites were observed in both sexes of mice and rats. The most sensitive site appears to be the urinary bladder. Both sexes of both species show similar sensitivities at this site. The potency derived from dose-response data on female mice (benign and malignant urinary bladder tumors) is slightly greater than those for the other groups and is taken as the best estimate here (see Table 2).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Because female mouse survival was poor, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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CUPFERRON (N-hydroxy-N-nitroso-benzenamine, ammonium salt)

CAS No: 135-20-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	155.16
Boiling point	not available
Melting point	163-164 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 6.346 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-5 (µg/m^3)$^{-1}$
Slope Factor: 2.2 E-1 (mg/kg-day)$^{-1}$
[Male rat hemangiosarcoma data (NCI, 1978), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of cupferron in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were exposed to diets containing cupferron (NCI, 1978). A summary of the experimental design is outlined in Table 1. Treatment periods were followed by an observation period during which animals were fed control diet. Male and female mouse dose levels were reduced after 35 weeks. Group sizes were 50 animals/sex/species/group except for the high-dose male mouse group, which consisted of 49 animals.

Cupferron induced significantly increased incidences of forestomach squamous-cell carcinomas, hepatocellular neoplastic nodules and carcinomas in male and female rats, hemangiosarcomas in male and female rats and mice, auditory sebaceous gland tumors in female mice and rats, hepatocellular carcinomas in female mice and Harderian gland adenomas in male and female mice. Hemangiosarcoma incidence data is listed in Table 2.

Table 1. Experimental design for carcinogenicity bioassay of cupferron using male and female Fischer 344 (F344) rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Group	Cupferron concentration (%)	Experiment duration (weeks)		Time-weighted average concentration[1]
			treatment period	observation period	
male rats	control	0	0	110	
	low dose	0.15	78	26	
	high dose	0.3	78	19	
female rats	control	0	0	110	
	low dose	0.15	78	28	
	high dose	0.3	78	28	
male, female mice	control	0		98	0
	low dose	0.3	35		0.2
		0.1	43	18	
	high dose	0.6	35		0.4
		0.2	43	17	

1. Time-weighted concentration $= \dfrac{\sum (\text{concentration} \times \text{weeks received})}{\sum (\text{weeks receiving chemical})}$

Table 2. Cupferron-induced hemangiosarcoma incidence in male and female F344 rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor incidence[2]
Male rat	control	0	0/50
	low dose	45	38/50
	high dose	96.5	35/49
Female rat	control	0	0/50
	low dose	55.2	28/50
	high dose	110	37/50
Male mouse	control	0	1/50
	low dose	185	3/50
	high dose	374	7/50
Female mouse	control	0	1/50
	low dose	200	5/50
	high dose	405	6/50

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1978) feeding study in male and female $B6C3F_1$ mice and Fischer 344 rats are listed in Gold *et al*. (1984). Benign and malignant vascular tumors as well as tumors at other sites were observed in mice and rats of both sexes treated with cupferron. Cancer potency is based on the data for vascular tumors in the male rat (see Table 2) because the rat is the more sensitive of the species tested, and the male appears to be slightly more sensitive than the female (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a p-value of ≤ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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National Cancer Institute (NCI) 1978. Bioassay of Cupferron for Possible Carcinogenicity. CAS No. 135-20-6. Carcinogenesis Technical Report Series No. 100. NCI-CG-TR-140. DHEW Publication No. (NIH) 78-1350. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

2, 4-DIAMINOANISOLE

CAS No: 615-05-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	138.17
Boiling point	not available
Melting point	67-68 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.651 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.6 E-6 (µg/m^3)$^{-1}$
Slope Factor: 2.3 E-2 (mg/kg-day)$^{-1}$
[Male rat thyroid tumors (NCI, 1978), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 2,4-diaminoanisole in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing 2,4-diaminoanisole (DAA) sulfate (NCI, 1978). Mice were fed diets containing 1200 or 2400 mg/kg DAA sulfate for 78 weeks and were observed for an additional 18-19 weeks. Rats were fed diets containing 5000 mg/kg DAA sulfate for 78 weeks, or diet containing 1250 mg/kg DAA sulfate for 10 weeks, then 1200 mg/kg diet for 68 weeks, followed by a 29 week observation period. Matched control groups were provided for each dose group. Group sizes were 50 animals/sex/species/group with the exception of the male rat high-dose control group (49 animals). Mortality of control and treated rats and mice were similar by the end of the study. Significantly increased incidences of thyroid tumors were seen in both mice (males - follicular cell adenomas; females - follicular cell adenomas, carcinomas) and rats (follicular cell adenocarcinomas, carcinomas, papillary adenocarcinomas and cystadenocarcinomas). Increased skin tumor incidences (squamous-cell carcinomas, basal-cell carcinomas, sebaceous adenocarcinomas) were observed in male rats. Male and female rats both had increased incidences of preputial or clitoral gland adenomas, papillomas or carcinomas and Zymbal gland tumors (males - squamous cell carcinomas, sebaceous adenocarcinomas; females - sebaceous adenocarcinomas). Tumor incidence data is listed in Table 1.

Table 1 Tumor induction in Fischer 344 rats and B6C3F$_1$ mice by dietary administration of 2,4-diaminoanisole (NCI, 1978)

Sex/species	Dose group	Average Dose[1] (mg/kg-day)	Tumor type	Tumor Incidence[2]
Male mouse	control	0	thyroid	1/100
	low dose	116		0/50
	high dose	234		11/50
Female mice	control	0	thyroid	0/100
	low dose	126		0/50
	high dose	253		8/50
Male rats	control	0	thyroid	2/99
	low dose	35.2		2/50
	high dose	146		17/50
	control	0	preputial gland	0/99
	low dose	35.2		2/50
	high dose	146		8/50
	control	0	skin	0/99
	low dose	35.2		2/50
	high dose	146		9/50
	control	0	Zymbal gland	0/99
	low dose	35.2		1/50
	high dose	146		6/50
Female rats	control	0	thyroid	3/100
	low dose	44		1/50
	high dose	182		10/50
	control	0	clitoral gland	3/100
	low dose	44		5/50
	high dose	182		8/50
	control	0	Zymbal gland	0/100
	low dose	44		0/50
	high dose	182		4/50

1. Doses reported by Gold *et al*., 1984.
2. Tumor incidences reported by Gold *et al*., 1984.

Diets containing 2,4-diaminoanisole at concentrations of 0, 1200, 2400 or 5000 mg/kg diet were fed to female F344 rats (40 - 60/group) for up to 82-86 weeks (Evarts and Brown, 1980). An additional 15 rats were fed diet containing 5000 mg/kg diet for 10 weeks, then fed control diet and observed for up to 87 weeks. Thyroid tumor incidences (follicular-cell adenomas or carcinomas or C cell carcinomas) were 1/37 in controls, 2/47 in the low-dose group, 3/33 in the mid-dose group and 31/40 in the high-dose group; in addition, 3/12 animals exposed to the 5000 mg/kg diet for 10 weeks had thyroid tumors. Clitoral gland tumors (squamous-cell, sebaceous-cell or squamous-sebaceous-cell carcinomas) were noted in 0/37 controls, 8/47 of the low-dose

group, 15/33 of the mid-dose group and 9/40 of the high dose-group, as well as in 1/12 of the animals in the 10 week high-dose group.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency for 2, 4-diaminoanisole was derived from that for the sulfate using a molecular weight conversion (Cal/EPA, 1992):

$$q_h\,(\text{base}) = q_h\,(\text{sulfate}) \times \frac{\text{MW(sulfate)}}{\text{MW(base)}}$$

where q_h is the human potency and MW is the molecular weight. This conversion assumes that the intake of equivalent moles of the two forms of the chemical results in equivalent concentrations of the active species *in vivo*. Gold *et al*. (1984) list the results of the NCI (1978) feeding studies in male and female F344 rats and $B6C3F_1$ mice, and the feeding study by Evarts and Brown (1980) in female F344 rats. Cancer potency is based on dose-response data for benign and malignant thyroid tumors in male rats, the most sensitive sex and species (see Table 1) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

Evarts, R.P., and Brown, C.A. 1980. 2,4-diaminoanisole sulfate: early effect on thyroid gland morphology and late effect on glandular tissue of Fischer 344 rats. J. Natl. Cancer Inst. 65:197-204.

Gold, L., Sawyer, C., Magaw, R., Backman, G., de Veciana, M., Levinson, R., Hooper, N., Havender, W., Bernstein, L., Peto, R., Pike, M., and Ames, B. 1984. A Carcinogenic Potency Database of the standardized results of animal bioassays. Environ. Health Perspect. 58:9-319.

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2, 4-DIAMINOTOLUENE

CAS No: 95-80-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	122.17
Boiling point	292 °C
Melting point	99 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.997 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-3 (µg/m^3)$^{-1}$
Slope Factor: 4.0 E+0 (mg/kg-day)$^{-1}$
[Female rat mammary gland tumors (NCI, 1978), contained in Gold *et* al. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the carcinogenic potential of 2,4-diaminotoluene in humans are known to exist.

Animal Studies

IARC (1978) reviewed a study by Umeda (1955) in which 20 rats of mixed strain and sex were injected subcutaneously with 0.5 ml of a 0.4% solution of 2,4-diaminotoluene at weekly intervals. No tumor induction was noted in 11 rats that died in the first 8 months of the study. All 9 surviving rats, which received 29-44 weekly injections, developed subcutaneous sarcomas. No concurrent control group was included in this study; however, another group of 12 rats exposed to 11 subcutaneous injections of xanthene in propylene glycol over 10 months did not develop local sarcomas.

Male Wistar rats were fed diets containing 0, 0.06% or 0.1% 2,4-diaminotoluene for 30-36 weeks (12 animals/treatment group, 6 animals/control group) (Ito *et al*., 1969). Exposure to 2,4-diaminotoluene caused an increased incidence of hepatocellular carcinomas in the treated animals (0/6, 7/11, and 9/9 in the control, low-dose and high-dose groups, respectively).

Male and female Fischer 344 (F344) and B6C3F$_1$ mice were fed diets containing 2,4-diaminotoluene (NCI, 1979). Treatment group sizes were 50 animals/sex/species/group; matched control group sizes were 20 animals/sex/species/group. The study design is outlined in Table 1. Male and female rat low- and high-dose levels were reduced after 40 weeks.

Table 1. Experimental design of 2,4-diaminotoluene carcinogenicity bioassay using male and female F344 rats and B6C3F$_1$ mice (NCI, 1979)

Sex/species	Study group	dietary 2,4-diaminotoluene (ppm)	Study time (weeks)	Time-weighted average dose[c] (ppm)
Male rat	matched control	0	103	0
	low dose	125	40	
		50	63	79
	high dose	250	40	
		100	39[a]	176
Female rat	matched control	0	103	0
	low dose	125	40	
		50	63	79
	high dose	250	40	
		100	44[b]	171
Male,female mouse	matched control	0	101	
	low dose	100	101	
	high dose	200	101	

a. Test diet administration was terminated at the time indicated and all high-dose males were killed because of morbidity.

b. Test diet administration was terminated at the time indicated and all high-dose females except four were killed because of morbidity.

c. Time-weighted average dose $= \dfrac{\sum \text{(dose in ppm} \times \text{weeks at that dose)}}{\sum \text{(weeks receiving each dose)}}$

Significantly increased tumor incidences were observed in treated rats; hepatocellular adenomas, carcinomas and neoplastic nodules in male and female rats, mammary gland adenomas and carcinomas in female rats, and subcutaneous fibromas in male rats. Significant increases in tumor incidence were also noted in female mice; hepatocellular carcinomas in the low- and high-dose groups, and lymphomas in the low-dose group. No significant tumor induction was noted in male mice. Tumor incidence data is listed in Table 2.

Table 2. 2,4-Diaminotoluene-induced tumor incidence in F344 rats and B6C3F$_1$ mice (NCI, 1978)

Sex/species	Study group	Average dose[a] (mg/kg-day)	Tumor type	Tumor incidence[b]
Male rats	matched controls	0	liver tumors[c]	0/20
			subcutaneous fibromas	0/20
	low dose	3.2	liver tumors[c]	5/50
			subcutaneous fibromas	15/50
	high dose	7.0	liver tumors[c]	10/50
			subcutaneous fibromas	19/50
Female rats	matched controls	0	liver tumors[c]	0/20
			mammary gland tumors	0/20
	low dose	3.95	liver tumors[c]	0/50
			mammary gland tumors	11/50
	high dose	8.55	liver tumors[c]	6/50
			mammary gland tumors	14/50
Female mice	matched controls	0	liver tumors	0/20
			lymphomas	2/20
	low dose	13.0	liver tumors	13/50
			lymphomas	29/50
	high dose	26.0	liver tumors	18/50
			lymphomas	11/50

a. Doses as reported by Gold *et al*. (1984).
b. Tumor incidences as reported by Gold *et al*. (1984)
c. Includes hepatocellular neoplastic nodules, adenomas and carcinomas

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results of the NCI (1978) feeding studies of 2, 4-diaminotoluene in male and female B6C3F$_1$ mice and F344 rats are listed by Gold *et al*. (1984). Significant increases in tumors were seen in rats of both sexes and in female mice. The study results indicated that rats are more sensitive than mice. The female rat appears to be slightly more sensitive than the male, although the study is not sensitive enough to definitively distinguish between the two. Cancer potency is based on mammary gland tumors in the female rat (see Table 2).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992). The individual

animal data for the time-to-tumor analysis were obtained from TOX_RISK (Crump *et al*., 1991). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

California Environmental Protection Agency (Cal/EPA) 1992. Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens. Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Section, Berkeley, CA.

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Umeda, M. 1955. Production of rat sarcoma by injections of propylene glycol solution of *m*-toluylenediamine. Gann 46:597-603.

1,2-DIBROMO-3-CHLOROPROPANE

CAS No: 96-12-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	236.36
Boiling point	195.5°C
Melting point	5°C
Vapor pressure	0.8 mm Hg @ 21°C
Air concentration conversion	1 ppm = 9.67 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.9 E-3 (µg/m^3)$^{-1}$
Slope Factor: 7.0 E+0 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Two occupational epidemiological studies, Hearn *et al*. (1984) and Wong *et al*. (1984), were conducted using data from workers exposed during the formulation or manufacture of 1,2-dibromo-3-chloropropane (DBCP). The study by Hearn *et al*. (1984) examined a cohort of 550 chemical workers exposed to a variety of compounds, including DBCP. Twelve of the subjects in this cohort died from cancer (7.7 expected). In the study by Wong *et al*. (1984) 9 cases of respiratory cancer were reported in a cohort of 1034 workers exposed to DBCP (5.0 expected). Neither of these studies produced statistically significant ($p < 0.05$) associations between DBCP exposure and expected cancer incidence. In addition, it was not possible to account for all confounding chemical exposures in these studies. Therefore these studies were considered by IARC (1987) to be inadequate and were not used for the derivation of the cancer potency of DBCP.

An epidemiological study conducted by Jackson *et al.* (1982) found an association between DBCP in drinking water and increased incidence of stomach cancer and leukemia. In this study, patterns of DBCP contamination of well water in Fresno County, California were compared with deaths from selected cancers in the same area from 1970 to 1979. The cancers studied included stomach, esophageal, liver, kidney, and breast cancers in addition to lymphoid leukemia. Significant relationships between DBCP exposure level and cancer deaths were tested by Bartholomew's trend test. Exposed individuals were grouped into those with less than 0.05 ppb, those with 0.05 up to 1.0 ppb, and those with greater than 1.0 ppb DBCP in the drinking water. Mortality was age-adjusted using 20-year age groups. Significant trends for incidence of stomach cancer and lymphoid leukemia were found. Results may have been confounded by smoking habits, ethnicity, and exposure to other carcinogens.

Additional analysis of these data by Environmental Health Associates (EHA, 1986) and sponsored by the Shell Oil Company did not show the above association. These data included corrections for ethnicity. This study used a different method for estimating DBCP concentrations. Although the associations between cancer incidence and DBCP exposure failed to reach significance at the $p < 0.05$ level in the EHA study, the magnitude of the associations in the high and low exposure groups were approximately the same as described in the Jackson *et al*. (1982) study. The trend for cancer risk and DBCP exposure is most closely related to the time of residence of the test subjects (Table 1).

Table 1. Relative risk of human gastric cancer in areas with high[1] concentrations of dbcp in the drinking water compared with areas of low[2] DBCP (Jackson *et al*., 1982).

Time of Residence	Relative Risk for Gastric Cancer
1 year at death	1.29
1 year prior to death	1.55
10 years prior to death	3.05

[1] DBCP concentrations greater than 1.0 ppb.
[2] DBCP concentrations less than 0.05 ppb.

Animal Studies

DBCP is a carcinogen in at least two laboratory rodent species by inhalation, ingestion, or dermal exposure. Tumors following DBCP exposure can arise not only at the site of application, but also at distal sites. Because of its carcinogenicity to multiple species, DBCP is assumed to represent a carcinogenic threat to humans (CDHS, 1985).

Three sets of long-term bioassays using mice and rats were conducted respectively by the National Cancer Institute (NCI, 1978), the National Toxicology Program (NTP, 1982) and Hazelton Laboratories (1977, 1978). In the NCI (1978) study, DBCP was administered by oral gavage to both sexes of rats and mice. Two major problems with this study, early mortality and nearly 100% forestomach carcinoma rate, precluded its usefulness in determining a cancer potency value. The inhalation study by NTP (1982) had much better survival rates than those observed in the gavage study, and carcinogenicity was observed for tissues at or near the site of the initial chemical contact.

In the NTP study, groups of 50 B6C3F1 mice or 50 F344 rats of either sex were exposed by inhalation to 0, 0.6 or 3.0 ppm DBCP for 6 hours/day, 5 days/week, for 76-103 weeks. Surviving high-dose rats were killed at week 84. High-dose female mice and low- and high-dose male mice were killed at week 76. Low-dose rats and female mice were killed at week 104. A significant increase in the combined incidence of nasal tumors was found in male and female rats at both concentrations (Table 2a, 2b). In mice, the combined incidence of nasal tumors was significantly increased in females at both concentrations, and in males exposed to the high concentration.

Proliferative lesions were observed at sites distal to the lung in the mice, including the kidney, forestomach, and spleen.

Table 2a. Incidence of combined nasal cancers from DBCP Inhalation exposure in rats and mice (NTP, 1982)

	Tumor Incidence DBCP Concentration (ppm)		
Species	0	0.6	3.0
F-344 Rats (males)	0/50	32/50	39/49
F-344 Rats (females)	1/50	21/50	32/50
B6C3F1 Mice (males)	0/45	1/42	21/48
B6C3F1 Mice (females)	0/50	11/50	38/50

Table 2b. Incidence of combined lung cancers from DBCP inhalation exposure in mice (NTP, 1982)

	Tumor Incidence DBCP Concentration (ppm)		
Species	0	0.6	3.0
B6C3F1 Mice (males)	0/41	3/40	11/45
B6C3F1 Mice (females)	4/50	12/50	18/50

In the studies conducted by the Hazelton Laboratories (1977, 1978), mice (50 males or females per group) or rats (60 males or females per group) were exposed to DBCP in the diet for 78 weeks. The intended daily doses were 0, 0.3, 1.0 and 3.0 mg/kg per day. Both species exhibited dose-dependent increases in forestomach squamous cell papillomas and carcinomas. The mouse study contained experimental errors in the diet preparation and food consumption measurements. Spillage of the food and evaporation in the mouse study may have resulted in an overestimate of the actual average daily exposure. For the rats, diets were prepared every two weeks, therefore loss of DBCP in the food due to evaporation was less significant than in the mouse study. The average amount of DBCP in the diet was estimated assuming first-order evaporation loss (Shell Oil Company, 1986). Using this model, the average daily doses of DBCP in the mouse study were 0, 0.3, 1.6 and 4.8 mg/kg per day. The study conducted by Hazelton Laboratories used lower doses than those in the NCI study, providing better information on the lower end of the dose-response curve. However, the times of death or times of tumor appearance were not reported. In addition, the study conducted by Hazelton Laboratories was terminated at 78 weeks in the case of the mice but lasted for 104 weeks in the case of the rats.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The Hazelton Laboratories (1977) study in female CD-1 mice was chosen as the critical study for the derivation of the cancer potency factor. In this study, female mice had a tumor incidence of 19/50 in the high dose group. No tumors were observed in the controls, and no histopathological examination was determined in the low and mid dose groups. The problem of food spillage and evaporation of the DBCP from the food bias the data toward an underestimation of the true cancer potency. Despite this fact, the data from this study gives a higher potency than that calculated from the rat data. The cancer potency for DBCP is based on the incidence of forestomach squamous cell carcinomas in the Hazelton Laboratory study, and is consistent with the incidence of stomach carcinomas in female mice in the NCI gavage study. In addition, the inhalation study conducted by NTP produced tumors at sites distal to the lung, including the forestomach. The cancer potency based on the NTP inhalation study is close to, but slightly lower than the potency derived from the Hazelton Laboratories study. The Hazelton Laboratory study was therefore taken to be the most appropriate animal data for the derivation of the cancer potency value.

Based on the calculated cancer potency derived from the animal studies, significant increases in cancer incidence would not be expected in the human occupational studies. The duration of exposure was too brief, the exposure too recent, and the number of subjects too small. In the ecological and case-control environmental studies by Jackson *et al*. (1982) and EHA (1986), a significant increase in the number of cancers would indicate that the true human cancer potency is an order of magnitude higher than that calculated from the animal studies.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of DBCP from the Hazelton Laboratories (1977) data in female CD-1 mice (Crump *et al*., 1982). The actual daily doses received by the mice were estimated to be 0, 0.3, 1.6 and 4.8 mg/kg/day (Shell Oil Company, 1986). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for DBCP.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 6.6 $(mg/kg \times day)^{-1}$ was derived (CDHS, 1988). An airborne unit risk factor was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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1,4 - DICHLOROBENZENE

CAS No: 106-46-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	147.01
Boiling point	174°C
Melting point	53.1°C
Vapor pressure	10 mm Hg @ 25°C
Air concentration conversion	1 ppm = 6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 (µg/m^3)$^{-1}$
Slope Factor: 4.0 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are several case reports of human leukemia associated with occupational exposure to chlorinated benzenes, including 1,4 - dichlorobenzene (1,4-DCB) (Girard *et al*., 1969). One case of chronic lymphocytic leukemia involved exposure to a solvent mixture of 80% ortho-, 2% meta-, and 15% para-dichlorobenzene. The association between leukemia and 1,4 - dichlorobenzene exposure was confounded by multiple chemical exposure.

Animal Studies

Loeser and Litchfield (1983) conducted a chronic inhalation carcinogenicity bioassay in male and female Alderly Park rats. In this study, groups of 76-79 rats were exposed to 0, 75, or 500 ppm p-DCB 5 hours/day, 5 days/week for 76 weeks. Control rats exhibited a high mortality rate and did not differ significantly from treated rats in overall tumor incidence (Table 1) or in the incidence of animals with multiple tumors and malignant tumors.

Table 1. Tumor incidence in rats exposed to 1,4-dichlorobenzene (DCB) in air for 76 weeks (Loeser and Litchfield, 1983)

Concentration of 1,4-DCB	Combined Tumors (males)	Combined Tumors (females)
0 ppm	39/60	55/61
75 ppm	31/60	54/61
500 ppm	35/60	53/58

A parallel experiment was conducted using groups of 75 Swiss mice of either sex (Loeser and Litchfield, 1983). In this experiment, female mice were exposed to 0, 75, or 500 ppm 1,4 - DCB for 5 hours/day, 5 days/week, for 57 weeks. A similar experiment in male mice was terminated due to high mortality due to fighting and respiratory infections. As with the rats, no significant increase in any tumor type was detected.

The National Toxicology Program (NTP, 1987) studied the carcinogenicity of 1,4 - DCB in male and female F344 rats and B6C3F1 mice via chronic (103 week) oral intubation. Male rats were given 0, 150, or 300 mg/kg 1,4 - DCB for 5 days/week for 103 weeks. Male and female mice, and female rats were given 0, 300, or 600 mg/kg for the same duration. Sentinel animals were killed periodically to test for infectious pathogenic agents. The survival of male rats given 300 mg/kg was significantly lower than controls after 97 weeks, but the survival of treated female rats was unchanged from controls. The time-weighted average doses in the study were 0, 214, and 428 mg/kg/day for the mice, and 0, 107, and 214 mg/kg/day for the rats. Male rats treated with 1,4-DCB displayed nephropathy and mineralization and hyperplasia of renal tubules. The incidence of renal tubular adenocarcinomas was also dose-dependently increased in the male rats (1/50, 3/50, or 7/50 for the 0, 107, or 214 mg/kg groups, respectively). A significant dose-dependent increase in the incidence of mononuclear cell leukemia (5/50, 7/50, or 11/50 for the 0, 107, or 214 mg/kg groups, respectively) was observed in the male rats. Additionally, an increasing trend in the incidence of mesothelioma was observed in the male rats (1/50, 0/50, 4/50, for the 0, 107, or 214 mg/kg groups, respectively).

Mice of both sexes exposed to 1,4 - DCB had significantly increased incidence of hepatocellular adenomas and carcinomas (NTP, 1987). In addition, four male mice exposed to 428 mg/kg were found to have hepatoblastomas, a rare hepatocellular carcinoma. The incidence of follicular thyroid cell adenomas was increased in female mice exposed to 428 mg/kg ($p < 0.038$). As with the male rats, male mice showed evidence of kidney tubule damage when treated with 1,4 - DCB. Females were not similarly affected.

NTP concluded from these data that 1,4 - DCB was carcinogenic to male rats, but not female rats. In addition, NTP concluded that the increased incidence of hepatocellular adenomas and carcinomas was evidence of carcinogenicity in male and female mice.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by NTP (1987) was chosen by CDHS (1988) as the key study for the development of a cancer potency value for 1,4-DCB. In the NTP (1987) study, mice and rats exhibited significant increases in several types of tumors. The mice were exposed for 5 days/week, resulting in average daily doses of 0, 214, and 428 mg/kg/day 1,4-DCB. Mice of either sex exhibited a significant increase in hepatocellular carcinomas or adenomas. The incidence of hepatocarcinomas or adenomas was 17/50, 22/49, and 40/50 in the control, 214, and 428 mg/kg/day groups, respectively. In addition, male rats showed a significant increase in kidney

adenomas and mononuclear cell leukemia. The cancer potency for 1,4-DCB was calculated from the male mouse hepatocarcinoma and adenoma data.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of 1,4-DCB from the NTP (1987) data in male B6C3F1 mice (Crump *et al*., 1982). The concentrations of 1,4-DCB given in the feed were 0, 214, or 428 mg/kg/day. The premature mortality of animals without tumors was subtracted from the sample groups. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 0.04 $[mg/kg \times day]^{-1}$ was calculated (CDHS, 1988). An airborne unit risk factor of 1.1E-5 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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3,3-DICHLOROBENZIDINE

CAS No: 91-94-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	253.1
Boiling point	402°C
Melting point	132-133°C
Vapor pressure	unknown
Air concentration conversion	1 ppm = 10.4 mg/m^3 (IARC, 1982)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.4 E-4 (µg/m^3)$^{-1}$
Slope Factor: 1.2 E+0 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The body of literature addressing the carcinogenicity of 3,3'-dichlorobenzidine in humans is scant. Three retrospective epidemiological studies of occupational exposure have been conducted, focusing on the possibility that 3,3'-dichlorobenzidine is a bladder carcinogen like its parent compound, benzidine. None of the studies approximates exposure levels.

Gerarde and Gerarde (1974) conducted a study of 175 workers involved in the manufacture and use of dichlorobenzidine in a chemical manufacturing plant in the United States between 1938 and 1957. Workers were segregated from benzidine exposure. No bladder tumors were found among the exposed workers. General population incidence of bladder tumors predicts 0-2 cases in a cohort of this size.

Gadian (1975) conducted a study of 35 British workers exposed to dichlorobenzidine who had been segregated from exposure to benzidine in a chemical plant from 1953 to 1973. Cumulative hours of exposure were tabulated for all workers. No tumors were reported among the exposed workers at the end of the study (through 1973).

MacIntyre (1975) reports on bladder tumor incidence among 225 Scottish production and service workers, 119 of which had more than 5 years of exposure to dichlorobenzidine and 36 of which were exposed more than 16 years before the time of the study. No bladder tumors were reported among the study subjects.

Animal Studies

Stula *et al.* (1975) conducted a study on ChR-CD rats (50/sex/group), exposing animals to 1000 ppm 3,3'-dichlorobenzidine in feed for life (mean survival 51 weeks), with an interim exposed group of 6 rats/group sacrificed after 12 months. Control animals receiving no added compound were observed for up to two years (mean survival 81 weeks (males) and 90 weeks (females)). Male animals showed statistically significant increases in incidences of granulocytic leukemias (9/44 treated vs. 2/44 control; $p<0.05$ by Fisher's exact test), mammary adenocarcinomas (7/44 treated vs. 0/44 control; $p<0.01$), and Zymbal gland carcinomas (8/44 treated vs. 0/44 control; $p<0.01$). Female animals only showed increased incidence of mammary adenocarcinomas (26/44 treated vs. 3/44 control; $p<0.01$).

Stula *et al.* (1978) later conducted a study on six female beagle dogs, administering 100 mg 3,3'-dichlorobenzidine in gelatin capsules 3 times/week for 6 weeks followed by 100 mg, 5 times/week for up to 7.1 years, plus 6 untreated control animals sacrificed at 8-9 years of age. One animal which died during the course of the study (3.5 years) showed no sign of tumors, whereas another animal which died at 6.6 years showed both undifferentiated liver carcinoma and papillary transitional cell carcinoma of the bladder. Among the animals surviving to the end of the study there was an increased incidence of hepatocellular carcinoma (3/4 treated vs. 0/6 control; $p<0.05$) and papillary transitional cell carcinoma of the bladder (4/4 treated vs. 0/6 control; $p<0.01$). Control animals showed a high incidence of adenocarcinoma and carcinoma of the mammary gland (4/6).

Pliss (1959) reports on carcinogenesis in Rappolovskii white rats exposed to 3,3'-dichlorobenzidine in feed for 12 months. The addition of 10-20 mg added to feed in the form of a paste (50% with water) 6 days/week resulted in an estimated total dose of 4.5 g/animal. A group of 130 animals receiving injections of octadecylamine and methylstearylamine were termed a "historical control". Twenty-two of 29 animals were examined for tumors at the time of the first tumor's appearance. Findings included tumors of Zymbal gland (7/29), mammary gland (7/29), skin (3/29), bladder (3/29), hematopoietic system (3/29), adenocarcinoma of the ileum (2/29), connective tissue (2/29), salivary gland (2/29), liver (1/29), and thyroid (1/29). No tumors were reported among "control" animals. Pliss (1959, 1963) also conducted studies exposing rats to 3,3'-dichlorobenzidine by the subcutaneous route. In the first study (Pliss, 1959), animals (25 female, 36 male) received 120 mg 3,3'-dichlorobenzidine weekly for 10-11 months. The dose was reduced to 20 mg/rat after the sixth month due to toxicity. The same "control"animals were used as with the feeding study. The author notes the appearance of tumors of the Zymbal gland (10/35), mammary gland (6/35), skin (5/35), hematopoietic system (2/35), connective tissue (2/35), salivary gland (1/35), and local subcutaneous sarcomas (7/35) among animals surviving to the time of the appearance of the first tumors.

Griswold *et al.* (1968) dosed 20 female Sprague-Dawley rats with 300 mg 3,3'-dichlorobenzidine in sesame oil by gavage (10 doses at three day intervals) and observed the animals after 9 months for incidence of mammary tumors. Control groups included a negative control (sesame oil only) and a positive control (7,12-dimethylbenz[a]anthracene). No tumors were observed in treated

animals, but a 3% incidence was observed in the negative controls and 100% incidence in positive control animals.

Osanai *et al.* (1976) treated 26 male ICR/JCL mice (plus 39 untreated control mice) with feed containing 0.1% 3,3'-dichlorobenzidine for 12 months with an interim sacrifice group at 6 months. Hepatomas were observed in all treated animals at 6 and 12 months ($p<0.01$) and among control animals at an incidence of 0%, 9.5% (2/21) and 38.55% (5/13) at 6,12, and 18 months, respectively.

Tatematse *et al.* (1977) fed 22 male Wistar rats a diet containing 0.3% 3,3'-dichlorobenzidine alone or in sequence with o-N-butyl-N-(4-hydroxybutyl)nitrosamine (0.1% in drinking water), N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (0.15% in the diet) and N-fluorenylacetamide (0.025% in the drinking water) over a four week period. Twelve untreated animals served as controls. Animals were observed for a 40 week period. Only animals receiving combined exposures showed effects which included some bladder tumors and histological changes of the liver.

Saffiotti *et al.* (1967) and Sellakumar *et al.* (1969) report on a feeding study in which Syrian golden hamsters (30/sex/group) were exposed to 0.1% or 0.3% 3,3'-dichlorobenzidine in feed; an untreated control group (30/sex) was included. No significant carcinogenic effects were observed in the 0.1% 3,3'-dichlorobenzidine group. The 0.3% 3,3'-dichlorobenzidine group, however, showed increased incidence of transitional cell carcinomas of the bladder (4/30 treated, 0/30 control; $p=0.056$ by Fisher's exact test). Other observations included some liver-cell and cholangiomatous tumors.

A single study suggests that 3,3'-dichlorobenzidine may act as a transplacental carcinogen (Golub *et al.*, 1974). Pregnant female BALB/c mice given 2 mg 3,3'-dichlorobenzidine (in 0.1 ml sesame oil) five times during the last week of pregnancy, showed increased incidence of lymphoid leukemia among the offspring of exposed animals (7/24 treated, 0/30 control; $p<0.01$). This effect, however, could also have occurred by exposure via lactation.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

An IARC (1982) review of the human epidemiological studies deemed them inadequate for evaluating carcinogencity due to the relatively small size of the cohorts, inadequate time since first exposure, and/or incomplete follow-up of exposed workers.

The only carcinogenesis studies amenable to the development of cancer potency values are those conducted by Stula *et al.* (1975, 1978) showing the induction of granulocytic leukemia, mammary adenocarcinoma, and Zymbal gland carcinoma in rats and papillary transitional cell carcinomas of the bladder and hepatocellular carcinomas in beagle dogs exposed to 3,3'-dichlorobenzidine. Limitations of the other available studies including poor study design,

inadequate scope of endpoints, and unclear interpretation of dose extrapolation, preclude the development of cancer potency values from these studies.

Methodology

The most sensitive experimentally determined endpoint for tumor development is mammary adenocarcinoma induction in female rats exposed to 3,3'-dichlorobenzidine (26/44 treated, 3/44 control) (Stula *et al*., 1975). A linearized multistage procedure (CDHS, 1985) applied to these data resulted in an estimation of the upper 95% confidence bound of cancer potency (q_1^*) of 0.023 $(mg/kg\text{-}day)^{-1}$. With a study duration of 49.9 weeks for females (T_e) and a natural lifespan assumption of 104 weeks (T), the cancer potency for animals (q_{animal}) was derived to be 0.21 $(mg/kg\text{-}day)^{-1}$ from the following relationship:

$$q_{animal} = q_1^* \times (T/T_e)^3$$

Human cancer potency (q_{human}) of 1.2 $(mg/kg\text{-}day)^{-1}$ based upon body weight assumptions of 0.35 kg for female rats (bw_a) and 70 kg for humans (bw_h) and the following relationship:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

A unit risk value of 3.4 E-4 $(\mu g/m^3)^{-1}$ based upon air concentrations was derived by OEHHA/ATES assuming a human breathing rate of 20 m^3/day, a human body weight of 70 kg, and 100% fractional absorption after inhalation exposure.

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1, 1-DICHLOROETHANE

CAS No: 75-34-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	98.97
Boiling point	57.3°C (ATSDR, 1990)
Melting point	-96.7°C (ATSDR, 1990)
Vapor pressure	230 mmHg at 25°C (ATSDR, 1990)
Air concentration conversion	1 ppm = 4.05 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.6 E-6 $(\mu g/m^3)^{-1}$
Slope Factor: 5.7 E-3 $(mg/kg\text{-}day)^{-1}$
[Female rat mammary gland adenocarcinoma tumor data (NCI, 1977), contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,1-dichloroethane in humans are known to exist.

Animal Studies

Male and female Osborne-Mendel rats and $B6C3F_1$ mice were exposed to 1,1-dichloroethane dissolved in corn oil by gavage (NCI, 1977). The study design is summarized in Tables 1a and 1b. Dosing was performed once/day, 5 days/week. Dosing of the low- and high-dose mouse treatment groups was performed cyclically in the latter part of the experimental period; one exposure-free week was followed by 4 weeks of exposure.

Dose-related increases were noted in mammary adenocarcinomas and hemangiosarcomas in female rats. Statistically significant increases were observed in endometrial stromal polyps in high-dose female mice (4/46 compared to 0/79 for controls, $p = 0.017$) and in hepatocellular carcinomas in high-dose male mice (8/32 compared to 6/72 in pooled vehicle controls, $p = 0.027$). Female rat tumor incidence data is listed in Table 2.

Klaunig *et al*. (1986) exposed male $B6C3F_1$ mice to 1,1-dichloroethane in drinking water for 52 weeks. Exposure levels were 0, 835 and 2500 mg/l. Group sizes were 35 mice/group; 10 mice/group were killed after 24 weeks. Histology was only performed on kidney, liver and lung

samples. No treatment-related increase in tumor incidence was noted. However, histological examination was only performed on a limited number of tissues, and only male mice were used.

Table 1a. Study design for carcinogenicity bioassay of 1,1-dichloroethane (1,1-DCE): Osborne-Mendel rats (NCI, 1977)

Sex	Group	Group Size	1,1-DCE dose (mg/kg bw)	Observation period (weeks)		Time-weighted average dosage[1] (78 weeks)
				Treated	Untreated	
Male	Untreated control	20	0		109	0
	Vehicle control	20	0	78	33	0
	Low dose	50	350	8		382
			450	23		
			450[2]	37	10	
			0		33	
	High dose	50	700	8		764
			900	23		
			900[2]	37	10	
			0		33	
Female	Untreated control	20	0		105	0
	Vehicle control	20	0	78	33	0
	Low dose	50	750	8		475
			900	9		
			450	14		
			450[2]	37	10	
			0		33	
	High dose	50	1500	8		950
			1800	9		
			900	14		
			900[2]	37	10	
			0		33	

1. Time weighted average dosage = $\sum$ [(dosage $\times$ number of weeks) / 78 weeks]
2. Gavage doses were cyclically administered; one exposure-free week was followed by 4 weeks (5 days/week) of exposure at the exposure level indicated.

Table 1b. Study design for carcinogenicity bioassay of 1,1-dichloroethane (1,1-DCE): $B6C3F_1$ mice (NCI, 1977)

Sex	Group	Group Size	1,1-DCE dose (mg/kg bw)	Observation period (weeks)		Time-weighted average dosage[1] (78 weeks)
				Treated	Untreated	
Male	Untreated control	20	0		90	0
	Vehicle control	20	0	78	12	0
	Low dose	50	900	6		1442
			1200	3		
			1500	69		
			0		13	
	High dose	50	1800	6		2885
			2400	3		
			3000	69		
			0		13	
Female	Untreated control	20	0		91	0
	Vehicle control	20	0	78	12	0
	Low dose	50	900	6		1665
			1200	3		
			1500	11		
			1800	58		
			0		13	
	High dose	50	1800	6		3331
			2400	3		
			3000	11		
			3600	58		
			0		13	

1. Time weighted average dosage = $\sum$ [(dosage $\times$ number of weeks) / 78 weeks]

Table 2 Tumor induction in female Osborne-Mendel rats after gavage exposure to 1,2-dichloroethane (NCI, 1977)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
vehicle control	0	mammary adenocarcinomas	0/20
		hemangiosarcomas	0/40
low dose	238	mammary adenocarcinomas	1/50
		hemangiosarcomas	0/50
high dose	477	mammary adenocarcinomas	5/50
		hemangiosarcomas	4/50

1. Dose as reported by Gold *et al*., 1984. 2. Tumor incidence as reported by Gold *et al*., 1984

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1984) list the results of the NCI (1977) gavage studies in male and female $B6C3F_1$ mice and Osborne Mendel rats. Cancer potency for 1, 1-dichloroethane is based on mammary gland adenocarcinomas observed in female rats, the most sensitive of the species/sex combinations tested (see Table 2). Because female rat survival was poor in this study, the potency was derived using a time-to-tumor analysis (Crump *et al*., 1991; Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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DI-(2-ETHYLHEXYL)PHTHALATE

CAS No: 117-81-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	390.54
Boiling point	230°C @ 5 mm Hg
Melting point	-50°C
Vapor pressure	1.32 mm Hg @ 200°C
Air concentration conversion	1 ppm = 16.0 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.4 E-6 (µg/m^3)$^{-1}$
Slope Factor: 8.4 E-3 (mg/kg-day)$^{-1}$
[calculated from a cancer potency value derived for a Proposed Maximum Contaminant Level (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Thiess *et al.* (1978; reviewed by US EPA, 1994) report on a study of mortality among 221 workers involved in di-(2-ethylhexyl)phthalate (DEHP) production. Potential exposure periods range from 3 months to 24 years and the mean follow-up period was 11.5 years. Among workers exposed for more than 15 years, incidences of pancreatic carcinoma (1 case) and uremia (1 case with urethral and bladder papillomas) were elevated over incidence in the corresponding age group of the general population. No quantitation of exposure levels was reported.

Animal Studies

The National Toxicology Program (NTP, 1982; Kluwe *et al.*,1982) assayed the carcinogenic effects of di-(2-ethylhexyl)phthalate on rats and mice. Fischer F344 rats (50/sex/group) were treated with diet containing 0, 6000, or 12000 ppm DEHP for 103 weeks. B6C3F$_1$ mice (50/sex/group) were treated with diet containing 0, 3000, or 6000 ppm DEHP for 103 weeks. Survivors were sacrificed and examined histologically at 105 weeks. Survival of rats was not found to be significantly influenced by DEHP treatment. Increased incidence of hepatocellular carcinoma or hepatic neoplastic nodules was reported in male and female high-dose treated rats (see Table 1). The increase in incidence was found to be dose-related ($p<0.01$). Among treated high-dose male and female mice, and low-dose female mice, hepatocellular carcinoma incidence was increased. The increase in incidence was found to be dose-related ($p<0.05$).

Table 1. Incidence of hepatocellular carcinoma in male and female $B6C3F_1$ mice and F344 rats fed diet containing DEHP (NTP, 1982).

species	treatment[1] (ppm in diet)	hepatocellular carcinoma incidence	
		male	female
F344 rats	0	3/50	0/50
	6,000	6/49	2/49
	12,000	12/49[2]	8/50[3]
$B6C3F_1$ mice	0	9/50	0/50
	3,000	14/48	7/50[3]
	6,000	19/50[2]	17/50[4]

[1] Fischer F344 rats were treated with 0, 6000, or 12000 ppm DEHP in their diet for 103 weeks. $B6C3F_1$ mice were treated with 0, 3000, or 6000 ppm DEHP in their diet for 103 weeks. Survivors were sacrificed after 105 weeks.
[2] $p<0.05$. [3] $p<0.01$. [4] $p<0.001$.

Carpenter *et al.* (1953) maintained 2 month old Sherman rats (32/sex/group) on a diet containing 0, 400, 1300, or 4000 ppm DEHP up to two years. Animals were sacrificed at one year with the exception of a subgroup of a maximum of 8 rats/sex/dose which were exposed for an additional year. A group of 80 F_1 generation rats, the progeny of females in the highest dose group exposed for more than 120 days, were exposed for one year to diet containing 4000 ppm DEHP. Survivors were sacrificed after one year. No malignant tumors were observed among treated animals. Three rats in the 4000 ppm DEHP dose group, four in the 1300 dose group, two in the 400 ppm dose group, and five in the control group were reported to have benign tumors. Two benign tumors in the treated F_1 rats (vs. one in the control group) had benign tumors. Mortality at two years was reported to be 70.3% among control animals and between 60 and 70% among the treated groups. Poor survival of animals precluded evaluation of carcinogenicity from this study.

Carpenter *et al.* (1953) also treated hybrid guinea pigs (~23/sex/dose) with diet containing 0, 1300, or 4000 ppm DEHP for 1 year, at which time animals were sacrificed. Survival among exposed animals was decreased. No carcinogenic effects were observed.

Carpenter *et al.* (1953) also treated 4 dogs with gelatin capsules containing a volume of 0.03 ml/kg body weight DEHP five days per week for 19 doses, then with 0.06 ml/kg body weight DEHP for 240 doses. Four control animals were also included in the study. No tumors were observed in treated or control animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The only data appropriate for the development of a cancer potency value come from the NTP (1982) study which showed a dose-related effect of DEHP on the incidence of hepatocellular carcinoma in Fischer 344 rats and $B6C3F_1$ mice. This study was conducted by standard protocols with an adequate number of animals and thorough reporting of results.

Methodology

For the purpose of developing a cancer potency in humans, US EPA (1986, 1987) converted the exposure levels of rats and mice in the NTP (1982) study to human equivalent doses (HEDs). Dosage levels were first converted from parts per million in the diet to mg/kg-day based upon reported food disappearance rates. The resulting daily low and high dose estimates were 322 and 674 mg/kg-day for male rats, 394 and 774 mg/kg-day for female rats, 672 and 1325 mg/kg-day for male mice, and 799 and 1821 mg/kg-day for female mice. HEDs were based on the following relationship, with D the applied dose level, bw_a the experimental animal body weight, bw_h the assumed human body weight, l_e the length of exposure, L_e the length of the study, and L the lifespan of the animal:

$$HED = D \times \frac{l_e}{L_e} \times \left(\frac{bw_a}{bw_h}\right)^{\frac{1}{3}} \times \left(\frac{L_e}{L}\right)^3$$

Using the derived HED values, US EPA (1987) applied the multistage procedure of Howe and Crump (Global 82; 1982) to the combined incidence data of hepatocellular carcinomas and neoplastic nodules reported by NTP (1982). The resulting upper 95% confidence bounds on the cancer potency (q_{human}) are presented in Table 2. The highest, and thus most sensitive, cancer potency value is derived from the incidence of hepatocellular carcinomas in male $B6C3F_1$ mice, with a q_{human} value of 8.4 E-3 $(mg/kg\text{-}day)^{-1}$. Selection of the cancer potency value for DEHP comes from the most sensitive site and species of tumor induction in experimental animals in the absence of human data appropriate for developing a potency value.

Table 2. Human cancer potency values derived by US EPA (1986, 1987) from the NTP (1982) study.

species	sex	q_{human} $[(mg/kg\text{-}day)^{-1}]$
F344 rats	male	2.95 E-3
	female	3.52 E-3
$B6C3F_1$ mice	male	8.36 E-3
	female	4.73 E-3

A unit risk value of 2.4 E-6 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES assuming a 70 kg average human body weight, 20 m^3/day human breathing rate, and 100% fractional absorption.

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p-DIMETHYLAMINOAZOBENZENE

CAS No: 60-11-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	225.28
Boiling point	not available
Melting point	114-117 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 9.214 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-3 (µg/m^3)$^{-1}$
Slope Factor: 4.6 E+0 (mg/kg-day)$^{-1}$
[Female rat liver tumor data (Kirby and Peacock, 1947), contained in Gold *et al.* database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992), cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-dimethylaminoazobenzene (DAB) in humans are known to exist.

Animal Studies

IARC (1974) reviewed a number of studies on the carcinogenic potential of DAB in animals. DAB was initially reported by Kinosita (1937) to induce liver tumors in rats after dietary exposure; tumors were produced after 50 or more days of treatment (smallest total dose, 176 mg DAB). Sherman, Wistar and Evans rats were found to be equally susceptible to the induction of liver tumors after exposure to diets containing 600 mg/kg DAB (Sugiura and Rhoads, 1941).

Kirby and Peacock (1947) exposed male and female Wistar-derived rats to a low-protein diet (12% casein) containing 0 or 600 mg/kg diet DAB. Group sizes were 8 animals/sex/group except for treated females, where the group consisted of 7 animals. Four male rats received treated diet for 28 weeks, followed by control diet; the other animals received treated diet for 33 weeks. At the end of the treatment period, all animals received control diet until sacrifice at 52 weeks. Both male and female rats developed hepatomas; Gold *et al*. (1984) list a tumor incidence of 0/8 and 5/7 for control and treated (average dose, 20.9 mg/kg-day) females, respectively.

Druckrey and Küpfmüller (1948; reviewed by IARC, 1975) exposed rats to 1, 3, 10, 20 or 30 mg DAB/day by gavage for the life of the animals. All doses induced the formation of liver tumors; the induction time was inversely proportional to the dose, ranging from 34 days (30 mg/day) to 700 days (1 mg/day). For exposure groups in the 3-30 mg/day range, the total carcinogenic dose was about 1000 mg. Daily exposures of 0.1 or 0.3 mg/rat did not induce tumors.

Druckrey (1967) exposed rats to 5 mg DAB/rat by gavage for 40, 60, 100, 140 or 200 days, then observed the animals for the remainder of their lifespan. Percent incidences of liver carcinomas were 20, 26, 49, 80 and 81, respectively.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The feeding study by Kirby and Peacock (1947) conducted in Wistar-derived albino rats is listed in Gold *et al*. (1984). Cancer potency is based on liver tumors in the female rats.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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2,4-DINITROTOLUENE

CAS No: 121-14-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	182.14
Boiling point	300°C
Melting point	71°C
Vapor pressure	0.00014 mm Hg @ 25°C
Air concentration conversion	1 ppm = 7.4 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 8.9 E-5 (µg/m^3)$^{-1}$
Slope Factor: 3.1 E-1 (mg/kg-day)$^{-1}$
[calculated from a potency factor derived by US EPA (1987) and adopted by CDHS (see Final Statement of Reasons)]

III. CARCINOGENIC EFFECTS

Human Studies

No data are available addressing the carcinogenicity of 2,4-dinitrotoluene (2,4-DNT) in humans.

Animal Studies

Lee *et al.* (1978) exposed male and female CD rats to practical grade 2,4-DNT in feed at concentrations of 0, 15, 100, and 700 ppm for 720 days. Animals were sacrificed at 750 days. Decreased weight gain and lifespan were observed among animals in the highest treatment group. Noncancer toxic effects observed included toxic anemia and aspermatogenesis. Tumors observed included fibromas of the connective tissue of male rats and fibroadenoma of the mammary gland of female rats. The incidence data for liver and mammary tumors in female rats are presented in Table 1. Significantly increased incidence was found in the highest dose group for liver tumors ($p = 4 \times 10^{-4}$; Fisher's exact test), mammary gland tumors ($p = 1.75 \times 10^{-4}$), and combined mammary gland and liver tumors ($p = 7 \times 10^{-5}$). Mammary tumor incidence among male rats was 1/37, 0/37, 0/29, and 17/23 in the 0, 15, 100, and 700 ppm 2,4-DNT dose groups, respectively. Only the highest dose group showed significantly increased tumor incidence ($p = 4 \times 10^{-9}$).

Table 1. Incidence of liver and mammary gland tumors among female CD rats exposed to practical grade 2,4-dinitrotoluene (2,4-DNT) in feed for 24 months (Lee *et al.*, 1978).

treatment level (ppm)	tumor incidence		
	liver[1]	mammary gland[2]	combined
0	0/31	11/31	11/31
15	3/43	12/43	13/43
100	3/35	18/35	18/35
700	30/42	34/43	35/43

[1] Tumor incidence includes neoplastic nodules and hepatocellular carcinoma of the liver.
[2] Tumor incidence includes adenoma, fibroadenoma, fibroma, or adenocarcinoma of the mammary gland.

The National Cancer Institute (NCI, 1978) conducted a study exposing Fischer rats and $B6C3F_1$ mice to practical-grade 2,4-DNT (>95% pure). Male and female Fischer rats (50/sex/group) were exposed to feed containing 0.02% or 0.008% 2,4-DNT (time-weighted concentrations). Control groups consisted of 25 rats/sex for the high-dose group and 50 rats/sex for the low-dose group. The treatment period was 78 weeks long and the observation period continued for 26 weeks. Among treated male rats in both high- and low-dose groups, the incidence of benign fibroma of the skin and subcutaneous tissue was increased over controls (high-dose: 13/49 treated vs. 0/25 control, $p = 0.003$; low-dose: 7/49 treated vs. 0/46 control, $p = 0.008$ by Fisher's exact test). Among treated female rats in the high-dose group, the incidence of fibroadenoma of the mammary gland was increased over control animals (23/50 treated vs. 4/23 control, $p = 0.016$).

In the same study (NCI, 1978), male and female $B6C3F_1$ mice (50/sex/group) were treated with diet containing 0.04% or 0.008% 2,4-DNT (time-weighted concentrations). Groups of 50 mice/sex served as controls for the high- and low-dose groups. The treatment period lasted 78 weeks and the animals were observed for an additional 13 weeks. No significant increase in tumor incidence was observed among treated animals.

Ellis *et al.* (1979) (also reported by Lee *et al.*,1985) exposed male and female CD (Sprague-Dawley) rats (38/sex/group) to 0, 15, 100, or 700 ppm 2,4-DNT in feed. At 12 months, 8 rats/group were sacrificed for necropsy; the remainder were sacrificed at 24 months. Cumulative deaths during the course of the study ranged from 55 to 100% in male rats and 60 to 97% in female rats, including control animals. Histopathological outcomes of animals that died during the course of the experiment (but after 52 weeks) were included in the final incidence data along with the incidence data among survivors. Tumors showing statistically significant increases ($p<0.05$ by Fisher's exact test) were hepatocellular carcinomas and mammary gland tumors among female rats in the highest dose group. Hepatocellular carcinomas were reported in 18/34 treated high-dose female rats vs. 0/23 control rats ($p = 4.3 \times 10^{-6}$). Mammary gland tumors, including both benign and malignant tumors of epithelial or mesenchymal origin, were reported in 33/35 treated high-dose female rats vs. 11/23 control rats ($p < 0.0001$).

Ellis *et al.*(1979) (also reported by Hong *et al.*, 1985) exposed male and female CD-1 mice (38/sex/group) to 0, 100, 700, or 5000 ppm 2,4-DNT in feed as described in the rat study above. Since over 70% of the mice in the highest dose group died before 12 months, these animals were not included in the analysis. Mortality among the remaining dose groups and controls ranged from 70 to 85%. Tumor incidence data were drawn from animals surviving at least 12 months. A significantly increased incidence of renal tumors was found among male mice in the 700 ppm 2,4-DNT dose group (19/28 treated vs. 0/33 control; $p = 1.32 \times 10^{-9}$, Fisher's exact test). Renal tumor types included cystic papillary adenomas, solid renal cell carcinomas, and cystic papillary carcinomas. No significantly increased tumor incidence was reported among female mice.

Ellis *et al.* (1979, 1985) treated beagle dogs (6/sex/group) with 2,4-DNT in gelatin capsules daily for 2 years at dose rates of 0, 0.2, 1.5, or 10 mg/kg body weight. The highest dose was lethal to five of the 12 treated animals. Throrough examination of all animals upon sacrifice showed no evidence of carcinogenicity of 2,4-DNT.

The Chemical Industry Institute of Toxicology (CIIT, 1982) exposed male and female F344 rats (130/sex/dose) to technical grade DNT (76% 2,4-DNT and 19% 2,6-DNT) feed such that daily dosing was 0, 3.5, 10.0, and 35.0 mg/kg-day. The entire high-dose group was sacrificed at 55 weeks due to significantly reduced survival. Twenty rats (/sex) were examined histopathologically at this time. The animals in the remaining dose groups were sacrificed at the scheduled time of 104 weeks. The incidences of hepatocellular carcinoma and neoplastic nodules of the liver are reported in Table 1. Cholangiocarcinomas were also reported in 3/20 high-dose male rats (at 55 weeks) and 2/23 mid-dose male rats (at 104 weeks).

Table 1. Tumor incidence in male and female F344 rats exposed to technical grade dinitrotoluene (DNT) in feed (CIIT, 1982).

	males (mg/kg-day)				females (mg/kg-day)			
tumor type	0	3.5	10.0	35.0*	0	3.5	10.0	35.0*
hepatocellular carcinoma	1/61	9/70	22/23	20/20	0/57	0/61	40/68	11/20
neoplastic nodules	9/61	11/70	16/23	5/20	5/57	12/61	53/68	12/20

*All the high-dose group animals were sacrificed at 55 weeks due to significantly reduced survival. Histopathological examinations were performed on 20 rats/sex.

Leonard *et al.* (1987) exposed 20 male CDF(F344)/CrlBR rats to 2,4-DNT in the diet for 12 months such that daily dose rate was 27 mg/kg-day. No evidence of carcinogenicity was found, however, the study was short in duration and the number of animals was small.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The US EPA (1980) derived a cancer potency value based on the tumor incidence data in the study by Lee *et al.* (1978) showing the induction of liver and mammary tumors in female CD rats. This study was selected over the NCI (1978) study because of published reservations by NCI concerning the adequacy of the study for estimating cancer potency in humans.

Methodology

The US EPA (1980) calculated a "transformed" dose rate of 0, 0.71, 3.9, and 34.0 mg/kg-day for the animals in the study by Lee *et al.* (1978) exposed to 0, 15 100 and 700 ppm 2,4-DNT in their diet, respectively. A linearized multistage procedure was applied to the combined mammary gland and liver tumor incidence data presented in Table 1 in order to calculate an animal cancer potency value (q_{animal}). The calculated q_{animal} was 0.058 $(mg/kg\text{-}day)^{-1}$. The q_{animal} was converted to a human cancer potency (q_{humna}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species (Lee *et al.*, 1978; bw_{animal} = 0.464 kg) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting q_{human} is 0.31 $(mg/kg\text{-}day)^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 8.9 E-5 $(\mu g/m^3)^{-1}$.

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1,4-DIOXANE

CAS No: 123-91-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From ACGIH, 1994)

Molecular weight	88.1
Boiling point	101.1°C
Melting point	11.8°C
Vapor pressure	29 mm Hg @ 20°C
Air concentration conversion	1 ppm = 3.6 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: (7.7 E-6 µg/m^3)$^{-1}$
Slope Factor: 2.7 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1989)]

III. CARCINOGENIC EFFECTS

Human Studies

The two human epidemiological studies of the potential carcinogenicity of 1,4-dioxane (Thiess *et al*. (1976); Buffler *et al*. (1978)) did not show significant changes in the incidence of carcinogenicity. However, neither study had sufficient statistical power to detect moderate changes in cancer incidence due to the small size of the sample groups or the short duration of the studies.

In the study by Thiess *et al*. (1976), 74 German workers were exposed to various concentrations of 1,4-dioxane for an average of 24.9 years. Of the 74 workers, 24 were working at the end of the follow-up period (1964 - 1974), 23 were no longer working, 15 had retired, and 12 had died. Of the 12 deaths, two were attributed to neoplastic diseases (1 lamellar epithelial carcinoma and 1 myelofibrotic leukemia). The expected number of deaths during this period in the cohort was 14.5, based on Federal Republic of Germany mortality statistics. The overall death rate and the cancer death rate were not significantly increased over controls.

Buffler *et al*. (1978) studied the mortality of 165 workers exposed to 1,4-dioxane in a dioxane-manufacturing and processing facility in Texas. The employees were exposed to dioxane for at least 1-month up to 21 years (April, 1954 to June, 1975), and were divided into two cohorts. The cohort of manufacturing workers was composed of 100 individuals, and the processing workers numbered 65. The concentrations of dioxane in the workplaces were less than 25 ppm. Seven deaths occurred in the manufacturing cohort (4.9 expected), two from neoplasms (0.9 expected). Five deaths occurred in the processing cohort (4.9 expected), one from cancer (0.8 expected). These mortality and cancer rates were not higher than the expected from Texas age- and sex-

specific death rates for 1960-1969. Due to the small sample size and short exposure period of the study, the authors concluded that the negative results were not conclusive.

Animal Studies

Male Wistar rats (n = 26) were given drinking water containing 1% dioxane for 63 weeks (Argus *et al*., 1965). A group of 9 rats given untreated water were used as controls. Six hepatomas, one kidney tumor, and one case of leukemia were found in the treated animals. One lymphosarcoma was found in the control group. The increased incidence of cancer in the treated animals was not statistically significant ($p < 0.05$). However, due to the small size of the control group, this study was of very limited sensitivity, and therefore inconclusive.

Another drinking water study in male rats was conducted by Hoch-Ligeti *et al*. (1969) and further reported on by Argus *et al*. (1973). In this study, male Charles River rats (30 per group) were given 0, 0.75, 1.0, 1.4, or 1.8% dioxane in their drinking water from 2-3 months of age for 13 months. Animals were killed 16 months following treatment or earlier if tumors in the nasal cavity were observed. Survival data was not reported. Nasal histological examinations were only performed on animals with grossly visible tumors. The incidence of tumors found in this study are presented in Table 1.

Table 1. Tumor incidence in male Charles River rats exposed to 1,4-dioxane in drinking water (Hoch-Ligeti *et al*., 1969; Argus *et al*., 1973).

	Tumor Incidence				
1,4-Dioxane Concentration (%)	0	0.75	1.0	1.4	1.8
Hepatocarcinomas	0/30	0/30	0/30	2/30	2/30
Nasal tumors	0/30	1/30	1/30	2/30	2/30
Hepatic tumors (total)	NR	4/30	8/30	16/30	25/30

NR = Not reported

Kociba *et al*. (1974) studied the effects of dioxane in the drinking water of male and female Sherman rats. Rats (60/sex/group) were exposed to 0, 0.01, 0.1, or 1.0% dioxane for 2 years. Actual dosages of dioxane were estimated using drinking water consumption and body weight data. The dosages were 0, 9, 94, or 1015 mg/kg/day for the males, and 0, 14, 148, or 1599 mg/kg/day in females. Because the tumor incidence data are averaged for the combined male and female responses, the doses were also averaged. Mortality in the combined high dose group was 45% after 1 year of exposure, compared with 12% in the control group. The tumor incidence data is summarized in Table 2.

King *et al*. (1975) exposed male and female B6C3F1 mice (50/sex/group) to dioxane in the drinking water for 40-43 weeks. Concentrations of dioxane used were 0, 0.5, or 1.0 %. No tumors were observed in any group at the end of the treatment period. According to IARC (1976), the duration of this study was insufficient to detect hepatocarcinoma, the tumor most commonly found in the National Cancer Institute (NCI, 1978) study.

Table 2. Tumor incidence in male and female Sherman rats exposed to dioxane in drinking water (Kociba *et al*., 1974).

	Tumor Incidence			
1,4-Dioxane Concentration (%)	0	0.01	0.1	1.0
Hepatocarcinomas	1/120	0/120	1/120	10/120
Nasal tumors	0/120	NR	NR	3/120

NR = Not reported

The NCI conducted a bioassay on male and female B6C3F1 mice (50/sex/group) given 0, 0.5, or 1.0% dioxane in the drinking water from 5 weeks to 90 weeks (NCI, 1978). Mortality of the male rats was only 10% in the male mice after 91 weeks. Mortality in the female mice increased with increasing dose, up to 44% in the high dose group. Tumor incidence data from this study is presented in Table 3. The incidence of hepatocarcinomas was significantly increased in both the male and female mice exposed to the low and high concentrations of dioxane, compared with controls.

Table 3. Tumor incidence in male and female B6C3F1 mice exposed to 1,4-dioxane in the drinking water (NCI, 1978).

	Tumor Incidence		
1,4-dioxane Concentration	0	0.5	1.0
Hepatocarcinomas (males)	2/49	18/50	24/47
Hepatocarcinomas (females)	0/50	12/48	29/37

In addition to the mouse study. the National Cancer Institute (1978) also exposed male and female Osborne-Mendel rats to 0, 0.1, or 1.0 % dioxane in their drinking water for 110 or 90 weeks, respectively. The incidences of nasal tumors in these groups were 0/33, 12/33, and 16/33 in the males, and 0/34, 10/35, and 8/35 in the females.

Male guinea pigs (20/group) were exposed to 0 or 0.5-2.0% dioxane in the drinking water for 23 months. After 28 months, the animals were killed and tumor incidence was recorded. Tumor incidences in the treated animals included 3 animals with hepatomas, 2 with gall bladder carcinomas, and one with adenoma of the kidney. Tumors were not found in the controls (n = 10). Although the cancer incidences were not significantly different from the controls, IARC (1976) concluded that dioxane caused liver and gall bladder tumors.

In an inhalation study, Torkelson *et al*. (1974) exposed groups of 288 male or female Wistar rats to 111 ppm 1,4-dioxane for 7 hours/day, 5 days/week, for 2 years. Control rats (192 male or female rats) were exposed to filtered room air. Weight gain among males and females was not

affected by dioxane treatment compared with controls. Survival rates were not significantly different between control and treated rats. Similarly, the tumor incidence was not significantly different with dioxane treatment. The estimated equivalent dose rate from the inhalation study was 100 mg/kg/day, based on default values for rat body weight and breathing rate. This estimated dose is much lower than that used in the drinking water studies described above.

Male and female Swiss-Webster mice (30/sex/group) were exposed dermally to an unspecified concentration of dioxane in acetone 3 times/week (King *et al*., 1975). Dioxane was tested either as a complete carcinogen for 60 weeks, or as a promoter, following a single exposure to DMBA followed by 59-week exposure to dioxane. Control mice were treated with the acetone vehicle alone or with DMBA. Dioxane was a significant promoter of skin carcinomas compared to controls treated with DMBA only. However, no significant increase in skin papillomas or carcinomas was observed in the test for complete carcinogenicity.

The tumor-intitiating properties of dioxane were investigated using the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) in Sencar mice (40 females/group) (Bull *et al*., 1986). Mice were exposed to a single oral, topical, or subcutaneous dose of 1,000 mg/kg dioxane, followed by TPA in acetone 3 times per week for up to 52 weeks. No significant increase in skin tumor incidence was reported in the mice, however, tumor incidence was not reported and length of observation was not specified.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Five studies (Argus *et al*., 1965; Hoch-Ligeti *et al*., 1969; Argus *et al*., 1973; Kociba *et al*., 1974; and NCI, 1978) allow the estimation of cancer potency values for dioxane. Of these studies, only the Kociba *et al*. (1974) and NCI (1978) studies were considered for the determination of the cancer potency factor for dioxane.

In the Argus *et al*. (1965) study, 26 adult male Wistar rats were given drinking water containing 1% dioxane for 63 weeks. The estimated dose of dioxane by the authors was 300 mg/day. The incidence of liver hepatomas (6/26) in the treated animals was significantly higher than in untreated control animals (0/9) but not significantly different from historical control animals. The cancer incidence in the treated animals is considered biologically significant, but is not quantitatively suitable for use as the basis of a cancer potency factor for dioxane.

The Hoch-Ligeti *et al*. (1969) and Argus *et al*. (1973) study failed to demonstrate significant differences in tumor incidences between treated and control rats. The trend for increasing tumors was marginally signficant ($p < 0.07$). When analyzed, these data yeild a human cancer potency factor of 2.0×10^3 to 5.8×10^3 $(mg/kg/day)^{-1}$.

In the Kociba *et al*. (1974) study, 60 male and female Sherman rats were exposed to concentrations of dioxane of 0, 0.01, 0.1, and 1.0 % for 716 days. The tumor incidence for the combined male and female data set was 1/120, 0/120, 1/120, and 10/120. Using the multistage

procedure and an interspecies scaling factor, an estimate for human cancer potency of dioxane was 5.7 x 10^{-4} $(mg/kg/day)^{-1}$. This dataset was not used since tumor incidences for males and females were averaged.

The National Cancer Institute (1978) exposed male and female Osborne-Mendel rats to 0, 0.1, or 1.0 % dioxane in their drinking water for 110 or 90 weeks, respectively. The incidence of nasal tumors were 0/33, 12/33, and 16/33 in the males, and 0/34, 10/35, and 8/35 in the females. From measured water consumption and body weight data, the human cancer potency from a multistage polynomial fit of these data was 9.5 x 10^{-3} $(mg/kg/day)^{-1}$ from male rat data, and 4.9 x 10^{-3} $(mg/kg/day)^{-1}$ from female rat data. An adjustment for early mortality following the procedure of EPA (1988) yielded cancer potencies of 1.1 x 10^{-2} $(mg/kg/day)^{-1}$ and 6.0 x 10^{-3} $(mg/kg/day)^{-1}$ from male and female rat data, respectively. The NCI (1978) study using B6C3F1 mice was used as the basis for the cancer potency for dioxane. This study contained the best data on the most sensitive species and sex, and the most sensitive target tissue. In this study, 50 male or female mice were exposed to 0, 0.5, or 1.0% dioxane for 90 weeks. Average doses were determined from weekly measurements of water consumption. The estimated doses were 0, 720, and 830 mg/kg/day for the males and 0, 380, and 860 mg/kg/day for the females. The incidence of hepatocarcinomas were 2/49, 18/50, and 24/47 for males, and 0/50, 12/48, and 29/37 for the females. The incidence of hepatocarcinomas or adenomas were 8/49, 19/50, and 28/47 in males, and 0/50, 21/48, and 35/37 in females.

Methodology

A linearized multistage procedure (CDHS, 1985) was applied to the female mouse combined hepatocellular carcinoma and adenoma incidence from the NCI (1978) study. The animal cancer potencies were 8.3 x 10^{-4} and 1.4 x 10^{-3} $(mg/kg/day)^{-1}$, for the males and females, respectively. The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The animal cancer potencies were therefore adjusted for the short duration of the experiment, using the factor $(104/90)^3$. A value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse). Body weights for interspecies scaling were assumed to be 0.04 and 0.035 kg for males and females, respectively. The combined incidence of hepatocarcinomas and adenomas in males and females gave human cancer potencies of 1.5 x 10^{-2}, and 2.7 x 10^{-2} $(mg/kg/day)^{-1}$, respectively. The combined incidence of hepatocarcinomas and adenomas in females was used to derive the human cancer potency for dioxane of 2.7 x 10^{-2} $(mg/kg/day)^{-1}$. The airborne unit risk factor for dioxane of 7.7 E-6 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES assuming a human body weight of 70 kg and an inhalation rate of 20 m^3/day.

V. REFERENCES

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EPICHLOROHYDRIN

CAS No: 106-89-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	92.5
Boiling point	116.5°C
Melting point	-48°C
Vapor pressure	10 mm Hg at 16.6°C
Air concentration conversion	1 ppm = 3.79 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 8.0 E-2 $(mg/kg\text{-}day)^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

A retrospective cohort mortality study of 533 white male Dow Chemical Company employees with potential epichlorohydrin (ECH) exposure for at least 1 month between October 1957 and November 1976 was performed by Shellenberger *et al*. (1979; reviewed by US EPA, 1984). Two cancer deaths were observed; this was less than the number expected (3.5) for the entire group. However, in a review of this study, US EPA (1984) pointed out that this study is inadequate for ECH carcinogenicity evaluation because of low exposures, short exposure duration, a short study period and the very young age of the cohort.

Enterline (1978, 1981; reviewed by US EPA, 1984) conducted a retrospective cohort mortality study of epichlorohydrin workers for Shell Oil Company. The cohort consisted of 864 workers at Shell plants in Louisiana and Texas; deaths were compared by cause with expected deaths in Louisiana and Texas, respectively. Study data were analyzed by vital status as of December 31, 1977 and as of December 31, 1979 (reported by Enterline in 1978 and 1981, respectively) for the cohort exposed to ECH for at least 3 months before January 1, 1966. Overall mortality in the ECH-exposed group was not increased compared to controls; a non-statistically significant increase in respiratory cancer and leukemias was reported (standardized mortality ratios (SMRs) of 146.2 and 224.7, respectively). Additionally, the data reported in 1978 indicated an apparent increase with increasing latent period since 11 of 12 of the respiratory cancer or leukemia deaths occurred in workers 15 or more years after first exposure. The possibility existed that increasing observation time would reveal more respiratory cancer/leukemia deaths. However, the 1981 report (Enterline, 1981) including the most recent data indicated that the SMRs for both respiratory cancer and leukemia in the ECH-exposed group decreased, especially for those with greater than 15 years since first exposure. US EPA (1984) also noted that smoking was a

potential confounder, exposure analysis failed to show a dose-response trend, and exposure to multiple chemicals was also a potential confounder. The SMR for respiratory cancer was much higher in workers exposed in the isopropyl alcohol manufacturing unit to other chemicals in addition to ECH than in the group exposed to ECH alone (SMRs = 214.8 and 63.3, respectively). US EPA (1984) concluded that the studies by Enterline (1978, 1981) provide only limited evidence for the human carcinogenicity of ECH.

Tassignon *et al*. (1983) studied the mortality of workers exposed to ECH in four European manufacturing plants which produced ECH, epoxy resins, glycerin and other ECH-derived specialty chemicals. Data was collected on 606 male workers with at least one year of exposure to ECH starting at least 10 years before December 31, 1978. No excess cancer mortality due to ECH exposure was observed; however, the authors noted that the small cohort size, short duration of the observation period and the limited number of deaths due to low average age (42 years) limited the power of the study.

Animal Studies

Female ICR/Ha Swiss mice were treated with ECH by dermal application, subcutaneous injection or intraperitoneal injection (Van Duuren *et al*., 1974). Dermal applications were performed 3 times/week; 2 mg ECH in 0.1 ml acetone was applied to 50 animals for 83 weeks. Untreated and vehicle control groups of 100 and 50 animals, respectively, were included. No increased incidence in skin tumors were noted in the treated animals. Intraperitoneal injections were performed weekly for 64 weeks; 1 mg ECH in 0.05 ml tricaprylin was injected into 30 animals. Untreated and vehicle control groups of 100 and 30 animals, respectively, were included. No treatment-related tumor induction was noted in the exposed animals. Subcutaneous injections were performed weekly for 83 weeks; 1 mg ECH dissolved in 0.05 ml tricaprylin was injected into 50 animals. Untreated and vehicle control groups of 100 and 50 animals, respectively, were included. An increased incidence of injection site tumors was noted (6/50 sarcomas, 1/50 adenocarcinomas) in the treated animals as compared to controls (no tumors in untreated controls, 1/50 sarcomas in vehicle controls).

Laskin *et al.* (1980) exposed male non-inbred Sprague-Dawley rats to 10, 30 or 100 ppm ECH by inhalation for the lifetime of the animals. Exposure durations were 6 hours/day, 5 days/week. Control groups consisted of 50 untreated animals and 100 air-treated animals. All groups demonstrated a high degree of early mortality, primarily due to respiratory disease (50% mortality by 64 weeks). Of a group of animals exposed to 100 ppm ECH for 6 weeks, 18/140 developed nasal cavity tumors, which were primarily squamous cell carcinomas. A group of 100 animals exposed for life (approximately 144 weeks) to 30 ppm developed 2 respiratory tract tumors; 1 larynx squamous papilloma and 1 nasal squamous cell carcinoma. The laryngeal tumor was misidentified in the original manuscript as a nasal tumor (US EPA, 1984). These tumor incidences were not significant when compared to those of the control group; however, they were significant when compared to the 1920 historical control animals from that laboratory, none of which had developed nasal squamous carcinoma. No nasal or respiratory tract tumors were noted in a group of 100 animals exposed for life to 10 ppm. No equivalent nasal or respiratory tumors were noted in the control groups. CDHS (1988) noted that only 18%, 26%

and approximately 50% of the animals in the 30 ppm, 10 ppm and 100 ppm dose groups, respectively, survived to mean time-to-tumor observed in the 100 ppm group (86 weeks).

Konishi *et al*. (1980) exposed male Wistar rats (18/group) to epichlorohydrin in drinking water at concentrations of 0, 375, 750 or 1500 ppm for up to 81 weeks; treatment was intermittently suspended between 60 and 81 weeks for all three epichlorohydrin treatment groups due to toxicity. Total dose for the 375, 750 and 1500 ppm treatment groups was 5.0, 8.9 and 15.1 g/animal, respectively. A dose-related increase in forestomach tumor (papillomas and squamous cell carcinomas) incidence was observed. Tumor incidence data is listed in Table 1.

Table 1: Incidence of forestomach tumors in male Wistar rats exposed to epichlorohydrin in drinking water (Konishi *et al*., 1980)

Concentration (ppm)	Calculated dose[1] (mg/kg-day)	Tumor incidence	
		papillomas	squamous cell carcinomas
0	0	0/10	0/10
375	15.1	0/9	0/9
750	31.9	1/10	1/10
1500	76.1	7/12	2/10

1. As listed in CDHS (1988).

Male and female ICR/HA Swiss mice (50/sex/group) were exposed to pure (99.9%) trichlorethylene (TCE), industrial grade (99.4%) TCE, or TCE containing 0.8% ECH, 0.8% 1,2-epoxybutane, or 0.8% ECH and 0.8% 1,2-epoxybutane by gavage for 104 weeks (Henschler *et al*., 1984). Corn oil vehicle control groups were included. Initial dosing provided TCE exposures of 2400 mg/kg/day^{-1} and 1800 mg/kg/day^{-1} for male and female mice, respectively. Because of toxicity, dosing was halted for all groups during weeks 35-40, 65 and 69-78. All doses were reduced by a factor of 2 at week 40. Mortality was significantly increased compared to controls in all male treatment groups, and in female treatment groups receiving pure TCE and TCE/ECH. Significant increases in the incidence of squamous cell carcinomas of the forestomach were observed in both male and female animals exposed to TCE/ECH. The tumor incidence in animals exposed to pure TCE was comparable to control values. Tumor incidence data is listed in Table 2.

Table 2. Epichlorohydrin-induced forestomach tumor incidence in male and female Swiss mice (Henschler *et al*., 1984)

Treatment group	Tumor incidence[1]	
	males	females
vehicle controls	1/50	1/50
pure trichloroethylene	1/50	0/50
pure trichloroethylene + 0.8% epichlorohydrin	8/50	12/50

Table 2 (continued). Epichlorohydrin-induced forestomach tumor incidence in male and female Swiss mice (Henschler *et al*., 1984)

1. Papilloma and squamous cell carcinoma incidences combined.

Male and female Wistar rats (50/sex/group) were exposed to 0, 2 or 10 mg/kg body weight epichlorohydrin by gavage 5 times/week for 2 years (Wester *et al*., 1985). Intestinal obstruction by trichobezoars (hairballs) resulted in intercurrent mortality after 4 months. Cumulative incidences for control, low-dose and high-dose animals, respectively, were 8, 16 and 19 for females, and 1, 0 and 5 for males. The study diet formulation was changed at 4 months; this resulted in decreased mortality from this cause for the remainder of the study. The percentage of surviving animals after 1 and 2 years of treatment is listed in Table 3.

Table 3. Survival of male and female Wistar rats exposed to epichlorohydrin by gavage (Wester *et al*., 1985)

Dose level (mg/kg body weight)	% survival after 1 year of treatment		% survival after 2 years of treatment	
	males	females	males	females
0	98	80	76	62
2	94	62	62	40
10	90	62	58	44

Treatment-related increases in the incidence of forestomach tumors (papillomas and squamous cell carcinomas) were observed in both male and female animals. Tumor incidence data is listed in Table 4.

Table 4. Epichlorohydrin-induced forestomach tumor incidence in male and female Wistar rats (Wester *et al*., 1985)

Sex	Dose level (mg/kg body weight)	Tumor type	Tumor incidence
male	0	papilloma	1/50
	2		6/49
	10		4/49
	0	squamous cell carcinoma	0/50
	2		6/49
	10		35/49
female	0	papilloma	2/47
	2		3/44
	10		0/39
	0	squamous cell carcinoma	0/47
	2		2/44
	10		24/39

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that a value derived from that data set would not be appropriate (CDHS, 1985). Several studies describe ECH-induced tumor incidence data which can be used to generate a cancer potency factor (male Wistar rat forestomach papilloma and squamous cell carcinoma data, Konishi *et al*. (1980); male Sprague-Dawley rat nasal tumor data, Laskin *et al.* (1980); male and female ICR/HA Swiss mouse forestomach squamous cell carcinoma data, Henschler *et al.* (1984); male and female Wistar rat papilloma and squamous cell carcinoma data, Wester *et al.* (1985). The data from the study by Konishi *et al*. (1980) was chosen by CDHS (1988) as the basis for a cancer potency factor for ECH. Data from the Laskin *et al*. (1980) study was considered to be less suitable for generating a cancer potency factor than data from the Konishi *et al*. (1980) study because of the poor survival of the study animals. The studies by Henschler *et al.* (1984) and Wester *et al.*, (1985) contained potential confounding factors. The ECH-exposed animals in the Henschler *et al.* (1984) study were also exposed to trichloroethylene. The animals used in the Wester *et al*. (1985) study exhibited trichobezoar-induced intestinal obstructions early in the study due to the diet composition; CDHS (1988) noted that those obstructions could have been a contributing factor to the observed forestomach carcinogenesis.

Methodology

A linearized multistage procedure (CDHS, 1985) was applied to male Wistar rat forestomach papilloma and carcinoma incidence data (Konishi *et al*., 1980). US EPA (1984) lists the half-life of ECH in water as 0.69 days. Assuming first order decay due to hydrolysis, this corresponds to an average concentration throughout the day of 63% of the concentration of the freshly prepared solution. The control, low, mid and high dose groups were reported to have received cumulative doses of 0, 5.0, 8.9 and 15.1 grams (Konishi *et al*., 1980); however, these data do not compensate for hydrolysis loss of ECH. CDHS (1988) estimated the actual daily exposures after hydrolysis compensation for the low, mid and high dose groups to be 15.1, 31.9 and 76.1 mg/kg-day, respectively. This assumes a body weight of 400 grams for a control Wistar rat, and utilizes the body weight data supplied by Konishi *et al*. (1980) which indicated that the low, mid and high dose animals weighed 7.7, 22.4 and 44.9% less than the controls, respectively. Upper 95% confidence bounds on carcinogenic potency (q_1^*) were estimated using the incidences of forestomach tumors in animals surviving to the end of the study (81 weeks) and the above dose estimates. Estimates of lifetime potency values (q_{animal}) were calculated from the q_1^* derived from the 81 week study using the relationship $q_{animal} = q_1^* * (104/81)^3$. Estimates for q_{animal} of 0.015 and 0.011 $(mg/kg\text{-}day)^{-1}$ were obtained for the benign squamous cell papillomas and malignant squamous cell carcinomas, respectively. The fitted dose response functions associated with these potency estimates exhibited significant upward curvature ($p = 0.03$). Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors, using the relationship ($q_{human} = q_{animal} * (bw_h / bw_a)^{1/3}$), where q_{human} is the human potency, q_{animal} is the animal potency, and bw_h and bw_a are the human and animal body weights,

respectively. Human carcinogenic potency values (q_{human}) of 0.08 and 0.06 mg/kg-day^{-1} were derived from the q_{animal} values for benign squamous cell papillomas and malignant squamous cell carcinomas, respectively. A unit risk factor was calculated by OEHHA/ATES from the benign squamous cell papilloma data-derived q_{human} value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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ETHYLENE THIOUREA (ETU)

CAS No: 96-45-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	102.17
Boiling point	not available
Melting point	200-203 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.179 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.3 E-5 $(\mu g/m^3)^{-1}$
Slope Factor: 4.5 E-2 $(mg/kg\text{-}day)^{-1}$
[Rat thyroid tumors (Graham *et al*., 1975), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of ethylene thiourea (ETU) in humans are known to exist.

Animal Studies

Male and female 7-day old $B6C3F_1$ and $B6AKRF_1$ mice (18/sex/group) were exposed to 215 mg/kg body weight ETU by gavage from 1 week of age until 4 weeks of age (Biogenics Research Labs, Inc., 1968; Innes *et al*., 1969). The animals were then fed diets containing 646 mg/kg diet ETU until the end of the experiment (82-83 weeks). Increases in liver tumors (hepatomas) were seen in males and females of both mouse strains used; an increased incidence of lymphomas was also seen in male and female $B6AKRF_1$ mice. Tumor incidence data is listed in Table 1.

Male and female Charles River CD rats (26 animals/sex/group) were fed diets containing 0, 175 or 330 ppm technical grade ETU (97% pure) for 18 months; 5 animals of each sex were then sacrificed (Ulland *et al*.,1972). The remaining animals were followed for 6 months. Increased incidences of thyroid carcinomas were noted in both males and females; thyroid carcinoma incidences were 0/26, 3/26 and 17/26 for control, low-dose and high-dose males, respectively, and 0/26, 3/26 and 8/26 for control, low-dose and high-dose females, respectively.

Table 1. Ethylene thiourea (ETU)-induced tumor incidence in (C57BL/6×C3H/Anf)F_1 and (C57BL/6×AKR)F_1 mice (Innes *et al*., 1969)

Sex/strain	Dose group	Tumor type	Tumor incidence
Male (C57BL/6×C3H/Anf)F_1	control	liver tumors	8/79
	treated		14/16
Female (C57BL/6×C3H/Anf)F_1	control	liver tumors	0/87
	treated		18/18
Male (C57BL/6×AKR)F_1	control	liver tumors	5/90
		lymphomas	1/90
	treated	liver tumors	18/18
		lymphomas	3/18
Female (C57BL/6×AKR)F_1	control	liver tumors	1/82
		lymphomas	4/82
	treated	liver tumors	9/16
		lymphomas	4/16

Graham *et al*. (1973, 1975) exposed male and female Charles River CD rats (initial group sizes 68 animals/sex/group) to diets containing ETU at levels of 5, 25, 125, 250 or 500 mg/kg diet. An untreated control group was included. Interim sacrifices were conducted at 2, 6, 12 and 18 months; the study was terminated at 24 months. An increased incidence of thyroid tumors (adenomas and carcinomas) was noted in males and females (combined). Tumor incidence data is listed in Table 2.

Table 2. Ethylene thiourea-induced thyroid tumor incidence in male and female (combined) Charles River CD rats (Graham *et al*., 1973, 1975)

Ethylene thiourea dietary level (mg/kg diet)	Average dose[1] (mg/kg-day)	Tumor incidence[2]
0	0	2/72
5	0.225	2/75
25	1.13	1/73
125	5.63	2/73
250	11.3	16/69
500	22.5	62/70

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

Male and female Charles River CD rats were exposed to diet containing 0, 175 or 350 mg/kg ETU for 78 weeks, then switched to control diet for an additional observation period of 26 weeks (Weisburger *et al*., 1981). A significantly increased incidence of thyroid follicular-cell carcinomas was noted in both male and female rats. Tumor incidences were 0/10, 2/26 and

15/26 in pooled control, low-dose and high-dose male rats, respectively, and 0/10, 2/26 and 6/26 in pooled control, low-dose and high-dose female rats, respectively.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results of several studies are listed in Gold *et al.* (1984). Innes *et al*. (1969) administered ethylene thiourea (ETU) to small groups of both sexes of $B6C3F_1$ and $B6AKF_1$ mice; Graham *et al*. (1973, 1975) performed relatively large multiple dose studies in Charles River CD rats of both sexes; Weisburger *et al.* (1981) and Ulland *et al.* (1972) conducted moderately sized studies in male and female Charles River CD rats. Because all male $B6C3F_1$ and female $B6AKF_1$ mice treated with ETU developed liver tumors, an upper bound estimate on potency could not be determined for these studies. The lower bound estimates of cancer potency derived from the mouse data are consistent with potencies derived from the studies in rats. Further, cancer potencies derived from the rat studies are consistent with one another. The value selected is derived from the highest quality study, Graham (1973, 1975), which had a large sample size and used multiple dose groups. The target site chosen for the analysis was the thyroid in the Charles River CD rats, the most sensitive site (see Table 2) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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HEXACHLOROBENZENE

CAS No: 118-74-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	284.8
Boiling point	323-326°C
Melting point	231°C
Vapor pressure	1.09 E-05 mm Hg at 20°C
Air concentration conversion	1 ppm = 11.65 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.1 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.8 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from potency derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

No adequate epidemiological studies of cancer in people exposed to hexachlorobenzene (HCB) are available. The only reported study found increases in porphyria, neurological, dermatological and orthopedic disorders and thyroid enlargement among 161 individuals (63 women, 98 men) studied out of a group of approximately 4000 who had suffered hexachlorobenzene poisoning 25 years previously as a result of eating HCB-treated wheat seed (Peters *et al.*, 1982, 1983). No increases in cancer incidence were reported; however, it should be noted that the methodology used in the study was not designed to evaluate excess cancer occurrence.

Animal Studies

A number of feeding studies have been conducted in hamsters, rats and mice. Hexachlorobenzene has been found to induce tumors in the liver, adrenal gland, thyroid gland, parathyroid gland, kidney, lymphoid tissue and endothelial tissue.

Cabral *et al.* (1977) fed male and female Syrian golden hamsters diets containing 0, 50, 100 or 200 mg/kg diet HCB for the life of the animals. Treatment group sizes for the control, low-dose, mid-dose and high-dose groups were 40, 30, 30 and 59, respectively, for males and 40,30,30 and 60, respectively, for females. Treatment-related increases in the incidence of liver tumors (hepatomas, hemangioendotheliomas) and thyroid adenomas were observed in both males and females. Tumor incidence data is listed in Table 1.

Table 1. Hexachlorobenzene-induced tumor incidence in male and female Syrian golden hamsters (Cabral *et al.*, 1977)

Dietary HCB concentration (mg/kg diet)	Calculated daily intake (mg/kg-day)	Tumor type	Tumor incidence	
			males	females
0	0	hepatomas	0/40	0/39
50	4		14/30	14/30
100	8		26/30	17/30
200	16		49/57	51/60
0	0	hemangioendotheliomas	0/40	0/39
50	4		1/30	0/30
100	8		6/30	2/30
200	16		20/57	7/60
0	0	thyroid adenomas	0/40	0/39
50	4		0/30	2/30
100	8		1/30	1/30
200	16		8/57	3/60

Outbred Swiss mice were fed diets containing 0, 50, 100, or 200 mg/kg hexachlorobenzene for 101-120 weeks; all surviving animals were killed at 120 weeks (Cabral *et al.*, 1979). Initial group sizes were 50 animals/sex for the control and 200 mg/kg diet groups, and 30/sex for the 50, 100 and 300 mg/kg diet groups. A dose-response related increase in the incidence of liver tumors (unspecified histological type) was noted in both male and female animals. An increased incidence of liver tumors was also found in a group of 30 males and 30 females fed diet containing 300 mg/kg diet HCB for 15 weeks followed by observation until 120 weeks. Tumor incidence data is listed in Table 2.

Table 2. Hexachlorobenzene-induced liver tumors in male and female Swiss mice (Cabral *et al.*, 1979)

Dose group (mg/kg diet)	Tumor incidence	
	males	females
0	0/47	0/49
50	0/30	0/30
100	3/29	3/30
200	7/44	14/41
300 (15 weeks exposure)	1/16	1/26

Smith and Cabral (1980) exposed female Agus and Wistar rats to diets containing 100 mg/kg HCB for up to 90 or 75 weeks, respectively. An increased incidence of liver tumors (histological

type not specified) due to HCB exposure was observed in both Agus and Wistar rats; tumor incidence was 14/14 and 4/6, respectively, compared to 0/12 and 0/4, respectively, in the control animals.

Male and female Syrian golden hamsters were exposed to diet containing 0, 200 or 400 mg/kg diet HCB for 90 days; 25-50 animals/group were sacrificed on the 91st day (Lambrecht *et al.*, 1982). The remaining 25 animals/group were placed on control diet and sacrificed at 6 week intervals up to 1 year. Hepatoma incidence in the 200 and 400 mg/kg diet groups was 1/13 and 1/20, respectively, for males and 1/15 and 1/7, respectively for females. No hepatomas were noted in 43-50 control animals for each sex.

Male and female Sprague-Dawley rats (94/sex/group) were fed diets containing 0, 75 or 150 mg/kg diet HCB for up to 2 years (Lambrecht *et al.*, 1983a, b, 1986). Four animals/sex/group were killed at 0, 1,2,3,4,8,16,32 and 64 weeks. Treatment-related increases in the incidence of hepatic tumors (hepatomas, hemangiomas, hepatocarcinomas and bile duct adenomas/carcinomas) and renal-cell adenomas were noted in both male and female animals. Tumor incidence data is noted in Table 3.

Table 3. Hexachlorobenzene-induced hepatic tumors in male and female Sprague-Dawley rats (Lambrecht *et al.*, 1983 a,b; 1986)

Dose group (mg/kg diet)	Tumor type	Tumor incidence	
		males	females
0	hepatoma/hemangioma	0/54	0/52
75		10/52	23/56
150		11/56	35/55
0	hepatocarcinoma	0/54	0/52
75		3/52	36/56
150		4/56	48/55
0	bile duct adenoma/carcinoma	0/54	1/52
75		2/52	19/56
150		2/56	29/55
0	renal-cell adenomas	7/54	1/52
75		41/52	7/56
150		42/56	15/55

Arnold *et al.* (1985) conducted two studies on the effects of chronic feeding of HCB in Sprague-Dawley rats. In the first study, male and female Sprague-Dawley rats were fed diets containing 0, 0.32, 1.6, 8 or 40 mg/kg diet HCB for 3 months after weaning. Group sizes were 40/sex except for the control and high-dose groups (64 and 66/sex, respectively). After 3 months, the F_0 rats were bred and 50 pups (F_1) of each sex were randomly selected from each group. The F_1 generation animals were fed their parent's diet from weaning for their lifetime (130 weeks). A significant positive trend was noted in the incidence of parathyroid adenomas in males ($p <$

0.01); the incidence in high-dose males was also significantly greater than controls ($p < 0.05$). A significant positive trend was also noted in the incidence of adrenal pheochromocytomas in both males and females ($p < 0.05$ and $p < 0.01$, respectively); the incidence in high-dose females was also significantly greater than controls ($p < 0.01$). Tumor incidence data is listed in Table 4.

Table 4. Hexachlorobenzene-induced tumor incidence in the male and female exposed F_1 progeny of exposed F_0 Sprague-Dawley rats (Arnold *et al.*, 1985)

Dose group (mg/kg diet HCB)	Average dose[1]	Tumor type	Tumor incidence	
			males	females
0	0	parathyroid adenomas	2/48	
0.32	0.01		4/48	
1.6	0.07		2/48	
8	0.35		1/49	
40	1.72		12/49	
0	0	adrenal pheochromocytomas	10/48	2/49
0.32	0.01		12/48	4/49
1.6	0.07		7/48	4/50
8	0.35		13/49	5/49
40	1.72		17/49	17/49

1. As reported by CDHS (1988)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results from the following 3 studies provide the basis for cancer potency derivation. Cabral *et al.* (1977) treated groups of male and female Syrian golden hamsters with hexachlorobenzene in feed over the lifetime of the animals. Significant dose-related increases in hepatomas were observed in both sexes (see Table 1). Lambrecht *et al.* (1983a, b; 1986) exposed male and female Sprague-Dawley rats to hexachlorobenzene in feed for 2 years. Treated male and female rats exhibited significant increases in the incidence of hepatomas and renal-cell adenomas. Female rats also demonstrated significant increases in the incidence of hepatocellular carcinomas. No hepatocellular carcinomas were noted in control animals (see Table 3). Arnold *et al.* (1985) also observed a significant dose related increase in the occurrence of adrenal pheochromocytomas in the male and female and parathyroid adenomas in the male exposed F_1 progeny of exposed F_0 Sprague-Dawley rats (see Table 4).

Methodology

Cancer potency values are based on the most sensitive site, species and study demonstrating carcinogenicity of a particular chemical, unless other evidence indicates that the value derived from that data set is not appropriate (CDHS, 1985). For hexachlorobenzene, similar cancer potencies were derived using data from several tumor sites in different test species. Cancer potency factors (q_1^*) were derived by applying a linearized multistage procedure (CDHS, 1985) to the dose-response data for induction of hepatomas in male Syrian golden hamsters (Cabral *et al.*, 1977), and hepatocellular carcinomas (Lambrecht *et al.*, 1983a, b) and pheochromocytomas (Lambrecht *et al.*, 1983a, b; Arnold *et al*., 1985) in female Sprague-Dawley rats. Surface area scaling was employed to transform animal cancer potency factors to human cancer potency factors. Assumed body weight values used for humans, hamsters and mice were 70 kg, 0.1 kg and 0.035 kg, respectively (CDHS, 1988). Lambrecht *et al.* (1983a, b) reported average body weights of 0.265 kg for female Sprague-Dawley rats; unpublished data cited by US EPA (1985) indicates that average body weights of female Sprague-Dawley rats in the study by Arnold *et al*. (1985) were 0.353 kg. A human cancer potency value (q_{human}) of 1.7 $(mg/kg\text{-}day)^{-1}$ was calculated from the male hamster hepatoma incidence data (Cabral *et al.*, 1977) and the female rat hepatocellular carcinoma incidence data (Lambrecht *et al.*, 1983a, b). A human cancer potency value of 1.8 $(mg/kg\text{-}day)^{-1}$ were calculated from female rat pheochromocytomas incidence data (Lambrecht *et al.*, 1983a, b; Arnold *et al.*, 1985). On the basis of the results stated above, a cancer potency of 1.8 $(mg/kg\text{-}day)^{-1}$ was selected for hexachlorobenzene (CDHS, 1988). The unit risk factor was derived by OEHHA/ATES from the low dose exposure cancer potency value using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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HEXACHLOROCYCLOHEXANE (TECHNICAL GRADE)

CAS No: 608-73-1

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	290.9
Boiling point	288°C (α-HCH); 323.4°C (γ-HCH)
Melting point	158°C (α-HCH); 113°C (γ-HCH)
Vapor pressure	0.02 mm Hg @ 20°C (α-HCH)
Air concentration conversion	1 ppm = 11.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1E-3 (μg/m^3)$^{-1}$
Slope Factor: 4.0 E+0 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for carcinogenicity of hexachlorocyclohexane (HCH; all isomers) was inadequate in humans. However, U.S.EPA (1988) designated α-HCH and technical grade HCH as B2 (probable human) carcinogens. Several case reports suggest an association between HCH isomers, including β- and γ-HCH, and exposure and leukemia, aplastic anemia, liver cancer, soft-tissue sarcomas, and lung cancer (IARC, 1987). In all of these case reports, the exposures are not well documented. In addition, exposures to other chemicals, including some pesticides, probably occurred in these cases.

Animal Studies

The incidence of liver tumors in male and female mice has been shown to be increased in two studies of technical HCH (Kashyap *et al*., 1979; Hanada *et al*., 1973). Hanada *et al*. (1973) exposed male and female dd mice (10-11 per group; 14 controls) to 100, 300, or 600 mg/kg diet of α-, β-, γ-, or technical HCH for 32 weeks, followed by a 6-week period without chemical exposure. The incidence of hepatomas was significantly increased in animals treated with increasing doses of α-, or technical HCH (Table 1).

Table 1. Liver hepatoma incidence in dd mice treated with hexachlorocyclohexane (HCH) (Hanada *et al*. (1973).

HCH Isomer	Sex	Hepatoma incidence mg/kg diet HCH 100	300	600
α-HCH	males	1/8	7/7	7/7
	females	0/8	2/3	6/8
β-HCH	males	0/9	0/8	0/8
	females	0/9	0/8	0/4
γ-HCH	males	0/10	0/9	3/4
	females	0/8	0/7	1/3
Technical HCH	males	0/10	4/4	4/4
	females	0/8	3/5	5/5

In the study by Kashyap *et al*. (1979), Swiss mice (30/sex/group) were exposed to 0 or 100 mg/kg diet for 80 weeks. Mice were also exposed to technical HCH by gavage (10 mg/kg/day) or skin painting (0.25 mg in 0.1 mg olive oil). A significant increase in liver hepatocarcinomas and lymphoreticular tumors of type B was observed in mice exposed to technical HCH in the diet or by gavage (Table 2).

Table 2. Tumor incidence in mice treated with technical hexachlorocyclohexane (HCH) (Kashyap *et al*., 1979).

HCH Treatment Group	Sex	Animals/ group	Liver tumors	Total tumors
Control	m	25	4	9
	f	26	1	5
100 mg/kg/day (diet)	m	23	16	22
	f	25	9	21
10 mg/kg/day (gavage)	m	26	12	17
	f	28	7	16
0.25 mg/0.1 mg (olive oil) (gavage)	m	25	5	11
	f	18	3	7

m = male, f = female

Wolff *et al*. (1987) reported on the carcinogenic effects of γ-HCH in several strains of mice. Female yellow, black, and pseudoagouti mice (36-96 per group) were exposed to 0 or 160 ppm γ-HCH in the diet for up to 24 months. Different response rates were observed between strains, indicating significant genetic variability in response to γ-HCH. In yellow mice, a significant increase in the incidence of Clara cell hyperplasia, papillary lung tumors and hepatocarcinomas and adenomas was observed (Table 3). The higher incidence of tumors in the obese yellow mice indicate that bioaccumulation of γ-HCH in obese animals may influence carcinogenicity. Similar experiments were not done using technical HCH.

Table 3. Tumor incidence in yellow mice exposed to γ-HCH (Lindane) (Wolff *et al*., 1987)

Concentration of γ-HCH (ppm)	Lung Tumors	Liver Adenomas
0	4/95	8/93
160	18/95	33/94

Thorpe and Walker (1973) showed an increase in liver tumors of male CF1 mice fed 400 ppm γ-HCH for 110 weeks, compared with controls. The time-weighted dose was estimated as 52 mg/kg/day by US EPA (1988). In this experiment, control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the 52 mg/kg/day group.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Hanada *et al*. (1973) and Kashyap *et al*. (1979) both show a carcinogenic effect on the liver in mice. The study by Nagasaki *et al*. (1975) also showed a positive carcinogenic effect in mice, but these data were considered less reliable since the tumor incidence was zero in all but the highest dose group, where it was 100%. In addition, the study by Kashyap *et al*. (1979) was among those of the longest duration available for HCH (80 weeks). The potency values from the Kashyap *et al*. (1979) and Hanada *et al*. (1973) studies are the same for liver tumors in mice. Therefore, these studies were used by CDHS (1988) to determine the cancer potency for HCH.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of technical HCH from the Kashyap *et al*. (1979) and Hanada *et al*. (1973) data in male Swiss mice (Crump *et al*., 1982). The concentrations of technical HCH given in the feed were 0 or 100 mg/kg diet (Kashyap *et al*., 1979), and 0, 100, 300, or 600 mg/kg diet (Hanada *et al*., 1973). The tumor incidence data are shown in Tables 1 and 2 above. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for HCH.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. The default lifespan for mice is 104 weeks. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 4.0 $[mg/kg \times day]^{-1}$ was derived (CDHS, 1988). An airborne unit risk factor of 1.1E-3 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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HYDRAZINE

CAS No: 302-01-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	32.05
Boiling point	113.5°C
Melting point	2.0°C
Vapor pressure	14.44 mm Hg @ 25°C
Air concentration conversion	1 ppm = 1.31 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.9 E-3 $(\mu g/m^3)^{-1}$
Slope Factor: 1.7 E+1 $(mg/kg\text{-}day)^{-1}$
[Calculated by US EPA (1991) from the male rat nasal cavity tumor data of MacEwan *et* al. (1980) using a linearized multistage procedure (Global 82), extra risk]

Oral Cancer Potency Factor: 3.0 E+0 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1991) from the male mouse liver tumor data of Biancifiori (1970) using a linearized multistage procedure (Global 82), extra risk]

III. CARCINOGENIC EFFECTS

Human Studies

A published letter (Roe, 1978) presented mortality data from two hydrazine manufacturing plants (belonging to one of nine companies in the trade). This study included 423 workers employed at one plant between 1963 and 1975 (151 workers) and at a second plant (272 workers) between 1945 and 1970. Five cancer deaths were reported (three of the stomach, one prostatic and one neurogenic). A follow-up study of this cohort extended the observation period to 1982 (Wald *et al*., 1984). The only excess cancer mortality was the result of two lung cancer cases in the highest exposure group (relative risk = 1.2, 95% confidence interval 0.2 - 4.5). The author concluded that neither group of workers demonstrated an increased risk of cancer associated with occupational exposure to hydrazine. No other studies on human hydrazine exposure have been published.

Animal Studies

Several studies have tested the ability of hydrazine sulfate administered by gavage or in drinking water to induce cancer. Lung adenomas and adenocarcinomas and liver hepatomas and hepatocarcinomas were observed in both mice and rats. These studies have been reviewed by IARC (1974) and US EPA (1988). Lung tumors, reticulum-cell sarcomas and myeloid leukemias have also been observed to occur in mice exposed to hydrazine by intraperitoneal injection

(Juhász *et al*., 1966; Kelly *et al*., 1969; Mirvish *et al*., 1969). MacEwan *et al*. (1981) reported that inhalation exposure to hydrazine induced lung adenomas in mice, nasal cavity tumors and thyroid adenocarcinomas in rats and nasal polyps in hamsters.

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Inhalation

MacEwan *et al*. (1981) exposed C57BL/6 mice, F344 rats, Syrian golden hamsters and beagle dogs to hydrazine vapor (97% pure) by inhalation for 6 hours/day, 5 days/week for 1 year followed by a variable observation period (12-38 months). Exposure levels were 0.05, 0.25 and 1.0 ppm for mice, 0.05, 0.25, 1.0 and 5.0 ppm for rats, 0.25, 1.0 and 5.0 ppm for hamsters and 0.25 and 1.0 ppm for dogs. Lung adenomas were reported in 12/379 female mice ($p < 0.05$) exposed to 1.0 ppm hydrazine. Male and female rats demonstrated nasal cavity tumors after exposure to 1.0 ppm (11/98 and 4/97, respectively) and 5.0 ppm (72/99 and 36/98, respectively). Male rats also developed thyroid adenocarcinomas (13/99) after exposure to 5.0 ppm hydrazine. Nasal polyps were induced in male hamsters exposed to 5.0 ppm hydrazine (16/160, $p < 0.01$). No significant tumor increase was seen in either dog exposure group. This study was selected as the basis of a cancer potency factor for exposure to hydrazine by inhalation because it demonstrated a dose response, used a relevant exposure route and used hydrazine vapor instead of hydrazine sulfate.

Oral

Biancifiori (1970) administered hydrazine sulfate by gavage to groups of 24 to 30 8-week-old CBA/Cb/Se mice of each sex at doses of 0.0, 0.14, 0.28, 0.56, or 1.13 mg/day, 6 days/week for 25 weeks. Animals were observed throughout their lifetimes. Liver carcinomas were induced in a dose-related manner in both sexes and lung metastases were observed in some of the mice treated with 1.13 mg/kg/day (Table 1). Pulmonary tumors were reportedly present in many of the treated mice, but incidences were not reported because the purpose of the study was to describe hepatic tumors.

Table 1. Tumor incidence in male CBA/Cb/Se mice exposed by gavage to hydrazine sulfate (Biancifiori, 1970)

Administered dose (ppm)	Human equivalent dose (mg/kg)/day[1]	Liver tumor incidence
0	0	3/30
0.14	0.044	1/26
0.28	0.103	7/25
0.56	0.222	12/25
1.13	0.403	15/25

1. Human equivalent dose calculated by US EPA (1991).

Methodology

Inhalation

A linearized multistage procedure (Global 82) was used to calculate a slope factor of 1.7 E+1 $(mg/kg/day)^{-1}$ from the male F344 rat nasal cavity adenoma and adenocarcinoma incidence data of MacEwan *et al*. (1980). Male F344 rats were the most sensitive species and sex to the carcinogenic effects of inhaled hydrazine. Administered doses were 1.0 and 5.0 ppm; human equivalent doses were 0.01 and 0.05 mg/kg/day. Human equivalent doses were calculated on the basis of a 365 day treatment and an experimental period of 910 days. Rat body weight was assumed to be 350 g, and the animal lifespan was assumed to be 910 days. Calculation of the unit risk from the slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day. EPA has stated that the unit risk should not be used if the air concentration exceeds 2 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

Oral

A linearized multistage procedure (Global 82) was used to calculate a slope factor of 3.0 E+0 $(mg/kg/day)^{-1}$ from the male CBA/Cb/Se mouse liver tumor incidence data of Biancifiori (1970) (Table 1). Human equivalent doses were calculated to reflect a treatment period of 175 days and an experimental period of 607 days, the mean length of the experiment for each treatment group. Mouse body weight was assumed to be 0.03 kg and the animal lifespan was assumed to be 730 days.

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LINDANE (γ-HEXACHLOROCYCLOHEXANE)

CAS No: 58-89-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	290.9
Boiling point	323.4°C
Melting point	113°C
Vapor pressure	9.4E-6 mm Hg @ 20°C
Air concentration conversion	1 ppm = 11.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.1E-4 (µg/m^3)$^{-1}$
Slope Factor: 1.1 E+0 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor reported by US EPA (1987)]

III. CARCINOGENIC EFFECTS

Human Studies

The International Agency for Research on Cancer (IARC) concluded in 1987 that the evidence for carcinogenicity of hexachlorocyclohexane (HCH; all isomers) was inadequate in humans. Several case reports suggest an association between lindane exposure and leukemia, aplastic anemia, liver cancer, soft-tissue sarcomas, and lung cancer (IARC, 1987). In all of these case reports, the exposures are not well documented. In addition, exposures to other chemicals, including some pesticides, probably occurred in these cases.

Animal Studies

Wolff *et al*. (1987) reported on the carcinogenic effects of lindane in several strains of mice. Female yellow, black, and pseudoagouti mice (36-96 per group) were exposed to 0 or 160 ppm lindane in the diet for up to 24 months. Different response rates were observed between strains, indicating significant genetic variability in response to lindane. In yellow mice, a significant increase in the incidence of lung and liver tumors was observed (Table 1). The higher incidence of tumors in the obese yellow mice indicate that bioaccumulation of lindane in obese animals may influence carcinogenicity.

Table 1. Tumor incidence in yellow mice exposed to γ-HCH (lindane) (Wolff *et al*., 1987)

Dietary Concentration of γ-HCH (ppm)	Tumor Type and Incidence	
	Lung Carcinomas	Liver Adenomas
0	4/95	8/93
160	18/95	33/94

Thorpe and Walker (1973) showed an increase in liver tumors of male CF1 mice fed 400 ppm lindane for 110 weeks, compared with controls. The time-weighted dose was estimated as 52 mg/kg/day by US EPA (1988). In this experiment, control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the 52 mg/kg/day group.

A study by Goto *et al*. (1972) showed a positive effect of lindane on cancer in mice. However, this experiment used only 10 animals per treatment group and was of a short duration. The NCI (1977) study on male mice showed a significant increase in cancer incidence in mice exposed to 80, but not 160 ppm γ-HCH. The absence of a clear dose-response precluded this data from use in determining the cancer potency for lindane.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The US EPA (1988) selected the study by Thorpe and Walker (1973) as the basis for the cancer potency for lindane. This was considered to be the best study for development of a cancer potency factor for lindane because of the large sample size of mice surviving for a full lifespan, and the large numbers of tumors in the treatment group. Thorpe and Walker (1973) showed an increase in liver tumors in male CF1 mice fed 400 ppm lindane in the diet for 110 weeks, compared with controls. Control mice exhibited an incidence of 11/45 for liver tumors, compared to 27/29 for the lindane-treated group ($p < 0.01$). Some lung metastases were also reported in the male and female mice treated with lindane.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of lindane from the Thorpe and Walker (1973) data in male CF1 mice (Crump *et al*., 1982). The concentrations of lindane given in the feed were 0 or 160 ppm. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for lindane.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 1.1 [mg/kg x day]$^{-1}$ was reported (US EPA, 1987). An airborne unit risk factor of 3.1E-4 ($\mu g/m^3$)$^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

V. REFERENCES

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4, 4'-METHYLENE BIS(2-CHLOROANILINE) (MOCA)

CAS No: 101-14-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	267.15
Boiling point	not available
Melting point	110°C
Vapor pressure	1.3×10^{-5} mm Hg at 60°C
Air concentration conversion	1 ppm = 10.9 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.3 E-4 (µg/m^3)$^{-1}$
Slope Factor: 1.5 E+0 (mg/kg-day)$^{-1}$
[Female beagle dog urinary bladder tumor data (Stula *et al*., 1977) , contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

IARC (1993) has reviewed several descriptive studies on the potential carcinogenic effects of 4, 4'-methylene bis(2-chloroaniline) (MOCA) in humans. An epidemiological study by Ward *et al*. (1990) examined cancer incidence in workers employed at a chemical plant in Michigan where MOCA was produced between 1968 and 1979. All 532 workers employed in 1968-79 and an additional 20 workers employed in 1980-81 who had possible exposure due to plant site contamination were included. Median duration of employment was 3.2 months. Quantitative exposure was not available; however, worker exposure may have been substantial, since worker urinary levels of MOCA several months after the end of production ranged up to 50,000 µg/l. Telephone interviews were conducted with 452 workers, and 385 participated in a urine screening examination. Three asymptomatic bladder tumors were identified. The screening procedure was supplemented for some workers with cytoscopy after a 28-year old worker was found to have a non-invasive papillary transitional-cell tumor. Low-grade papillary transitional cell carcinoma was diagnosed in 2 of 200 examined workers; one was less than 30 years old. Mean interval time from first exposure to study initiation was 11.5 years, while the latency period for most bladder carcinogens is about 20 years (Ward *et al*., 1990). This finding increases the concern that MOCA is a human bladder carcinogen, since bladder carcinoma in young men is very uncommon. A limitation of this study was that expected numbers of bladder tumors could not be calculated, as no data exists on the incidence of bladder tumors diagnosed by cytoscopy in an asymptomatic nonexposed population.

Animal Studies

Male and female HaM/ICR mice and male Charles River CD-1 rats (25/sex/species/group) were exposed to MOCA hydrochloride in the diet for 18 months by Russfield *et al*. (1975). Mice were fed diet containing 0, 1000 or 2000 mg/kg diet MOCA hydrochloride; rats were fed diet containing 0, 500 or 1000 mg/kg diet MOCA hydrochloride. Surviving animals were killed after 24 months; about 55% of the control and treated animals were still alive at 20-22 months. Hemangiomas or hemangiosarcomas were noted in 0/10 control, 3/13 low dose and 8/20 high dose male mice; hepatomas were noted in 0/20 control, 9/21 low dose and 7/14 high dose female mice ($p < 0.01$, Fisher exact test), and in 0/22 control, 1/22 low dose and 4/19 high dose rats ($p < 0.05$, Cochran-Armitage trend test).

Male and female Charles River CD rats (50/sex/group) were fed diet containing 0 or 1000 mg/kg diet MOCA in a standard diet (23% protein) for life (Stula *et al*., 1975). Average experiment duration was 80 weeks for treated and control males, 89 weeks for female controls and 78 weeks for treated females. Six animals from each group were killed for an interim evaluation at one year. Lung carcinomas were observed in 21/44 treated males ($p < 0.05$, χ^2 test) and in 27/44 treated females ($p < 0.05$, χ^2 test); a lung squamous-cell carcinomas was also observed in one treated male and female. Pleural mesotheliomas occurred in 4/44 treated males and 2/44 treated females. Hepatocellular adenomas and carcinomas occurred in 3/44 and 3/44 treated males and 2/44 and 3/44 treated females, respectively. No lung tumors, pleural mesotheliomas or hepatocellular adenomas and carcinomas were noted in control animals.

Male Charles River CD rats were fed a "protein-adequate" diet containing 0, 250, 500 or 1000 mg/kg diet MOCA (group sizes 100, 100, 75 and 50, respectively) for 18 months followed by a 32 week observation period (Kommineni *et al*., 1979). MOCA exposure was associated with decreased survival; mean survival time was 89, 87, 80 and 65 weeks for controls, low-dose, mid-dose and high-dose animals, respectively. Dose-related increases in the incidences of lung tumors, mammary adenocarcinomas, Zymbal gland adenocarcinomas and hepatocellular carcinomas were noted. Tumor incidence data is listed in Table 1.

Table 1. 4, 4'-methylene bis(2-chloroaniline) (MOCA)-induced tumor incidence in male Charles River CD rats (Kommineni *et al*., 1979)

Tumor type	dietary MOCA (mg/kg diet)			
	0	250	500	1000
lung tumors	1/100	23/100	28/75	35/50
Zymbal gland carcinomas	1/100	8/100	5/75	11/50
mammary adenocarcinomas	1/100	5/100	8/75	14/50
hepatocellular carcinomas	0/100	3/100	3/75	18/50

Stula *et al*. (1977) exposed a group of 6 female beagle dogs to a daily dose of 100 mg MOCA by capsule 3 days/week for 6 weeks, then 5 days/week for up to 9 years. A second group of 6 females served as untreated controls. One treated dog died at 3.4 years of age because of an

infection. The other animals were killed at 8.3-9 years. Transitional-cell carcinomas of the urinary bladder occurred in 4 of 5 treated dogs ($p < 0.025$, Fisher exact test), and a composite tumor (transitional-cell carcinoma/adenocarcinoma) of the urethra was noted in one dog. No urinary tract tumors were noted in the untreated controls. Tumor incidence data is listed in Table 2.

Table 2. 4, 4'-Methylene bis(2-chloroaniline) (MOCA) -induced urinary bladder tumor incidence in female beagle dogs (Stula *et al*., 1977)

Average Dose[1] (mg/kg-day)	Tumor Incidence[2]
0	0/6
7.31	4/5

1. Doses as reported by Gold *et al*. (1984).
2. Tumor incidences as reported by Gold *et al*. (1984)

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Results from a number of studies using Charles River CD and Wistar rats, as well as female beagle dogs, are listed in Gold *et al*. (1984). 4, 4'-Methylene bis(2-chloroaniline) induced papillary transitional cell carcinomas of the urinary bladder in dogs, whereas the liver was the most common target site in the rat studies. Dogs are more sensitive to the carcinogenic effects of the compound than rats. The compound is similar in structure to benzidine, a human bladder carcinogen, which appears to be significantly more potent in humans than rodents. Results from the Stula *et al*. (1977) dog study are used as the basis of potency estimation, despite the small numbers of animals used, because dogs may be better predictors of human carcinogenicity of this compound than rodents (Cal/EPA, 1992). Dose-response data are listed in Table 2.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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4, 4'-METHYLENEDIANILINE

CAS No: 101-77-9

4, 4'-METHYLENEDIANILINE DIHYDROCHLORIDE

CAS No: 13552-44-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

4, 4'-Methylenedianiline

Molecular weight	198.26
Boiling point	398-399 °C at 768 mm Hg
Melting point	91.5-92 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 8.109 mg/m^3

4, 4'-Methylenedianiline didihydrochloride

Molecular weight	271.21
Boiling point	not available
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 11.09 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-4 (µg/m^3)$^{-1}$
Slope Factor: 1.6 E+0 (mg/kg-day)$^{-1}$
[Male mouse liver tumors (NTP, 1983), contained in Gold *et al*. (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 4,4' methylenedianiline in humans are known to exist.

Animal Studies

Griswold *et al*. (1968) exposed a group of 20 female Sprague-Dawley rats to 30 mg 4,4' methylenedianiline dihydrochloride in 1 ml sesame oil by gavage every third day for 30 days (total dose, 300 mg/rat). The animals were then observed for a further 9 months. A group of 140 female Sprague-Dawley rats served as a negative control group. No treatment-related increase in tumor incidence was noted; however, the study duration was short, a small number of animals

was used, only one sex was used, and the primary aim of the study was to develop methods of detecting carcinogens inducing mammary tumors.

The potential carcinogenicity of 4,4' methylenedianiline dihydrochloride was studied using Fischer 344 (F344) rats and $B6C3F_1$ mice (50 animals/sex/species/group) (NTP, 1983). Animals were exposed to 150 mg/l or 300 mg/l 4,4' methylenedianiline dihydrochloride in drinking water for 103 weeks followed by one week without treatment. Untreated control groups were included. A significantly increased incidence of thyroid follicular-cell adenomas was observed in male and female mice and rats. Significantly increased incidences of hepatocellular adenomas and carcinomas were observed in female and male mice; increased incidences of neoplastic nodules were observed in male rats. Tumor incidence data is listed in Table 1.

Table 1 4,4' methylenedianiline dihydrochloride-induced tumor incidences in male and female F344 rats and $B6C3F_1$ mice (NTP, 1983; Weisburger *et al*., 1984)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male mice	control	0	thyroid tumors	0/50
	low dose	24.5		3/50
	high dose	49.5		16/50
	control		liver tumors	17/50
	low dose			43/50
	high dose			37/50
female mice	control	0	thyroid tumors	0/50
	low dose	29.4		1/50
	high dose	59.1		15/50
	control		liver tumors	4/50
	low dose			15/50
	high dose			23/50
male rats	control	0	thyroid tumors	1/50
	low dose	7.36		4/50
	high dose	14.7		10/50
	control		hepatic neoplastic nodules	1/50
	low dose			12/50
	high dose			25/50
female rats	control	0	thyroid tumors	0/50
	low dose	8.41		5/50
	high dose	16.7		22/50

1. Doses as reported by Gold *et al*. (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

4, 4'-Methylenedianiline

The potency for this compound was derived from the potency for the dihydrochloride using a molecular weight conversion:

$$q_h \text{ (anhydrous)} = q_h \text{ (hydrate)} \times \frac{\text{MW (hydrate)}}{\text{MW (anhydrous)}}$$

where q_h is the human potency and MW is the molecular weight. This conversion assumes that the intake of equivalent moles of the two forms of the chemical (e.g. the anhydrous and hydrate forms) results in equivalent concentrations of the active species *in vivo*.

4, 4'-Methylenedianiline didihydrochloride

Results are listed for the drinking water studies by NTP (1983) in male and female $B6C3F_1$ mice and F344 rats. Significant increases in tumors of the liver or thyroid or both are observed for all sex/species combinations tested, with male mice the most sensitive. The cancer potency listed is based on the combined incidence of benign and malignant liver tumors in male mice (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≤ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

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MICHLER'S KETONE (4,4′-bis(dimethylamino) benzophenone)

CAS No: 90-94-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	268.35
Boiling point	>360 °C (with decomposition)
Melting point	172 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 10.98 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.5 E-4 (µg/m^3)$^{-1}$
Slope Factor: 8.6 E-1 (mg/kg-day)$^{-1}$
[Female rat liver tumor data (NCI, 1979), contained in Gold *et* al. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of Michler's ketone in humans are known to exist.

Animal Studies

Male and female Fischer 344 (F344) rats and B6C3F$_1$ mice were fed diets containing Michler's ketone (NCI, 1979). Mice were fed diets containing 1250 or 2500 mg/kg diet Michler's ketone for 78 weeks; animals were then maintained on control diet for an additional 13 weeks. Rats were fed diets containing 250 or 500 mg/kg diet Michler's ketone for males, 500 or 1000 mg/kg diet for females; the treatment period for both sexes was 78 weeks. The treatment period was followed by an observation period; 28 weeks for male rats and high dose female rats and 29 weeks for low dose female rats. Treatment group sizes were 50 animals/sex/species/group; control group sizes were 20 animals/sex/species.

Significant dose-related increases in incidences of liver tumors (hepatocellular adenomas and carcinomas) were observed in rats and female mice, and of hemangiosarcomas in male mice. Tumor incidence data is listed in Table 1.

Table 1. Michler's ketone-induced tumor incidence in male and female F344 rats and $B6C3F_1$ mice (NCI, 1979)

Sex/species	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
Male mice	control	0	hemangiosarcomas	0/20
	low dose	128		5/50
	high dose	257		20/50
Female mice	control	0	liver tumors	0/20
	low dose	139		41/50
	high dose	278		49/50
Male rats	control	0	liver tumors	0/20
	low dose	7.4		17/50
	high dose	14.4		43/50
Female rats	control	0	liver tumors	0/20
	low dose	18		46/50
	high dose	37		48/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results from feeding studies by NCI (1979) are listed by Gold *et al*. (1984). Rats are more sensitive than mice to induction of tumors due to exposure to Michler's ketone, with male and female rats having similar sensitivity. The cancer potency factor for Michler's ketone was derived from dose-response data for liver tumors in female rats as listed in Table 1 (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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National Cancer Institute (NCI) 1979. Bioassay of Michler's Ketone for Possible Carcinogenicity. CAS No. 90-94-8. Carcinogenesis Technical Report Series No. 181. NCI-CG-TR-181. DHEW Publication No. (NIH) 79-1737. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

N-NITROSO-N-DIBUTYLAMINE

CAS No: 424-16-3

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	158.2
Boiling point	116° C @ 14 mm Hg
Melting point	0.5° C
Vapor pressure	Not found
Air concentration conversion	1 ppm = 6.46 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.0 E-2 (µg/m^3)$^{-1}$
Slope Factor: 3.1 E-3 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There is no direct evidence that links nitrosamines, including N-Nitroso-N-dibutylamine (NDBA), to human cancer. The US EPA (1980) and IARC (1978) concluded that the epidemiological studies to date were inadequate to establish a valid causal relationship between nitrosamine exposure and human cancer. The US EPA (1980) also concluded that it was highly improbable that humans are refractory to the carcinogenic effects of nitrosamines considering the number of animal species that show increased tumor incidence following nitrosamine exposure. IARC (1978) concluded: "Although no epidemiological data were available, N-nitrosodi-n-butyl amine should be regarded, for practical purposes, as if it were carcinogenic to humans."

Animal Studies

Groups of DB rats were exposed to NDBA in the drinking water for an unspecified duration (Druckrey *et al*., 1967). The rats were exposed to 10, 20, 37, and 75 mg/kg-day NDBA. The incidence of liver carcinomas and adenomas was 2/10, 4/10, 13/16, and 4/4, respectively. No data on control rats were reported. Median time-to-tumor decreased from 540 days at 10 mg/kg - day, to 150 days at 75 mg/kg - day.

Male Wistar rats (15 total) were exposed for 24 weeks to 0.05% NDBA in drinking water (Okajima *et al*., 1971). Nine animals served as controls. At the end of this period, the 12 remaining animals were necropsied and found to have papillomas of the bladder. Eleven of the 12 animals had bladder carcinomas, 4 had hepatocellular carcinomas, and all had papillomas or carcinomas of the esophagus. The increased incidence of bladder carcinomas and esophageal

tumors was statistically significant compared to the control group ($p < 0.001$). The incidence of liver carcinomas was not statistically different from controls ($p < 0.083$).

A group of 20 male Fischer-F344 rats was exposed to 5.4 mg NDBA by gavage twice per week for 30 weeks (Lijinsky and Reuber, 1983). Six animals survived to 100 weeks. Three animals survived to the end of the 108-week experiment. All treated animals were necropsied and examined for tumors. Of the 20 treated animals, liver carcinomas were observed in 12, lung carcinomas and adenomas in 9 and 4, respectively, forestomach cancer in 10, and bladder cancer in 7. In the control group of 20 male rats, one animal had a lung carcinoma, but no carcinomas of the esophagus, liver, or bladder were observed. The incidences of liver, lung, forestomach, and bladder carcinomas were significantly increased over controls ($p < 0.001$, 0.004, 0.001, and 0.004, respectively.).

A group of 42 male Fischer F344 rats were exposed to 0.005% (50 ppm) NDBA for 4 weeks (Imaida and Wang, 1986). The rats were followed for 100 weeks post-exposure and the median survival was 93 weeks. Esophageal cancer (unspecified type) was found in 26 of the 42 animals and esophageal papillomas in 7 of 42. In addition, liver nodules and carcinomas were found in 8/42 and 3/42 treated animals, respectively, and forestomach papillomas and carcinomas occurred in 6/42 and 2/42 treated animals, respectively. Bladder papillomas and carcinomas were found in 5/42 and 2/42 treated animals, respectively. In the control group of 39 animals, 2 animals had liver nodules, but no other tumors were detected.

Tsuda *et al*. (1987) exposed groups of 20 male F344 rats to 650, 1250, and 2500 ppm NDBA in the diet for 2 weeks. The rats were then fed an untreated diet for 50 weeks, at which time the animals were killed and necropsied. The incidence of bladder papillomas and hepatocellular carcinomas are shown in Table 1.

Table 1. Tumor incidence in male F344 rats exposed to diet containing N-nitroso-N-dibutylamine (NDBA) (Tsuda *et al*., 1987)

NDEA Treatment Group (ppm in diet)	Bladder papillomas	Hepatocellular carcinomas
650	2/20	0/20
1250	2/20	2/20
2500	4/20	4/20

Male ICR mice (39 total) were exposed to 50 ppm NDBA in the diet for 12 months (Takayama and Imaizumi, 1969). Of the surviving 33 mice at the end of 12 months, 27/33 had squamous cell carcinomas of the forestomach, 15/33 developed liver tumors (5 trabecular hepatomas and 10 adenomas), 8/33 developed lung adenomas, and 4/33 developed esophageal papillomas. Examination of the 28 surviving control animals revealed that 2 had lung adenomas, but no other tumors were reported in the controls.

Male or female C57Bl/6 mice (50/sex/group) were exposed to 60 or 240 ppm NDBA in their drinking water from age 10-12 weeks until moribund or dead (Bertram and Craig, 1970). The

incidence of bladder carcinomas in males was 17/47 and 36/45 at the 60 and 240 ppm concentrations, respectively. Females developed bladder carcinomas with an incidence of 2/42 and 8/45 for the 60 and 240 ppm groups, respectively. Esophageal papillomas were found in 45/47 and 40/42 for males and 40/42 and 45/45 for females at the 60 and 240 ppm groups, respectively. No data on unexposed controls were presented.

Male and female Syrian Golden Hamsters (5/sex/group) were given single doses of 400, 800, or 1600 mg/kg NDBA by gavage; groups of 20 males or females served as controls (Althoff *et al*., 1973). Animals were observed for their lifespan and were killed when moribund. Mean survival times were affected in a dose-dependent manner; controls survived 63.5 weeks, and low-, medium- and high-dose groups survived for 59.6, 54.5, and 49.3 weeks, respectively. Respiratory neoplasms (unspecified type) were found in 0/40, 3/10, 5/10 and 7/10 hamsters of the control, low-, medium-, and high-dose groups, respectively. In a later study, Althoff *et al*. (1974) exposed groups of 20 (10/sex/group) male and female Syrian Golden hamsters to 0, 29, 58, 116, 232, or 464 mg/kg NDBA once pre week for life. In this study, the incidences of respiratory neoplasms were 0/20, 0/20, 0/19, 2/16, 12/20, and 8/16 for the groups exposed to 0, 29, 58, 116, 232, or 464 mg/kg NDBA, respectively.

Several studies in mice, rabbits and hamsters have shown NDBA to be carcinogenic following subcutaneous injection (Fuji *et al*., 1977; Flaks *et al*., 1973; Althoff *et al*., 1973 & 1974; Reznik *et al*., 1976; Cohen *et al*., 1975).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by Bertram and Craig (1970) was used by CDHS (1988) to derive the cancer potency for NDBA. The upper bound estimate of cancer potency from these data is the most reliable upper bound from dose-response data in sensitive species.

The upper 95% bound on the multistage polynomial could not be determined from the tumor incidence data in two other studies: Althoff *et al*. (1974) and Okajima *et al*. (1971). The potency estimates from the studies by Lijinsky and Reuber (1983), and Takayama and Imaizumi (1971) both rely on assumptions about the time of sacrifice and corrections for less than lifetime dosing.

Methodology

The study by Bertram and Craig (1970) showed that several organ sites developed tumors in both sexes of mice exposed to NDBA. The combined incidence of bladder and esophageal neoplasms in male mice was used for the potency estimate. These data depict the most reliable dose-response for the most sensitive site and species.

A linearized multistage procedure was used to estimate the cancer potency of NDBA from the Bertram and Craig. (1970) data in male C57Bl/6 mice (Crump *et al*., 1982). The 95% upper

confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 10.8 $[mg/kg \times day]^{-1}$ was calculated for NDBA (CDHS, 1988). An airborne unit risk factor of 1.0E-2 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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N-NITROSO-*N*-METHYLETHYLAMINE

CAS No: 10595-95-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	88.13
Boiling point	163ºC
Melting point	not available
Vapor pressure	not available
Conversion factor	1 ppm = 3.61 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-3 (µg/m^3)$^{-1}$
Slope Factor: 3.7 E+0 (mg/kg-day)$^{-1}$
[Female rat hepatocellular carcinoma data (Druckrey *et al*., 1967), one hit model, time to tumor incidence (US EPA, 1993), cross-route extrapolation]

III. CARCINOGENIC EFFECTS

Human Studies

No human carcinogenicity data on specific exposure to N-nitroso-N-methylethylamine (NMEA) have been reported. Human exposure to nitrosamines is usually the result of exposure to complex mixtures containing these compounds (e.g. cutting oils, tobacco products). Carcinogenicity data on these mixtures are of limited use in evaluating the carcinogenicity of individual nitrosamines because of the presence of other potentially confounding substances.

Animal Studies

Fifteen female BD rats were exposed to N-nitroso-N-methylethylamine (NMEA) in drinking water at doses of approximately 1 mg/kg/day (4 rats) or 2 mg/kg/day (11 rats). Exposure was continuous for the lifetime of the animals. Nine of 15 animals developed hepatocellular carcinomas and one developed a fibrosarcoma of the vagina. Average tumor induction times and total doses to produce tumors in 50% of the animals were 500 days and 0.42 g/kg for the low dose group and 360 days and 0.75 g/kg for the high-dose group. No control group was included in this study (Druckrey *et al*., 1967; reviewed in IARC, 1974 and US EPA, 1993).

DMEA also induced hepatocellular carcinomas (19/20 animals), hemangiosarcomas (17/20) and cholangiocarcinomas (3/20) with accompanying lung metastases and esophageal papillomas and carcinomas in male and female Fisher 344 (F344) rats (20/group) (Lijinsky and Reuber, 1981). Study animals received drinking water (20 ml/day/rat) containing 150 mg/l DMEA 5 days/week (tap water provided on the untreated days) for 30 weeks (total dose 450 mg) with lifetime observation. Untreated control groups were not included in this study. In a similar study, male

F344 rats dosed with 600 µg or 3000 µg DMEA/week (6 or 30 mg/l in drinking water 5 days/week) for 30 weeks developed tumors. Three of 20 animals in the low-dose group developed hepatocellular carcinomas; 12 of 20 animals in the high-dose group developed hepatocellular carcinomas, nasal tumors and esophageal papillomas (Lijinsky and Reuber, 1980). This study also did not include an untreated control group. Liver (hepatocellular carcinoma; 9/20 animals) and nasal cavity (4/20 animals) tumors were also observed in male F344 rats exposed to drinking water containing 30 mg/l NMEA 5 days/week for 30 weeks (total dose 90 mg) (Lijinsky *et al*., 1982). In contrast, the only possibly exposure-related increase in tumor incidence seen in female F344 rats receiving drinking water containing 6 mg/l NMEA was an increased leukemia incidence (18/20 treated compared to 12/20 controls) (Lijinsky *et al*., 1983).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The study by Druckrey *et al*. (1967) in which 9 of 15 female BD rats exposed to 1 mg/kg/day (4 rats) or 2 mg/kg/day (11 rats) DMEA in drinking water over their lifetime developed hepatocellular carcinomas was chosen as the basis of a cancer potency factor for NMEA. This study used lifetime exposure to NMEA in a sensitive species and sex.

Methodology

A one-hit model was fitted to time-to-tumor data from the study by Druckrey *et al*. (1967). The dose associated with a lifetime risk of 0.5 was calculated as follows:

$$d = Ck/(t_{50})^n = \frac{88.1 \text{ mg/mmol} * 0.81 \times 10^4 \text{ mmol/kg/day}}{(728)^{2.3}}$$

where C is the conversion between mmol and mg, k is an empirically derived constant (carcinogenicity index) (Druckrey *et al*., 1967), t_{50} is the median time of tumor induction in days, and n is an empirically generated representative value for dialkylnitrosamines (Druckrey *et al*., 1967). This relationship was derived from experimental data from studies on a number of different N-nitroso compounds. The one-hit model was used to derive a cancer potency factor of 3.72 $(\text{mg/kg/day})^{-1}$. Adjusting this factor by the cube root of the human body weight/assumed rat body weight ratio $[(70 \text{ kg}/0.35 \text{ kg})^{1/3}]$ results in a human cancer potency factor of 2.2 E+1 $(\text{mg/kg/day})^{-1}$. A unit risk of 6.3 E-3 $(\mu\text{g/m}^3)^{-1}$ was then calculated by OEHHA/ATES from the cancer potency factor (20 m^3/day inspiration rate).

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N-NITROSODI-N-PROPYLAMINE

CAS No: 621-64-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	130.12
Boiling point	not available
Melting point	not available
Vapor pressure	0.086 mm Hg @ 20°C
Air concentration conversion	1 ppm = 5.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-3 (µg/m^3)$^{-1}$
Slope Factor: 7.0 E+0 (mg/kg-day)$^{-1}$
[calculated from a cancer slope factor derived by US EPA (1986)]

III. CARCINOGENIC EFFECTS

Human Studies

No studies addressing the carcinogenicity of N-nitrosodi-n-propylamine to humans have been conducted.

Animal Studies

Druckrey *et al.* (1967) treated a total of 48 BD rats (sex unspecified) orally with N-nitrosodi-n-propylamine at concentrations of 4, 8, 15, or 30 mg/kg body weight 7 days per week for life (16, 16, 15, and 1 animal, respectively). An untreated control group was not included in the study, although background tumor incidence was reported to be negligible. Liver carcinoma incidence was 14/16, 15/16, 15/15, and 1/1 in the four dose groups, respectively. Tumor induction time was dose-related. The authors also note tumors of the esophagus (8/48) and tongue (6/48).

Lijinsky and Taylor (1978, 1979) exposed 15 male Sprague-Dawley rats to N-nitrosodi-n-propylamine in drinking water 5 days/week for 30 weeks at 1.8 mg/day resulting in a daily dose of 5.1 mg/kg-day. No control group was included. Liver carcinomas (9/15), esophageal papillomas (6/15) and carcinomas (8/15), and nasal adenocarcinomas (8/15) were observed among exposed rats.

Lijinsky and Reuber (1981) exposed 20 Fischer 344 rats (sex unspecified) to N-nitrosodi-n-propylamine in drinking water at 0.9 mg/day for 5 days/week for 30 weeks resulting in a daily

dose of 2.6 mg/kg-day. No control group was included. Esophageal carcinomas (20/20) and forestomach tumors (12/20) developed in exposed animals.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

US EPA (1986) based its selection of a cancer potency on a study which demonstrates induction of liver tumors by N-nitrosodi-n-propylamine. US EPA (1986) used the data from Druckrey *et al.*(1967) in the induction of hepatocellular carcinoma in BD rats exposed to N-nitrosodi-n-propylamine in drinking water to calculate a cancer potency value.

Methodology

The high tumor incidence in all the N-nitrosodi-n-propylamine treated animals suggests time-dependent analysis is more appropriate than multistage analysis in the derivation of a cancer potency value. A dosage estimate for use in deriving the cancer potency value was based on the following relationship, where d is the daily dose, C is the mmol to mg conversion factor (130.2 mg/mmol), k is an empirically derived constant estimated from a plot of k versus the number of carbon atoms for lower di-N-alkylnitrosamines ($k=1.7 \times 10^4$ mmol/kg-day), t_{50} is the median time of tumor induction, and n is a representative value for dialkylnitrosamines (n=2.3; Druckrey *et al.*, 1967):

$$d = \frac{C \times k}{t_{50}^{\,n}}$$

The resulting daily dose estimate was 0.578 mg/kg-day. Applying this estimate to a rearrangement of the one-hit model gave an animal cancer potency value (q_{animal}) of 1.2 $(\text{mg/kg-day})^{-1}$.

$$q_{animal} = -\ln(0.5/\text{day}) / d$$

Conversion of the q_{animal} to a human cancer potency estimate (q_{human}) was made based on the following relationship, where bw_h is the assumed human body weight (70 kg) and bw_a is the assumed experimental animal body weight (0.35 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimate of q_{human} was 7.0 $(\text{mg/kg-day})^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-3 $(\mu g/m^3)^{-1}$.

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N-NITROSODIETHYLAMINE

CAS No: 55-18-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	102.1
Boiling point	175-177° C
Melting point	Not found
Vapor pressure	0.86 mm Hg @ 20° C
Air concentration conversion	1 ppm = 4.2 mg/m^3 @ 25° C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.0 E-2 (µg/m^3)$^{-1}$
Slope Factor: 3.6 E+1 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There is no direct evidence that links nitrosamines, including N-nitrosodiethylamine (NDEA), to human cancer. The US EPA (1980) concluded that the epidemiological studies to date were inadequate to establish a valid causal relationship between nitrosamine exposure and human cancer. The US EPA (1980) also concluded that it was highly improbable that humans are refractory to the carcinogenic effects of nitrosamines considering the number of animal species that show increased tumor incidence following nitrosamine exposure.

Animal Studies

A number of qualitative studies were conducted in a range of species, including rats, mice, hamsters, guinea pigs, rabbits, dogs, and monkeys (Yamamoto *et al*., 1972; Druckrey *et al*., 1967; Magee *et al*., 1976; Rajewski *et al*., 1966; Tomatis, 1973). In addition to these studies, a number of later studies show evidence of quantitative dose-response relationships.

Drinking water containing a range of concentrations from 0.033 to 16.896 ppm NDEA was administered to male and female Colworth rats (60/sex/group) for their natural lifespan (Peto *et al*., 1982; 1984). The control groups consisted of 240 rats/sex. Nearly all animals exposed to the high dose of NDEA died from tumors of the liver or esophagus (Table 1). Other sites showing an increase in tumors included the lower jaw, stomach, kidney, ovaries, seminal vesicles, and nasopharynx.

Table 1. Liver tumors in Colworth male and female rats exposed to drinking water containing N-nitrosodiethylamine (NDEA) (Peto *et al*., 1982)

NDEA concentration (ppm)	Observed deaths from liver tumors	
	males	females
0	1/240	1/240
0.033	1/60	0/60
0.066	0/60	0/60
0.132	5/60	1/60
0.264	2/60	1/60
0.528	4/60	3/60
1.056	8/60	23/60
1.584	14/60	37/60
2.112	7/60	38/60
2.640	17/60	47/60
3.168	17/60	42/60
4.224	26/60	42/60
5.280	26/60	43/60
6.336	30/60	47/60
8.448	25/60	55/60
16.896	44/60	49/60

A later analysis by Peto *et al*. (1984) showed that, in rats, the initial age of contact with NDEA was important in determining the probability of liver cancer. Young rats were much more susceptible than adults to NDEA-induced liver neoplasia than adults exposed for an equal amount of time.

Lijinsky *et al*. (1981) administered NDEA in the drinking water to 11 groups of female Fisher-344 rats (20 per group) for varying durations, up to 104 weeks. The animals were observed for their lifespan. The treatment groups are shown in Table 2.

Table 2. Treatment groups, concentrations, and durations of N-nitrosodiethylamine (NDEA) exposures in female Fisher 344 rats (Lijinsky *et al*., 1981).

Treatment Group	NDEA concentration(mg/l)	Treatment duration (weeks)
Control	0	104
1	113	17
2	45	22
3	18	30
4	7	30
5	2.8	30
6	1.1	30
7	1.1	60
8	0.45	30
9	0.45	60
10	0.45	104

Treatment related increases in the incidence of tumors were observed in the liver, forestomach, esophagus and tongue. The incidence of tumors in the animals exposed to the lowest concentration are shown in Table 3.

Table 3. Tumor incidence in female rats exposed to 0.45 mg/l N-nitrosodiethylamine (NDEA) in drinking water for 0, 30, 60, or 104 weeks (Lijinsky *et al*., 1981).

Treatment duration (weeks)	Total dose (mg) of NDEA	Esophageal carcinoma or papilloma	Forestomach papilloma	Tongue carcinoma	Liver carcinoma	Liver carcinoma or hyperplastic nodule
0	0	0/20	0/20	0/20	0/20	1/20
30	1.35	1/20	1/20	1/20	1/20	6/20
60	2.70	3/20	2/20	2/20	6/20	11/20
104	4.68	13/20	5/20	2/20	4/20	7/20

Habs and Schmahl (1980) exposed male Sprague-Dawley rats (90 per group) to 0 or 0.1 mg/kg/day NDEA in the drinking water 5 times weekly until natural death of the animals. Another group of rats received NDEA followed by a 25% solution of ethanol. Liver tumors (histological type unspecified) were observed in 0/82 controls and 36/82 NDEA-treated rats, respectively. The rats receiving ethanol in addition to NDEA showed a liver tumor incidence of 4/59. A similar pattern was seen for the development of esophageal tumors. Rats exposed to NDEA alone developed esophageal tumors (type unspecified) at a rate of 33/82. Rats exposed to NDEA and ethanol developed esophageal tumors in 18/59 cases, and controls had a tumor incidence of 0/82.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The studies by Peto *et al*. (1982; 1984) were used by CDHS (1988) to derive the cancer potency for NDEA. These studies utilized relatively large numbers of animals (60-240 per group) over a wide dose range. The Peto *et al*. (1982) study contained more information about the dose-response at the low range of experimental doses than the other studies described. Therefore, the cancer potency for NDEA was calculated from the Peto *et al*. (1982) study even though the calculated value is lower than other potency estimates from Lijinsky *et al*. (1981) or Habs and Schmahl (1980).

Methodology

The study by Peto *et al*. (1982) showed that several organ sites developed tumors in both sexes of rats exposed to NDEA. The incidence of hepatocellular neoplasms (histological designation unknown) in males resulted in the highest potency value when only the 6 lowest doses were considered. Water consumption by male rats was reported by Peto *et al*. (1984) to be 41 mL/kg/day. Low-dose group mortality did not differ significantly from that observed in the control group, therefore no time corrections were applied to the calculation.

A linearized multistage procedure was used to estimate the cancer potency of NDEA from the Peto *et al*. (1982) data in male Colworth rats (Crump *et al*., 1982). The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime of the animal. In this case, the scaling factor was equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the body weight of human or animal, in this case, 450 grams for male rats.

Using these relationships, a human cancer potency (q_{human}) of 36 $[mg/kg \times day]^{-1}$ was calculated for NDEA (CDHS, 1988). An airborne unit risk factor of 1.0E-2 $(\mu g/m^3)^{-1}$ was calculated by OEHHA/ATES from the q_{human} value using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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N-NITROSODIMETHYLAMINE

CAS No: 62-75-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	74.1
Boiling point	151°C
Melting point	unknown
Vapor pressure	2.7 mm Hg @ 20°C
Air concentration conversion	1 ppm = 3.08 mg/m^3 @ 20°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-3 (µg/m^3)$^{-1}$
Slope Factor: 1.6 E+1 (mg/kg-day)$^{-1}$
[calculated from a cancer potency value derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

Epidemiological studies correlating exposure to N-nitrosodimethylamine (NDMA) and human cancers are inadequate to establish a causal relationship.

Animal Studies

Terracini *et al* .(1967) exposed male and female MRC Porton rats to feed containing 0, 2, 5, 10, 20 or 50 ppm for up to 120 weeks. Daily dose rates were calculated based upon observed food consumption rates of 15 g/day. Most survivors were sacrificed at 104 weeks, with the exception of an unspecified number of animals which were sacrificed at 120 weeks. Liver tumor incidence data were grouped into those which occured among animals surviving greater than or less than 60 weeks. No liver tumors were reported among 29 untreated animals, four of which died before 60 weeks. Combined incidence data of liver tumors among female rats dying at any time during the course of the experiment were 0/18, 4/62, 2/5, 15/23, and 10/12 for the 2, 5, 10, 20, and 50 ppm dose groups, respectively. Significant dose-related increase in incidence of liver tumors and mortality in female rats was reported (level of significance not stated).

Terracini *et al*. (1973) exposed 4-5 week old female BALB/c mice to 3 ppm NDMA in drinking water for up to 80 weeks in a two generation study. The first generation treated group consisted of 62 animals and the second generation treated group consisted of 66 animals. Among first and second generation animals, an increased incidence of lung tumors was found (first generation:

44/62 treated vs. 20/62 control, $p = 10^{-5}$; second generation: 44/66 treated vs. 15/69 control, $p = 10^{-8}$).

Terao *et al.* (1978) exposed 4 week old male Wistar rats to feed containing NDMA and/or sterigmatocystin (STG) for 54 weeks. Five exposure groups included 10 ppm STG alone, 10 ppm STG and 1 ppm NDMA, 1 ppm STG and 10 ppm NDMA, 10 ppm NDMA, and a group receiving basal diet alone. Animals were sacrificed at 69 weeks with the exception of one animal from each group sacrificed after 5 weeks of exposure. Rats in all groups exposed to NDMA showed an increased incidence of Leydig-cell tumors (p=0.002). Liver tumors were not observed in the group receiving NDMA alone; however, liver tumor incidence was elevated in the group receiving STG alone and in the group receiving 10 ppm STG and 1 ppm NDMA.

Arai *et al.* (1979) exposed 6 week old male and female Wistar rats (7 to 17/sex/group) to feed containing 0, 0.1, 1 or 10 ppm NDMA for 96 weeks. Food intake was monitored. Treated female animals were found to have a higher incidence of nodular hyperplastic liver lesions ($p<0.05$, Fisher's exact test).

Griciute *et al.* (1981) treated 8 week old male and female C57BL mice with NDMA (0.03 mg) and/or ethanol (0.8 ml) in 0.2 ml water by intragastric intubation for 50 weeks. Control animals received only water. Survivors were sacrificed at 80 weeks. No liver tumors developed in animals receiving ethanol alone. Among animals receiving NDMA alone, the incidence of malignant liver tumors was increased over controls (14/37 treated males, $p = 10^{-5}$; 16/29 treated females, $p < 10^{-6}$). Among animals receiving both NDMA and ethanol, the incidence of forebrain olfactory neuroepithelioma was increased (24/66 treated vs. 0/66 control; $p<0.001$). No tumors of this type were observed in animals receiving NDMA or ethanol alone.

Peto *et al.* (1982, 1984) exposed Colworth rats (60/sex/group) to NDMA in drinking water at 15 concentrations ranging from 0.033 to 16.896 ppm for life. A group of 240 animals receiving only drinking water served as controls. Additional treatment groups of 6 animals/group were sacrificed at 6 and 12 months. Water consumption for male and female rats was 41 ml/kg and 72 ml/kg, respectively. Among exposed animals, the incidence of fatal liver neoplasms (see Table 1) was significantly increased over controls ($p\leq0.005$) and the increase was found to be dose-related. Other tumors with trends toward increased incidence include tumors of the lung (p=0.004), skin (p=0.001), lymphatic/hematopoietic tissues (p=0.032), and seminal vesicles (p=0.004).

Lijinski and Reuber (1984) exposed 7-8 week old female Fischer 344 rats (20/group) to NDMA in drinking water at concentrations of 13 and 5.5 mg/l for 5 days/week for 30 weeks. Animals were observed for life. Hepatocellular carcinomas, hemangiosarcomas, and neoplastic nodules were observed in treated animals. Significantly increased incidence of liver tumors of all types was observed in both low-dose (14/20 treated vs. 2/20 controls; $p = 10^{-4}$) and high-dose (19/20 treated vs. 2/20 controls; $p < 10^{-5}$) animals.

Table 1. Liver tumor incidence data in Colworth rats exposed to NDMA in drinking water (Peto *et al.*, 1982).

dose level (ppm)*	fatal liver tumor incidence	
	male	female
0	1/240	1/240
0.033	1/60	1/60
0.066	3/60	0/60
0.132	3/60	2/60
0.264	3/60	3/60
0.528	3/60	5/60
1.056	5/60	5/60
1.584	3/60	27/60
2.112	13/60	33/60
2.640	27/60	44/60
3.168	33/60	48/60
4.224	36/60	53/60
5.280	46/60	52/60
6.336	49/60	51/60
8.448	55/60	55/60
16.896	59/60	58/60

*Colworth rats (48/sex/group) were exposed to NDMA in drinking water for life.

Druckrey *et al.*(1967) exposed BD rats (sex unspecified) to NDMA by inhalation twice per week for 30 minutes. One group of 6 rats received 100 ppm NDMA and a group of 12 rats received 50 ppm NDMA. No information on a control group was reported. Tumors of the nasal turbinates were reported at the time of death in 4/6 and 8/12 of the high- and low-dose groups, respectively. Three animals in the low-dose group died prematurely (time unspecified). No liver tumors were reported in either group.

Moiseev and Benemansky (1975; reviewed in IARC, 1978) exposed Balb/c mice and Wistar rats to NDMA by inhalation at concentrations of 0.005 and 0.2 mg/m^3. Exposure duration was 17 months for mice and 25 months for rats. At 0.2 mg/m^3 NDMA, tumors of the lung, liver, and kidney were reported to arise earlier and in greater numbers than in control animals (IARC, 1978). Exposures to the lower concentration did not result in significantly increased incidence in tumors over controls.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Five studies showing tumor induction in animals by NDMA have been deemed appropriate by CDHS (1988) for the development of cancer potency values. The values derived from the studies

are presented in Table 2. The methodologies used to derive the values are described below as well as the rationale for selection of the OEHHA unit risk value for NDMA.

Methodologies

Peto *et al* .(1982, 1984) derived potency values from the incidence data of fatal liver tumors in male and female Colworth rats. The cumulative risk was calculated based on the assumption that the risk increases with the seventh power of exposure duration and the observation that a dose of 1.0 µg/kg-day results in a 0.03-0.04% incidence of liver tumors at two years. Estimated cancer potency at low doses (q_{animal}) was found to be 0.29 and 0.4 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively. Peto *et al.* (1982,1984) also scaled these potencies up by a factor of 7 to account for calculated increased risk from the observation that median experimental animal lifespan was beyond 2 years in this study. Conversion to human potency values (q_{human}) was based on the body weight scaling relationship described below, with an assumed human body weight (bw_h) of 70 kg and experimental animal body weights (bw_a) of 450 and 250 g for male and female rats:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting q_{human} values were 12 and 16 $(mg/kg\text{-}day)^{-1}$ from the male and female rat data, respectively.

Dose rate estimates of 0.82 mg/kg-day for female BALB/c mice receiving NDMA in drinking water in the study by Terracini *et al.* (1973) were based on a US EPA (1988) reference animal body weight value and water consumption rate (CDHS, 1988). Using a multistage procedure, experimental potencies (q_1^*) derived from this dose rate using the incidence of lung tumors in F_0 and F_1 generation animals were 1.5 and 1.6 $(mg/kg\text{-}day)^{-1}$, respectively. Potency in animals (q_{animal}) was estimated assuming cancer incidence increases with the third power of age, with T_e the experimental duration and T the natural lifespan of the animals (104 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

Further conversion to human cancer potencies with a body weight scaling factor were made as described for Peto *et al.*(1982,1984) resulting in human potency estimates (q_{human}) of 49 and 53 $(mg/kg\text{-}day)^{-1}$ from the F_0 and F_1 generation mouse tumor incidence data, respectively.

High- and low-dose rates estimates of 0.80 and 0.35 mg/kg-day in the study by Lijinsky and Reuber (1984) were based on US EPA (1988) animal body weight reference values in the induction of liver tumors in Fischer 344 rats (CDHS, 1988). Using the Crouch (1983) correction for variable dosing and a multistage procedure, the animal cancer potency estimate (q_{animal}) was 5.8 $(mg/kg\text{-}day)^{-1}$. Using the body weight conversion factor as described in the Peto *et al.* (1982, 1984) potency derivation (bw_a=0.229 kg; US EPA, 1988), the resulting q_{human} was 39 $(mg/kg\text{-}day)^{-1}$.

Dose rate estimates to MRC Porton rats exposed to NDMA in diet in the study by Terracini *et al.* (1967) were made by the method of Crouch (1983) to account for variable dosing during the

course of the experiment (CDHS, 1988). Using liver tumor incidence among female rats surviving less than 60 weeks, a q_{animal} value of 5.8 $(mg/kg\text{-}day)^{-1}$ was derived from a multistage procedure. Conversion to q_{human} based on a body weight scaling factor resulted in a potency value of 34 $(mg/kg\text{-}day)^{-1}$. Using liver tumor incidence of animals surviving more than 60 weeks resulted in a q_{human} value of 7.6 $(mg/kg\text{-}day)^{-1}$; however, this value may be an underestimate because of early mortality in exposed animals.

Arai *et al.* (1979) estimated an NDMA dose rate of 0.018 and 0.033 mg/kg-day for male and female Wistar rats, respectively, based on experimentally reported food consumption rates and animal body weights. Applying a multistage procedure to the incidence of liver fibrosarcoma in male rats resulted in an estimated q_{animal} of 5.0 $(mg/kg\text{-}day)^{-1}$. Similarly, a q_{animal} for incidence of liver cancer in female rats was found to be 3.8 $(mg/kg\text{-}day)^{-1}$. The resulting q_{human} values from each of these tumor types were 29 and 25 $(mg/kg\text{-}day)^{-1}$, respectively.

Terao *et al.* (1978) demonstrated induction of Leydig-cell tumors in male Wistar rats fed diet containing NDMA. Dose rate calculations of 0.736 mg/kg-day were based on US EPA (1988) reference food intake and body weight values (CDHS, 1988). The dose correction method of Crouch (1983) was applied to account for variable dosing during the course of the experiment. Applying a multistage procedure to the tumor incidence data resulted in a q_{animal} value of 5.8 $(mg/kg\text{-}day)^{-1}$. The corresponding q_{human} value based on the body weight conversion factor was 31 $(mg/kg\text{-}day)^{-1}$.

Table 2. Cancer potencies derived from animal studies.

Study	Tumor type	Sex	q_{human} $(mg/kg\text{-}day)^{-1}$
Peto *et al.*(1982,1984)	fatal liver tumor	male female	12 16
Terracini *et al.*(1973)	lung tumor	F_0 female F_1 female	49 53
Lijinsky and Reuber (1984)	liver tumor	female	39
Terracini *et al.*(1973)	liver tumor	female	34
Arai *et al.* (1979)	liver fibrosarcoma liver cancer	male female	29 25
Terao *et al.*(1978)	Leydig cell tumor	male	31

Cancer potency estimates from these studies range from 12 to 53 $(mg/kg\text{-}day)^{-1}$. Of these, the q_{human} values from the Peto *et al.* (1982,1984) study were derived from the experiment with the lowest daily dose rate and the data, therefore, are most appropriate for performing a low-dose risk extrapolation. Although the q_{human} values from Peto *et al.* (1982,1984) are lower than those derived from other studies, the fact that this study was conducted at low-doses and demonstrated sensitive and significant induction of liver tumors indicates it is useful for estimation of the cancer potency of NDMA. Furthermore, the other studies were neither as large in scale nor as long in duration, suggesting potency estimates from these studies may be overly conservative and

not as representative of the true value. The most sensitive q_{human} value of 16 $(mg/kg\text{-}day)^{-1}$ derived from Peto *et al.* (1982,1984) was therefore adopted as a cancer potency value.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 4.6 E-3 $(\mu g/m^3)^{-1}$.

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N-NITROSODIPHENYLAMINE

CAS No: 86-30-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	198.2
Boiling point	66.5°C
Melting point	unknown
Vapor pressure	0.1 mm Hg @ 25°C
Air concentration conversion	1 ppm = 8.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.6 E-6 (µg/m^3)$^{-1}$
Slope Factor: 9.0 E-3 (mg/kg-day)$^{-1}$
[calculated from a cancer potency value derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for N-nitrosodiphenylamine (NDPA).

Animal Studies

Seven day-old B6C3F$_1$ and B6AKF$_1$ mice (18/sex/group) were treated with 1000 mg NDPA in dimethyl sulfoxide per kg body weight by oral gavage for 4 weeks (initial dose was not adjusted) (NTIS, 1968; Innes *et al.*, 1969). Mice were then exposed to 3769 ppm NDPA in feed to 79 weeks of age. Animals were observed for a total of 18 months. Among male B6C3F$_1$ mice, 6/15 surviving animals developed hepatomas versus 1/17 matched controls. Among female B6AKF$_1$ mice, 3/18 developed lung adenomas versus 0/17 matched controls. No statistically significant increases in tumor incidence were reported by NTIS (1968). However, a re-analysis of incidence data by current methodology showed significant increases in hepatoma incidence among male B6C3F$_1$ mice (p=0.027 by Fisher's exact test) and borderline significant increase in lung adenoma incidence among female B6AKF$_1$ mice (p=0.07) (CDHS, 1988).

B6C3F$_1$ mice (50/sex/group) were fed diet containing NDPA at two dose levels (NCI, 1979; Cardy *et al.*, 1979). Male mice received either 10000 or 20000 ppm NDPA in their diet for 101 weeks. The low- and high-dose groups of female mice received 5000 or 10000 ppm NDPA , respectively, for 38 weeks, no NDPA for 3 weeks, then 1000 or 4000 ppm NDPA for 60 weeks. Groups of 20 mice/sex fed only standard diet served as controls. No statistically significant

increases in tumor incidence were observed over controls. Some incidence of epithelial hyperplasia of the urinary bladder was noted which was not seen in control animals.

Six-week old Fischer 344 rats (50/sex/group) were exposed to diet containing 1000 or 4000 ppm NDPA for 100 weeks, with groups of 20 rats/sex serving as controls (NCI, 1979; Cardy *et al.*, 1979). No dose-related increase in mortality was observed in male mice; however, a dose-related increase in mortality was observed in females (p=0.024). Among male rats, incidence of transitional-cell carcinoma of the urinary bladder was 16/45 in the high-dose group, 0/46 in the low-dose group, and 0/19 in the control animals (p=0.001). Among female rats, incidence of transitional-cell carcinoma of the bladder was 40/49 in the high-dose group, 0/46 in the low-dose group, and 0/18 in the control animals (p<0.001). Among male mice, a dose-related trend in increased incidence of fibroma of the subcutis and skin was observed (p=0.003).

Argus and Hoch-Ligeti (1961) treated 25 male Wistar rats (92 g average body weight) with 1070 μg NDPA in 1 ml of 1.1% aqueous methylcellulose by oral gavage for 45 weeks, 5 days per week. At 53 weeks, all rats were alive and upon autopsy, no tumors were observed.

Druckrey *et al.* (1967) exposed 20 BD rats (sex unspecified) to NDPA in drinking water at a daily dose of 120 mg/kg body weight. No tumors were observed within 700 days.

Iverson (1980) applied 0.1 ml of 1% NDPA in acetone weekly for 20 weeks to the interscapular skin of 16 male and 24 female hairless hr/hr Oslo mice. Appropriate control mice were not included. Upon necropsy at 80 weeks, lung adenomas were observed in three of the 14 male survivors.

Boyland *et al.* (1968) injected 6-7 week old male CB rats (24/group) intraperitoneally with 2.5 mg NDPA in polyethylene glycol 400 once per week for six months. Control animals were injected with vehicle alone. After 2 yrs of observation, one of five treated and one of ten control rats which survived the treatment had hepatomas. One treated rat also had a pituitary adenoma.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Two animal studies described above are adequate for the derivation of cancer potency values for N-nitrosodiphenylamine. The studies initiated by Cardy *et al.* (1979) and Innes *et al.* (1969) were conducted with adequate numbers of animals and with appropriate controls such that statistically significant increases in tumor incidence were established. Cardy *et al.* (1979) report increased incidence of transitional-cell carcinomas of the bladder in male and female Fischer 344 rats. Innes *et al.*(1969) report increased incidence of hepatomas in male $B6C3F_1$ mice. The derivation of cancer potency values from these studies and the selection of a reference unit risk value are described below.

Methodology

Dosage estimates of NDPA from the Cardy *et al.* (1979) study were made based on reference body weights of 0.380 and 0.229 kg and daily food consumption rates of 0.030 and 0.021 kg for male and female mice, respectively. The resulting daily dosage calculations are 79 and 92 mg/kg-day for males and females, respectively, for the groups fed 1000 ppm in their diet, and 316 and 368 mg/kg-day for males and females, respectively, for the groups fed 4000 ppm in their diet. Fitting a multistage procedure to the incidence data for transitional-cell carcinoma of the bladder gives upper 95% confidence bounds on the cancer potency (q_1^*) of 0.00050 and 0.00048 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively (Crump and Howe (1984)).

Calculation of the cancer potency for animals (q_{animal}) can be made using q_1^* and the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (100 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} values of 0.00056 and 0.00050 $(mg/kg\text{-}day)^{-1}$ for male and female rats, respectively, can be converted to human cancer potency values (q_{human}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species and bw_{human} is the assumed human body weight (reference values from US EPA (1986)):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

The resulting estimates of q_{human} are 0.0032 and 0.0034 $(mg/kg\text{-}day)^{-1}$.

Daily dosage estimates for animals from the Innes *et al.*(1969) study were made with estimates of food consumption rates of 12% and 13% for male and female mice, respectively, based on Gold *et al.* (1984). During the oral gavage dosing period (days 7 to 28) it is assumed that a linear threefold increase in body weight occurs. The method of Crouch (1983) was used to account for variable dosing during the study period. Calculations of daily dosage are 444 and 476 mg/kg-day for male and female mice, respectively. Fitting the linear model below to the significant tumor incidence data for hepatomas in male $B6C3F_1$ mice results in a cancer potency estimate (q_{animal}) of 0.0046 $(mg/kg\text{-}day)^{-1}$. In this relationship, D is the estimated daily dose, $p(T_e)$ is the probability of dying with a tumor at time T_e, and A is the background (control) tumor incidence.

$$q_{animal} = \frac{-\ln[1 - p(T_e)] - A}{D}$$

Conversion of the q_{animal} to q_{human} is achieved as described for the Cardy *et al.* (1979) data, with an assumed experimental animal body weight (bw_{animal}) of 0.03 kg. The resulting q_{human} for this study is 0.061 $(mg/kg\text{-}day)^{-1}$.

Selection of a reference cancer potency value comes from identification of the most sensitive site, species, sex and study, in the absence of evidence that the data are not representative. The Innes *et al.*(1969) study presents the highest, and thus most sensitive, cancer potency value of

0.061 (mg/kg-day)$^{-1}$. The lower 95% confidence bound on the Innes *et al.* (1969) potency value also exceeds the potency values derived from Cardy *et al.* (1979) indicating the mouse strain used by Innes *et al.* (1969) may be more sensitive. The small number of animals used in this preliminary study, however, suggests the possibility this value may be overly conservative. The two q_{human} values for NDPA in male and female rats derived from Cardy *et al.* (1979) are close, 0.0032 and 0.0034 (mg/kg-day)$^{-1}$, respectively. Since these data were derived from a large, thorough study, the development of a reference cancer potency value should include these values. The potency estimate was therefore derived from the geometric mean of the three q_{human} values described above according to the approach of Anderson *et al.* (1983). The resulting reference q_{human} is 0.009 (mg/kg-day)$^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.6 E-6 ($\mu g/m^3$)$^{-1}$.

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p-NITROSODIPHENYLAMINE

CAS No: 156-10-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	198.24
Boiling point	not available
Melting point	144-145 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 8.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.3 E-6 (µg/m^3)$^{-1}$
Slope Factor: 2.2 E-2 (mg/kg-day)$^{-1}$
[Male rat liver tumor data (NCI, 1979), contained in Gold *et al.* (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *p*-nitrosodiphenylamine in humans are known to exist.

Animal Studies

Male and female Fischer 344 rats and B6C3F$_1$ mice were fed diets containing technical grade *p*-nitrosodiphenylamine (73% active material, 25% water, unspecified impurities). Rats were fed diets containing 2500 or 5000 mg/kg diet *p*-nitrosodiphenylamine for 78 weeks, followed by a 27 week observation period. Mice were fed diets containing either 5000 mg/kg diet *p*-nitrosodiphenylamine for 40 weeks, then 2500 mg/kg diet for 17 weeks, or 10000 mg/kg diet for 40 weeks, followed by control diet for 7 weeks, then 5000 mg/kg for 10 weeks. Both dose groups were then maintained on control diet for an additional 35 weeks. Treatment groups consisted of 50 animals/sex/species/group; matched control groups consisted of 20 animals/sex/species and were kept under observation for 105 and 92 weeks for rats and mice, respectively. Rat survival was 90, 86 and 92% for males and 85, 84 and 92% for females in the control, low-dose and high-dose groups, respectively. Mouse survival was 85, 88 and 60% for males and 90, 84 and 52% for females in the control, low-dose and high-dose groups, respectively. Significant increases in the incidence of liver tumors (neoplastic nodules, hepatocellular adenomas and carcinomas) was noted in treated male mice and rats. Tumor incidence data is listed in Table 1.

Table 1. *P*-Nitrosodiphenylamine-induced liver tumor incidence in male Fischer 344 rats and $B6C3F_1$ mice (NCI, 1979)

Species	Dose group	Average dose[1] (mg/kg-day)	Tumor incidence[2]
rat	control	0	0/20
	low dose	74.3	10/50
	high dose	149	19/50
mouse	control	0	2/20
	low dose	316	22/50
	high dose	587	12/50

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The results of NCI (1979) feeding studies of *p*-nitrosodiphenylamine in male and female F344 rats and $B6C3F_1$ mice are listed by Gold *et al.* (1984). NTP (1991) characterizes the studies in male rats and male mice as positive. Significant increases in malignant liver tumors were observed in males of both species, with rats displaying greater sensitivity to the compound. However, survival was significantly reduced in the study in male mice, so the apparently lower sensitivity of these animals may have been due to the fact that they were at risk for a shorter time period than the rats. Cancer potency is based on the dose-response data for liver tumors in male rats as seen in Table 1 (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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Hazardous Substance Data Bank (HSDB) 1994. National Library of Medicine, Bethesda MD (CD-ROM Version). Micromedix, Inc., Denver CO, Edition 22.

National Cancer Institute (NCI) 1979. Bioassay of *p*-Nitrosodiphenylamine for Possible Carcinogenicity. CAS No. 156-10-5. Carcinogenesis Technical Report Series No. 190. NCI-CG-TR-190 DHEW Publication No. (NIH) 79-1746. U.S. Department of Health, Education and Welfare, NCI Carcinogenesis Testing Program, Bethesda, MD.

N-NITROSOMORPHOLINE

CAS No: 59-89-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	116.11
Boiling point	224-225 °C (@ 747 mm Hg)
Melting point	29 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.75 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.9 E-3 (µg/m^3)$^{-1}$
Slope Factor: 6.7 E+0 (mg/kg-day)$^{-1}$
[Female hamster respiratory tract tumor data (Ketkar *et al*., 1983), contained in Gold *et al.* (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of N-nitrosomorpholine in humans are known to exist.

Animal Studies

IARC (1978) reviewed a study in which 58 male NMRI mice were exposed to N-nitrosomorpholine in drinking water at a concentration of 100 mg/l for the life of the animals (Bannasch and Müller, 1964; Müller, 1964). Increases in liver tumor incidence were noted; 16/58 animals developed hepatocellular adenomas. Treated animals also developed "numerous" lung adenomas and one lung squamous cell carcinoma was observed. Only 1/17 controls developed lung adenomas.

Male and female MRC rats (15 animals/sex) were exposed to *N*-nitrosomorpholine in drinking water (100 mg/l; total dose 500 mg) for 50 weeks, then observed for the life of the animal (Garcia and Lijinsky, 1972). Male and females displayed increased incidences of liver tumors (hepatocellular carcinomas and hemangioendotheliomias; 13/15 and 13/14 in males and females, respectively) and nasal cavity tumors (9/15 and 5/14 in males and females, respectively). The study did not report that a control group was included.

Male and female Syrian golden hamsters (20/sex/group) were given weekly subcutaneous injections of *N*-nitrosomorpholine, which were one-fifth, one-tenth or one-twentieth of the LD50

of *N*-nitrosomorpholine, for life (Haas *et al*., 1973). Males received 24.6, 49.2 or 98.4 mg/kg body weight; females recieved 28.1, 56.2 or 112.4 mg/kg body weight. Treatment-related increases in the incidence of respiratory tract tumors (primarily in the nasal cavity and trachea) were observed.

Lijinsky *et al*. (1976) exposed male Sprague-Dawley rats (30/exposure group) to *N*-nitrosomorpholine in drinking water (8 or 40 mg/l, 5 days/week; total dose 0.21 and 1.05 mM, respectively) for 30 weeks. The animals were then observed for the remainder of their lifetime. Hepatocellular (benign or malignant) tumors were reported in 11/30 and 16/30 low- and high-dose animals, respectively. Hemangioendothelial tumors were reported in 1/30 and 2/30 low- and high-dose animals, respectively. The authors did not report the inclusion of a control group in this study.

Ketkar *et al*. (1983) exposed male and female Syrian golden hamsters (30/sex/group) to 0.001, 0.005 or 0.01% *N*-nitrosomorpholine in the drinking water for life; untreated control groups (50 animals/sex) were also included. Increased incidences of benign and malignant tumors of the respiratory tract (primarily papillary polyps, papillomas and epidermoid carcinomas of the larynx and trachea) and the gastrointestinal tract (primarily liver tumors, including hepatocellular adenomas and carcinomas) were observed in both males and females. No corresponding tumors were observed in the control groups. Tumor incidence data is listed in Table 1.

Table 1. *N*-nitrosomorpholine-induced tumor incidence in male and female Syrian golden hamsters (Ketkar *et al*., 1983)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male controls	0	respiratory tract	0/50
male low dose	1.2		8/29
male mid dose	6		13/29
male high dose	12		21/30
male controls	0	liver tumors	0/50
male low dose	1.2		4/29
male mid dose	6		9/29
male high dose	12		18/30
female controls	0	respiratory tract	0/50
female low dose	1.36		14/28
female mid dose	6.82		16/30
female high dose	13.6		22/30
female controls	0	liver tumors	0/50
female low dose	1.36		0/28
female mid dose	6.82		2/30
female high dose	13.6		6/30

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1987) list results from a drinking water study in male and female Syrian Golden hamsters (Ketkar *et al.*, 1983). Tumors of the respiratory system and liver were observed at significant levels in both sexes; females were slightly more sensitive than males. Cancer potency for N-nitrosomorpholine is based on tumors of the respiratory system, the more sensitive site, in female hamsters (see Table 1) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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N-NITROSOPIPERIDINE

CAS No: 100-75-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	114.15
Boiling point	217 °C (@ 721 mmHg)
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.7 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.7 E-3 (µg/m^3)$^{-1}$
Slope Factor: 9.4 E+0 (mg/kg-day)$^{-1}$
[Rat liver tumors (Eisenbrand *et al*., 1980), contained in Gold *et* al. (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *N*-nitrosopiperidine in humans are known to exist.

Animal Studies

Takayama (1969) fed 33 male ICR mice diets containing 50 mg/kg *N*-nitrosopiperidine for a period of 12 months; a 30 animal untreated control group was included. An increased incidence of forestomach (squamous cell carcinoma), liver and lung (adenomas) tumors were observed in treated animals when compared to controls. Tumor incidence data is listed in Table 1.

Table 1. *N*-nitrosopiperidine-induced tumor incidence in male ICR mice (Takayama, 1969)

Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
controls	0	forestomach liver lung	0/30 0/30 2/30
treated	6	forestomach liver lung	18/33 6/33 10/33

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

Male and female Sprague-Dawley rats were exposed to *N*-nitrosopiperidine in the drinking water 5 days/week for the life of the animals at exposure levels of 0, 0.024, 0.12, 0.6 and 3 mg/kg body weight (group sizes were 40, 78, 75, 34 and 34 animals, respectively) (Eisenbrand *et al*., 1980). Significant increases were noted in the incidence of esophageal squamous cell carcinomas and liver tumors (hemangioendotheliomas, and hepatocellular adenomas and carcinomas). Tumor incidence data is listed in Table 2.

Table 2. Induction of liver tumors in male and female Sprague-Dawley rats by *N*-nitrosopiperidine (Eisenbrand *et al*., 1980)

Dose group (mg/kg/day)$^{-1}$	Average dose[1] (mg/kg/day)$^{-1}$	Tumor incidence[2]
0	0	0/40
0.024	0.0171	3/78
0.12	0.0857	5/75
0.6	0.429	16/34
3.0	2.14	11/34

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences (males and females combined) as reported by Gold *et al*. (1987).

Adamson and Sieber (1982) exposed male and female rhesus and cynomolgus monkeys to *N*-nitrosopiperidine by gavage (400 mg/kg body weight, 5 days/week; average dose 279 and 280 mg/kg-day for cynomolgus and rhesus monkeys, respectively); male and female rhesus monkeys were also exposed to *N*-nitrosopiperidine by intraperitoneal injection (40 mg/kg body weight; average dose 5.59 mg/kg). Exposure and total experimental (exposure and untreated observation period) durations were 90 and 92 months, respectively for cynomolgus monkeys, 8 and 9 years, respectively for rhesus monkeys exposed by gavage, and 91 and 93 months, respectively, for rhesus monkeys exposed by intraperitoneal injection. Increased incidences of hepatocellular carcinomas were found in treated cynomolgus monkeys (5/5 compared to 0/38 in controls), rhesus monkeys exposed by gavage (6/7 compared to 0/32 in controls) and in rhesus monkeys exposed by intraperitoneal injection (3/5 compared to 0/32 in controls).

Ketkar *et al*. (1983) exposed male and female Syrian golden hamsters (30/sex/treatment group; 50/sex for controls) to 0, 0.006, 0.025 or 0.05% *N*-nitrosopiperidine in drinking water for the life of the animals. Increased incidences were noted for respiratory tract tumors (papillary polyps, papillomas and epidermoid carcinomas of the larynx, pharynx and trachea), liver tumors (hepatocellular adenomas and carcinomas, cholangiomas and cholangiocarcinomas) and digestive tract tumors (forestomach and colon adenocarcinomas). Tumor incidence data is listed in Table 3.

Table 3. *N*-Nitrosopiperidine-induced tumor induction in male and female Syrian golden hamsters (Ketkar *et al*., 1983)

Dose group (% *N*-nitrosopiperidine)	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male		respiratory tract	
0	0		0/50
0.006	7.2		5/30
0.025	30		10/30
0.05	60		15/30
female		respiratory tract	
0	0		0/50
0.006	8.18		4/30
0.025	34.1		6/30
0.05	68.2		10/30
male		liver tumors	
0	0		0/50
0.006	7.2		1/30
0.025	30		2/30
0.05	60		10/30
female		liver tumors	
0	0		0/50
0.006	8.18		1/30
0.025	34.1		2/30
0.05	68.2		4/30
male		digestive tract	
0	0		0/50
0.006	7.2		0/30
0.025	30		4/30
0.05	60		13/30
female		digestive tract	
0	0		0/50
0.006	8.18		4/30
0.025	34.1		5/30
0.05	68.2		7/30

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984, 1987) list results from drinking water studies in male and female Syrian Golden hamsters, feeding studies in male ICR mice, feeding studies in rhesus and cynomolgus monkeys, intraperitoneal studies in rhesus monkeys (combined data for males and females), and drinking water studies in Sprague-Dawley rats (combined data for males and females). N-Nitrosopiperidine induced liver tumors in all species and strains. Hamsters are the least sensitive of the species tested. The majority of treated primates developed liver tumors, including all cynomolgus monkeys given the compound in feed. Rats and mice exhibit sensitivity similar to primates. Because treatment groups in the primate studies are small and incidences observed are high, accurate estimates of cancer potency cannot be obtained from these studies. Of the dose-response data available for rats and mice, the highest quality data set is reported by Eisenbrand *et al.* (1980) for liver tumors in Sprague-Dawley rats. Cancer potency is derived from this data set (Table 2) (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. Analysis of the data set using the computer program TOX_RISK (Crump *et al*., 1991) indicated that inclusion of the high dose group resulted in a *p*-value of ≤ 0.05 based on the chi-square goodness-of-fit test, indicating non-linearity. Following procedures described by US EPA (Anderson *et al*., 1983), the high dose group was excluded from the analysis to correct for the poor fit (Cal/EPA, 1992). A unit risk factor of 6.0 E-6 $(\mu g/m^3)^{-1}$ was derived by OEHHA/ATES from the human q_1^* using an inspiration rate of 20 m^3/day.

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N-NITROSOPYRROLIDINE

CAS No: 930-55-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	100.1
Boiling point	214°C
Melting point	not available
Vapor pressure	not available
Air concentration conversion	1 ppm = 4.10 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.0 E-4 (µg/m^3)$^{-1}$
Slope Factor: 2.1 E+0 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by US EPA/IRIS (1994) from rat liver tumor data (Preussmann *et al*. 1977) using a linearized multistage procedure]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of *N*-nitrosopyrrolidine in humans are known to exist. Human exposure to nitrosamines occurs through contact with complex mixtures (e.g., metal cutting fluids) containing these compounds. US EPA (1994) states that data from such exposures are of limited use in evaluating the carcinogenicity of individual nitrosamines due to potential confounding by other substances present in the mixtures.

Animal Studies

Druckrey (1967) (reviewed by IARC, 1978) exposed 25 BD rats to drinking water containing *N*-nitrosopyrrolidine; average doses were 5 or 10 mg/kg body weight-day. After 150 days of treatment, the doses were increased to 10 or 20 mg/kg-day. Hepatocellular carcinomas were noted in 23/25 animals; the average induction time for the low- and high-dose animals was 470 and 290 days, respectively.

Male and female MRC rats (15/sex) were exposed to *N*-nitrosopyrrolidine in drinking water 5 days/week at a concentration of 200 mg/l for 67 weeks (mean total dose 1340 mg/animal, mean daily intake 16 mg/kg) (Greenblatt and Lijinsky, 1972a). After treatment, animals were observed for an additional 105 weeks. An untreated control group of 35 animals/sex was also included. An increased incidence of liver tumors (primarily hepatocellular carcinomas) were observed in both males (12/12) and females (13/13); 7/12 male rats also developed papillary mesotheliomas of the testes. No liver or testicular tumors were noted in the corresponding controls.

Greenblatt and Lijinsky (1972b) exposed male and female (30/sex/group) Swiss mice to 0 or 0.01% *N*-nitrosopyrrolidine in drinking water 5 days/week for 26 weeks (average dose 7-8 mg/kg-day). All surviving animals were killed after 38 weeks. Animals were only histopathologically evaluated for lung adenomas. Lung tumor incidence in treated mice was not significantly increased when compared to controls; however, the duration of treatment was short and the mean survival time of the treated animals was only 12 weeks, with the primary cause of mortality being liver necrosis.

Male and female Sprague-Dawley rats (14 males, 15 females) were exposed to 200 mg/l *N*-nitrosopyrrolidine in drinking water 5 days/week for 50 weeks (total dose 1000 mg/animal), then observed for the remainder of their lifetime (Lijinsky and Taylor, 1976). An increased incidence of hepatocellular tumors was noted in both males (12/14) and females (13/15). No liver tumors were reported in the control group (group size not reported).

Exposure of male and female Sprague-Dawley rats to N-nitrosopyrrolidine in drinking water at levels of 0, 0.3, 1, 3 or 10 mg/kg body weight for the life of the animals resulted in significant increases in the incidence of hepatocellular tumors (adenomas and carcinomas) (Preussmann *et al*., 1977). Tumor incidence data is listed in Table 1. Equal numbers of male and female animals were used.

Table 1: Incidence of hepatocellular carcinomas and adenomas in male and female Sprague-Dawley rats treated with *N*-nitrosopyrrolidine via drinking water (Preussmann *et al*., 1977)

Number of animals/ group[1]	*N*-nitrosopyrrolidine exposure level (mg/kg-day)	Human equivalent dose[2] (mg/kg-day)	Hepatocellular tumor incidence[1]
61	0	0	0/61
60	0.3	0.051	3/60
62	1.0	0.17	17/62
38	3.0	0.51	31/38
24	10	1.70	14/24

1. Males and females combined.
2. Calculated by US EPA (1994).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Tumor incidence data from the study by Preussmann *et al*. (1977) were the basis of cancer potency factor derivation. There were significant increases in the incidence of hepatocellular carcinomas and adenomas (see Table 1). Overall, there appeared to be dose-related increases in hepatocellular tumors, as well as shorter latency periods with increasing dose.

Methodology

Cancer potency values are based on the most sensitive site, species and study, in the absence of other evidence indicating that such a value is not appropriate (CDHS, 1985). Based on the dose-response data for hepatocellular tumors in male and female Sprague-Dawley rats, the cancer potency factor for *N*-nitrosopyrrolidine was calculated to be 2.1 $(mg/kg\text{-}day)^{-1}$ using a linearized multistage procedure with surface area scaling for conversion of the rat administered dose to a human equivalent dose (US EPA, 1994). A unit risk factor was calculated from the cancer potency factor by OEHHA/ATES using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day. US EPA has stated that the unit risk should not be used if air concentrations exceed 20 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

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PENTACHLOROPHENOL

CAS No: 87-86-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995)

Molecular weight	266.35
Boiling point	309°C
Melting point	190°C
Vapor pressure	0.00011 mm Hg @ 25°C
Air concentration conversion	1 ppm = 10.9 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 4.6 E-6 (µg/m^3)$^{-1}$
Slope Factor: 1.8 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by CDHS (1991) from male mouse liver tumor data (NTP, 1989) using a linearized multistage procedure.]

III. CARCINOGENIC EFFECTS

Human Studies

No human epidemiological studies were located that were adequate to evaluate a possible association between exposure to pentachlorophenol and cancer.

Animal Studies

The National Toxicology Program (NTP, 1989) conducted 2 studies on the carcinogenic effects of lifetime exposure of mice to pentachlorophenol (PeCP). In these studies, B6C3F$_1$ mice were exposed to dietary PeCP, as either the technical grade or EC-7 grade, for 2 years. The technical grade PeCP contained polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) as contaminants in significantly higher concentrations than the EC-7 grade. The NTP found dose-related increases in liver and adrenal medullary tumors in male and female mice, and an increase in hemangiosarcomas in the females exposed to the EC-7 grade (Table 1). The incidence of liver neoplasms and hemangiosarcomas was higher in female mice exposed to technical grade PeCP. The incidence of hemoangiosarcomas in female mice was 0/35, 3/50, and 6/50 for the 0, 100, and 200 ppm PeCP groups, respectively.

Table 1. Tumor incidence in male and female $B6C3F_1$ mice exposed to technical or EC-7 grade pentachlorophenol (PeCP) (NTP, 1989).

Grade of PeCP	Sex	Adrenal gland/medullary tumor incidence (benign and malignant pheochromocytomas) Dietary concentration (ppm)[a]				Liver tumor incidence (hepatocellular adenomas and carcinomas) Dietary concentration (ppm)[a]			
		0	100	200	600	0	100	200	600
EC-7	males	1/34	4/48	21/48	45/49	6/35	19/48	21/48	34/49
	females	0/35	2/49	2/46	38/49	1/34	4/50	6/49	31/48
technical	males	0/31	10/45	23/45	NT	7/32	26/47	37/48	NT
	females	2/33	2/48	1/49	NT	3/33	9/49	9/50	NT

a) EC-7 dose levels for males and females were 0, 18, 37 and 118 mg/kg-day and 0, 17, 34 and 114 mg/kg-day, respectively.
NT = not tested

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NTP (1989) study in mice was used as the basis for the cancer potency for PeCP. This represents the only adequate, long-term, positive study of the carcinogenic effects of PeCP. The NTP study shows that PeCP exposure in mice results in several types of tumors in males and females. In the NTP (1989) study, mice (35-50 per group) were exposed to 0, 100, 200, or 600 mg/kg diet PeCP (EC-7 grade) for 2 years. In a parallel series of experiments, mice were exposed to 0, 100, or 200 mg/kg diet of technical grade PeCP. Results of these bioassays included a significant incidence of liver and adrenal neoplasms in male and female mice exposed to PeCP. In addition, female mice exhibited a significant increase in hemangiosarcomas. Although there were trace amounts of PCDD's and PCDF's in the EC-7 grade, the amount of these contaminants was determined by CHDS (1991) to be insufficient to result in the observed tumor incidence.

Methodology

A linearized multistage procedure was used to estimate the cancer potency of EC-7 grade PeCP from the NTP (1989) liver tumor (hepatocellular adenomas and carcinomas) data in male $B6C3F_1$ mice (Crump *et al*., 1982). The concentrations of PeCP given in the feed were 0, 100, 200, or 600 mg/kg diet. The tumor incidence data are shown in Table 1. The 95% upper confidence bound on the dose-response slope was used to derive the human cancer potency value for PeCP.

The animal cancer potency, q_{animal}, was calculated from the linear slope using the lifetime scaling factor $q_{animal} = q_1^* \times (T/T_e)^3$, where T/T_e is the ratio of the experimental duration to the lifetime

of the animal. The default lifespan for mice is 104 weeks. In this case, the lifetime scaling factor is equal to 1. An estimated value for the human cancer potency was determined using the relationship $q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$, where bw is the default body weight of human or animal (mouse).

Using these relationships, a human cancer potency (q_{human}) of 1.8E-2 $[mg/kg\text{-}day]^{-1}$ was derived (CDHS, 1991). An airborne unit risk factor of 4.6E-6 $(\mu g/m^3)^{-1}$ was calculated from the q_{human} value by OEHHA/ATES using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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POLYCHLORINATED BIPHENYLS (PCBs)

CAS No: 1336-36-3 (all congeners)

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1995 except as noted)

Molecular weight	154 - 499
Boiling point	Unknown
Melting point	340-375° C
Vapor pressure	4.06E-4 mm Hg @ 25°C (Aroclor 1242)
	7.71E-5 mm Hg @ 25°C (Aroclor 1254)
Air concentration conversion	1 ppm = 10.87 mg/m^3 (Aroclor 1242)
	1 ppm = 13.33 mg/m^3 (Aroclor 1254)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor:	5.7 E-4 (µg/m^3)$^{-1}$	(For use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs)
	2.0 E-5 (µg/m^3)$^{-1}$	(For use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs)

[Calculated from a cancer potency factor derived by US EPA/IRIS (1996c) from rat liver tumor data (Norback and Weltman, 1985; Brunner *et al*., 1996), using a linear-quadratic multistage procedure and ¾ power body weight scaling to calculate an ED10 (estimated dose associated with 10 percent increased incidence), and its lower bound, LED10.]

III. CARCINOGENIC EFFECTS

Human Studies

The evidence for the human carcinogenicity of PCBs has been determined by IARC (1987) to be limited, due to concurrent exposures of test subjects to other chemicals, and to the small numbers of individuals examined. A study of workers heavily exposed to Aroclor 1254 (54% chlorine, by weight) for 9 years, showed 2 out of 31 heavily exposed workers developed malignant melanoma, while 1 out of 41 less heavily exposed workers developed this tumor (Bahn *et al*., 1976; 1977). The expected number of melanomas in a population this size was 0.04. IARC (1978) concluded that there was suggestive evidence of carcinogenicity in humans.

Brown and Jones (1981) and Brown (1987) found an increase in the mortality caused by liver or biliary passage cancer (5 observed, 1.9 expected) in 2567 US workers exposed to Aroclor 1254 during the manufacture of capacitors. Four of the 5 deceased workers were female.

Bertazzi *et al*. (1982) reported on a study of capacitor manufacturing workers in Italy. Workers were exposed to mixtures of PCB congeners containing 54% chlorine prior to 1964, and 42% chlorine after that time. In these workers, significant increases in the incidence of cancers of the digestive, lymphatic, and hematopoietic systems were observed in both male and female workers. An expanded study was later conducted by Bertazzi *et al*. (1987) who recorded cancer mortality in 2100 male and female workers from 1946 to 1982. Cancers of the gastrointestinal tract were significantly increased in male workers (6 observed, 2.2 expected) and hematopoietic cancers were significantly increased in female workers (4 observed, 1.1 expected).

PCB content in human fat tissues has been correlated with the occurrence of stomach, colon, pancreas, ovary, and prostate cancers (Unger *et al*., 1982; 1984).

A large population of people in Japan were exposed to PCBs from contaminated cooking oil (Umeda, 1984). In these patients, a 5-fold increase in liver cancer was reported, but a dose-response was not established. In a cohort of 887 male intoxicated patients with "Yusho" disease, Kuratsune *et al*. (1986) found an increase in mortality from malignant tumors (33 observed, 15.5 expected). Deaths from malignant liver and lung tumors were particularly high (9 observed, 1.6 expected; 8 observed, 2.5 expected, respectively). Female Yusho patients (n = 874) did not show the increase in cancer mortality.

Animal Studies

Early studies by Kimura and Baba (1973) and Ito *et al*. (1974) did not demonstrate carcinogenicity of PCBs in male or female rats orally exposed to highly chlorinated (60% by weight) PCBs in the diet for up to 77 weeks. In this study, 20 rats (10/sex) were exposed to diets ranging from 38.5 to 462 ppm PCBs. Ten rats (5/sex) served as experimental controls. Each rat was exposed to a unique treatment regimen that differed by amount of PCB ingested and duration of exposure. Female rats exhibited several benign adenomatous lesions in the liver, but no statistical comparisons were made. In these studies, small sample sizes (10 per group), less than lifetime exposure, and excess deaths unrelated to PCB exposure prevented definitive conclusions about the carcinogenicity of PCBs.

The NCI (1978) conducted a 2-year bioassay on male or female Fisher-344 rats (24 per group) exposed to Aroclor 1254 in the diet. Concentrations of PCBs in the feed were 0, 25, 50, or 100 ppm. A significant increase in the numbers of lymphomas and leukemias was observed in the male rats. The NCI did not conclude that these hematological tumors were treatment related. The incidence of hepatocarcinomas in the male rats was 0/24, 1/24, and 3/24 for the 0, 50, and 100 ppm groups, respectively. In other tissues, such as the stomach, jejunum, and cecum, rare tumors were found. The incidence of these tumors, while not statistically significant, were considered to be treatment-related due to the low incidence of these tumors in historical controls. The NCI concluded that PCBs were capable of inducing proliferative lesions in the liver, but were not carcinogenic to rats in this bioassay.

A reanalysis of the NCI data by Morgan *et al*. (1981) found that the incidence of focal metaplasia in the stomach increased in a dose-dependent fashion with a 6, 10, 17, and 35% occurrence in the 0, 25, 50, and 100 ppm groups, respectively. The incidence of stomach adenocarcinomas was significantly higher than in historical controls (4% vs. 0.03%, $p < 0.001$). With this reanalysis, the authors concluded that Aroclor 1254 was carcinogenic.

A chronic dietary exposure to Aroclor 1260 in rats was reported by Kimbrough *et al*. (1975). In this study, 200 young rats were fed 0 or 100 ppm Aroclor 1260 for 94 weeks. Actual dosages of PCB were estimated to be 11.6 mg/kg/day for the first week, 6.1 mg/kg/day at 3 months, and 4.3 mg/kg/day at 20 months. The time-weighted average dose was estimated to be 4.42 mg/kg/day (U.S. EPA, 1985). Almost all treated rats developed liver nodules (170/184). In addition, the incidence of hepatocellular carcinomas was highly significantly increased over controls (1/173 for controls vs. 26/184 for treated rats; $p < 1.0E-6$). Neoplastic nodules and total neoplastic lesions were also highly significantly increased over concurrent controls.

Schaeffer *et al*. (1984) reported results from a 2-year bioassay in rats using 2 PCB mixtures: Clophen A 30 (30% chlorine by weight) and Clophen A 60 (60% chlorine by weight) in the diet. Groups consisted of approximately 140 male weanling rats exposed to 100 ppm of either Clophen A 30 or Clophen A 60. A significant increase in the percentage of hepatocellular carcinomas was seen in the rats treated with Clophen A 60 (62%), but not with Clophen A 30 (3%). Hepatocarcinomas were observed in 2% of control animals. Preneoplastic lesions were not observed before 71 weeks.

The incidence of hepatocarcinoma was increased in rats exposed to Aroclor 1260 in a 2-year study by Norback and Weltman (1985). In this study, 70 male or female rats were exposed to 100 ppm Aroclor 1260 in the diet for 16 months, followed by 50 ppm in the diet for 8 months. The time-weighted average doses were calculated to be 5 mg/kg/day for the male rats, and 4.2 mg/kg/day for the females. The incidence of neoplastic lesions in control rats living 18 months or longer was 1.2% (1/81). The treated rats had an incidence of 95% (45/47) for the females, and 15% (7/46) for the males. The combined tumor incidences were significantly higher in treated rats compared with controls. The authors also reported an increase in incidence of cholangiomas, but these lesions were designated by CDHS as benign, since no specific discussion of their malignancy was given.

Brunner *et al*. (1996) fed male and female Sprague-Dawley rats (50 animals/sex/Aroclor dose group) diets containing 25, 50 or 100 ppm Aroclor 1260 or 1254; 50 or 100 ppm Aroclor 1242; or 50, 100 or 200 ppm Aroclor 1016 for 104 weeks. Control groups were also included (100 animals/sex). Surviving animals were killed at 104 weeks. Statistically significant increases in liver adenoma or carcinoma incidence were observed in female rats for all Aroclors tested, and in male rats for Aroclor 1260 (Table 1).

Table 1. Liver tumor incidence in Sprague-Dawley rats exposed to PCBs (Brunner *et al*., 1996; contained in US EPA, 1996a)

Mixture	Exposure level (ppm)	Tumor incidence Females	Males
Aroclor 1260	0	**1/85 (1%)	**7/98 (7%)
	25	10/49 (20%)	3/50 (6%)
	50	11/45 (24%)	6/49 (12%)
	100	24/50 (48%)	10/49 (12%)
Aroclor 1254	0	**1/85 (1%)	7/98 (7%)
	25	19/45 (42%)	4/48 (8%)
	50	28/49 (57%)	4/49 (8%)
	100	28/49 (57%)	6/47 (13%)
Aroclor 1242	0	**1/85 (1%)	7/98 (7%)
	50	11/49 (24%)	1/50 (2%)
	100	15/45 (33%)	4/46 (9%)
Aroclor 1016	0	**1/85 (1%)	7/98 (7%)
	50	1/48 (2%)	2/48 (4%)
	100	6/45 (13%)	2/50 (4%)
	200	5/50 (10%)	4/49 (8%)

**Statistically significant ($p < 0.05$) by Cochran-Armitage trend test.

In mice, two studies indicate that PCBs are carcinogenic, particularly with respect to hepatocarcinomas. Kimbrough and Linder (1974) exposed groups of 50 male BALB/cj mice to Aroclor 1254 at 0 or 300 ppm in the diet for 11 months, or for 6 months with a 5 month recovery period. The incidences of hepatoma were 0/34, and 0/24 for the 11- and 6-month exposure groups, respectively. The treated animals had incidences of 9/22, and 1/24 for the 11- and 6-month groups, respectively.

Ito *et al*. (1973) exposed groups of 12 mice to 500 ppm Kaneclor 500 (54% chlorine) in the diet for 32 weeks. No liver lesions were seen in 6 untreated controls. The incidence of hepatocellular carcinoma in the treated mice was 5/12 and the incidence of liver nodules was 7/12.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Several studies (Kimbrough *et al*., 1975; Schaeffer *et al*., 1984; Norback and Weltman, 1985; Brunner *et al*., 1996) have demonstrated increased liver tumor incidence in rats exposed to PCB mixtures. The mixtures found to induce liver tumors range in chlorine content from 60%

(Aroclor 1260; (Norback and Weltman, 1985; Brunner *et al*., 1996)), through 54% (Brunner *et al*., 1996), to 41% (Brunner *et al*., 1996). Female Sprague-Dawley rat liver tumor incidence data for Aroclor 1260 from the study by Norback and Weltman (1985) was chosen by US EPA as the basis of a cancer potency value for "high risk and persistence" PCB exposures. Female Sprague-Dawley rat liver tumor incidence data for Aroclor 1242 and 1016 from the study by Brunner *et al*. (1996) were chosen by US EPA as the basis of cancer potency values for "low risk and persistence" and "lowest risk and persistence" PCB exposures, respectively.

Methodology

The September 1996 US EPA document "PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures" (US EPA, 1996a) differs from the prior US EPA PCB risk assessment (US EPA, 1988) which was also used for Proposition 65 purposes in that it includes data from a new study of rats fed diets containing Aroclors 1260, 1254, 1242, or 1016 which found statistically significant, dose-related, increased incidences of liver tumors from each mixture (Brunner *et al*., 1996). Earlier studies used in the previous US EPA IRIS listing for PCBs found high, statistically significant incidences of liver tumors in rats ingesting Aroclor 1260 or Clophen A 60 (Kimbrough *et al*., 1975; Norback and Weltman, 1985; Schaeffer *et al*., 1984) in addition to partial lifetime studies which found precancerous liver lesions in rats and mice ingesting PCB mixtures of high or low chlorine content. However, the studies used for the previous IRIS listing had no data available indicating that PCBs with chlorine contents of less than 60% induced frank tumors.

The new US EPA PCB risk assessment document also uses dose scaling to humans using a factor based on the ¾ power of relative body weight. Cancer potency is described by an ED10 (estimated dose associated with 10 percent increased incidence) and its lower bound, LED10. These measures are expressed as equivalent human doses. Formerly, upper-bound slopes were calculated by the linearized multistage procedure; these were reported as " q1*"s. The LED10 method and the linearized multistage procedure give similar upper-bound slopes; for example, for female rats fed Aroclor 1254, the LED10 method and the linearized multistage procedure give upper-bound slopes of 1.5 and 1.6 per mg/kg-d, respectively. These changes conform to the 1996 draft US EPA cancer risk assessment guidelines (US EPA, 1996b).

The range of potency values is summarized in Table 2. It is based primarily on the range for Aroclors 1260, 1254, 1242, and 1016 in female Sprague-Dawley rats (Brunner *et al*., 1996), but considers the other available studies also.

Table 2. Range of human potency and slope estimates (from US EPA, 1996a)

	ED10 (mg/kg-d)	LED10[a] (mg/kg-d)	Central slope[b] $(mg/kg\text{-}d)^{-1}$	Upper-bound slope[c] $(mg/kg\text{-}d)^{-1}$
Highest observed potency	0.086	0.046	1.2	2.2
Lowest observed potency	2.4	1.4	0.04	0.07

[a]95% lower bound on ED10.
[b]Computed as 0.10/ED10 and rounded to one significant digit.
[c]Computed as 0.10/LED10 and rounded to one significant digit.

The new upper-bound slopes are lower than the previous estimate of 7.7 per mg/kg-d average lifetime exposure (U.S. EPA, 1988). The previous estimate was derived from female rats in the Norback and Weltman (1985) study; the new estimate from the same study is 2.2 per mg/kg-d. This difference is attributable to three factors, each responsible for reducing the slope by approximately one-third: a rat liver tumor reevaluation (Moore *et al*., 1994), use of the new cross-species scaling factor (U.S. EPA, 1996b), and not using a time-weighted average dose. The difference between the highest observed new upper-bound slope (2.2 per mg/kg-d) and the lowest (0.07 per mg/kg-d) is entirely attributable to the availability of tests on several commercial mixtures (Brunner *et al*., 1996). This 30-fold range in potency reflects differences in commercial mixture composition, as reflected in Table 3.

Table 3. Typical composition (%) of some commercial Aroclor PCB mixtures (from US EPA, 1996a)

	1016	1242	1248	1254	1260
Mono-CBs	2	1	—	—	—
Di-CBs	19	13	1	—	—
Tri-CBs	57	45	21	1	—
Tetra-CBs	22	31	49	15	—
Penta-CBs	—	10	27	53	12
Hexa-CBs	—	—	2	26	42
Hepta-CBs	—	—	—	4	38
Octa-CBs	—	—	—	—	7
Nona-CBs	—	—	—	—	1
Deca-CB	—	—	—	—	—

U.S. EPA (1991) examined the toxic effects, including cancer, of four structural classes: dioxin-like PCBs, ortho-substituted PCBs, hydroxylated metabolites, and sulfonated metabolites. Different mechanisms were discussed for dioxin-like and other PCBs. It was concluded that congener toxicity could not be characterized by chlorine content alone. Chlorine content was formerly regarded by some scientists as correlated with cancer risk. Recently, however, Aroclor 1254 was found to be a more potent liver tumor inducer than 1260, which was only slightly more potent than 1242 (Brunner *et al*., 1996). This suggests that both the number and position of chlorines are a more useful indicator of cancer potency than total chlorine content.

US EPA designated three reference points for each range (see Table 4): a "high risk" point based on studies of Aroclor 1260 and 1254, which give the highest observed potencies; a "low risk" point, based on the study of Aroclor 1242; and a "lowest risk" point, based on the study of Aroclor 1016. The "high risk" point is used for exposure pathways associated with environmental processes that tend to increase risk, including early life exposure. The "low risk" point is used for exposure pathways resulting in decreased risk. The "lowest risk" point is used in cases where congener or isomer analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs.

Table 4. Tiers of human potency and slope estimates for environmental mixtures (from US EPA, 1996)

HIGH RISK AND PERSISTENCE

ED10	LED10	Central slope	Upper-bound slope	Criteria for use
0.086	0.067	1.	2.	Food chain exposure Sediment or soil ingestion Dust or aerosol inhalation Dermal exposure, if an absorption factor has been applied to reduce the external dose Presence of dioxin-like, tumor- promoting, or persistent congeners in other media Early-life exposure (all pathways and mixtures)

LOW RISK AND PERSISTENCE

ED10	LED10	Central slope	Upper-bound slope	Criteria for use
0.38	0.27	0.3	0.4	Ingestion of water-soluble congeners Inhalation of evaporated congeners Dermal exposure, if no absorption factor has been applied to reduce the external dose

LOWEST RISK AND PERSISTENCE

ED10	LED10	Central slope	Upper-bound slope	Criteria for use
2.4	1.4	0.04	0.07	Congener or isomer analyses verify that congeners with more than 4 chlorines comprise less than 1/2% of total PCBs

Less-than-lifetime exposure induced statistically significant increased incidences of liver tumors in female rats fed Aroclors 1260, 1254, and 1242 (Brunner *et al*., 1996). This result was most pronounced for Aroclor 1260, where tumor incidences at the highest dose were higher for a 12-month exposure than for a 24-month lifetime exposure. Only Aroclor 1016 showed no significant increases from less-than-lifetime exposure. The earlier less-than-lifetime studies in rats and mice suggest that less-than-lifetime exposure can quickly induce high incidences of early stages of tumor development (Kimbrough *et al*., 1972; Ito *et al*., 1973, 1974). With further exposure, these can progress to malignancy (Kimbrough *et al*., 1975; Norback and Weltman, 1985). Tumor incidences from less-than-lifetime exposure were sometimes lower (Kimbrough and Linder, 1974), and sometimes similar (Rao and Banerji, 1988), to those from full lifetime exposure to PCBs.

Infants can be highly exposed to PCBs during pregnancy and lactation (Dewailly *et al*., 1991, 1994). The accumulation of PCBs in human adipose tissue creates a store for subsequent release of PCBs into the bloodstream and then into the fetal circulation. During the postpartum period, PCBs are mobilized from adipose stores, transferred into human milk, and delivered to the neonate via nursing (Dewailly *et al*., 1991). This pathway may account for a substantial fraction of neonatal exposure to dioxin-like and other PCBs.

Additionally, normal fetal development depends on the timing and rate of release of T3 and T4. Some evidence indicates that PCBs can alter normal T3 and T4 metabolism, thereby disturbing thyroid function and provoking secondary impacts on organogenesis during development. Any estrogenic/anti-estrogenic, androgenic/anti-androgenic, or other hormonal activity of PCB mixtures has the possibility of altering the development of reproductive organs or the urogenital tract, potentially causing cancer or other adverse effects through a mechanism different from those causing liver cancer (US EPA, 1996b).

Few studies, however, have investigated early-life sensitivity. In human infants, glucuronidative mechanisms are not fully developed; additionally, some nursing infants receive a steroid in human milk that inhibits the activity of glucuronyl transferase, further reducing PCB metabolism and elimination (Calabrese and Sorenson, 1977). In animals, Aroclor 1260 induced high incidences of liver tumors when fed to 5-week-old rats for a short time (Rao and Banerji, 1988). On the other hand, acute perinatal dosing with Aroclor 1254 promoted nitrosamine-initiated lung and liver tumors in mice but did not induce cancer in the offspring when administered alone (Anderson *et al*., 1983, 1986, 1994). A study of polybrominated biphenyls (PBBs) found that perinatal exposure enhanced susceptibility to liver tumors for female rats also exposed as adults and increased the incidence of liver tumors in male and female mice not further exposed as adults (NTP, 1993). Because of the potential magnitude of early-life exposures, the possibility of greater perinatal sensitivity, and the likelihood of interactions among thyroid and hormonal development, it is reasonable to conclude that early-life exposures may be associated with increased risks; this would indicate using the "high-risk" potency estimates for early-life exposure.

US EPA has listed three different cancer potency values for PCBs; the choice of which factor to use depends on the physical form of the PCBs and the expected route of exposure. However, US

EPA states that the "high risk and persistence" factor (2.2 $(mg/kg\text{-}day)^{-1}$) should be used when an "early-life exposure (all pathways and mixtures)" exposure scenario is expected. Since this is the most likely exposure scenario expected for Hot Spots emissions, this is the appropriate cancer potency factor to list for PCBs in the Hot Spots cancer document, with the exception of PCB emissions in cases where congener or isomer analyses verify that congeners with more than four chlorines comprise less than one-half percent of total PCBs. For these cases, this would support use of the "lowest risk and persistence" cancer potency value (0.07 $(mg/kg\text{-}day)^{-1}$).

Inhalation unit risk factors of 5.7 E-4 $(\mu g/m^3)^{-1}$ (for use in cases where congeners with more than four chlorines do not comprise less than one-half percent of total PCBs) and 2.0 E-5 $(\mu g/m^3)^{-1}$ (for use in cases where congeners with more than four chlorines comprise less than one-half percent of total PCBs) were calculated from the cancer potency values 2.0 $(mg/kg\text{-}day)^{-1}$ and 0.07 $(mg/kg\text{-}day)^{-1}$, respectively, using the default parameters of 70 kg human body weight and 20 m^3/day breathing rate.

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POTASSIUM BROMATE

CAS No: 7758-01-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	167.01
Boiling point	not available
Melting point	434 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 6.8 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.4 E-4 (µg/m^3)$^{-1}$
Slope Factor: 4.9 E-1 (mg/kg-day)$^{-1}$
[Male rat kidney tumor data (Kurokawa *et al*., 1983), contained in Gold *et al.* (1987) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of potassium bromate in humans are known to exist.

Animal Studies

Male and female Wistar rats (90/sex/group) (Fisher *et al*., 1979) and "Theiller's Original" strain mice (60/sex/group) (Ginocchio *et al*., 1979) were fed diets consisting of 79% bread crumbs made from untreated flour, or flour containing 50 mg/kg or 75 mg/kg potassium bromate. Mice and rats were fed treated diet for 80 and 104 weeks, respectively. No significant increase in tumor induction was reported; however, IARC (1986) noted that bromates are substantially degraded during bread baking.

Male and female Fischer 344 (F344) rats were exposed to 0, 250 or 500 mg/l potassium bromate in drinking water for 100 weeks (Kurokawa *et al*., 1983). Group sizes were 52-53/sex/group. Total doses were 9.6 and 21.3 mg/kg body weight for low and high dose males, respectively, and 9.6 and 19.6 mg/kg body weight for low and high dose females, respectively. Significant increases in the incidences of renal andenomas and adenocarcinomas were noted in both males and females; significant increases were also noted in the incidence of peritoneal mesotheliomas in males, and of thyroid tumors in females. Tumor incidence data is listed in Table 1.

Table 1. Potassium bromate-induced tumor incidences in male and female Fisher 344 rats (Kurokawa *et al*., 1983)

Sex	Dose group	Average dose[1] (mg/kg-day)	Tumor type	Tumor incidence[2]
male	control	0	kidney tumors[3]	3/53
	low dose	12.4		32/53
	high dose	22.5		46/52
	control	0	peritoneal mesotheliomas	6/53
	low dose	12.4		17/52
	high dose	22.5		28/46
female	control	0	kidney tumors[3]	0/47
	low dose	14.2		28/50
	high dose	28.3		39/49
	control	0	thyroid tumors	3/52
	low dose	14.2		10/52
	high dose	28.3		12/52

1. Doses as reported by Gold *et al.* (1987).
2. Tumor incidences as reported by Gold *et al*. (1987).
3. Adenomas and adenocarcinomas

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al*. (1987) list the results from positive drinking water studies in male and female F344 rats (Kurokawa *et al*., 1983) and from negative feeding studies in male and female Wistar rats (Fisher *et al*., 1979) and "Theiller's Original" mice (Ginocchio *et al*., 1979). Male and female rats are of similar sensitivity. Cancer potency is based on results from Kurokawa *et al.* (1983). The dose-response data for renal adenomas and adenocarcinomas in male rats are listed in Table 1 and are the basis for the cancer potency for potassium bromate (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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1,3-PROPANE SULTONE

CAS No: 1120-71-4

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	122.1
Boiling point	180°C at 30 mm Hg
Melting point	31°C
Vapor pressure	not available
Air concentration conversion	1 ppm = 5.01 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 6.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 2.4 E+0 $(mg/kg\text{-}day)^{-1}$
[Male rat cerebellar malignant glioma tumor data (Ulland *et al*., 1971; Weisburger *et al*., 1981), contained in Gold *et al*. database (1984), expedited Proposition 65 methodology (Cal/EPA, 1992)]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,3-propane sultone on humans are known to exist.

Animal Studies

Several studies exist on the potential carcinogenic effects of 1,3-propane sultone in animals. These studies have been reviewed by IARC (1974).

BD rats (12/group, sex unspecified) were given 30 mg/kg body weight 1,3-propane sultone as a 3% aqueous solution weekly by gavage (Druckrey *et al*., 1970). Four of 10 survivors developed tumors between days 248 and 377; tumors noted were 1 glial-mesodermal mixed tumor, 1 advential cell sarcoma of the brain, 1 nephroblastoma and 1 subcutaneous spindle cell sarcoma.

Local sarcomas resulting in mortality were induced in all of 18 BD rats given weekly subcutaneous injections of 15 mg/kg 1,3-propane sultone in water (total dose 225 mg/kg) between 208 and 387 days. Additionally, single subcutaneous injections of 30 or 100 mg/kg produced local sarcomas at the injection site resulting in mortality in 12/18 animals and 18/18 animals, respectively (Druckrey *et al*., 1970). In the same study, BD rats were given 1,3-propane sultone as a 1% solution in arachis oil by subcutaneous injection weekly at doses of 15 or 30 mg/kg. Mortality resulted from local sarcomas which developed (myosarcomas and

fibrosarcomas) at the site of injection (7/12 and 11/11 rats in the low and high-dose groups, respectively) within 217-360 days (total dose up to 390 mg/kg) (Druckrey *et al*., 1968, 1970).

Weekly intravenous injections of a 2% solution of 1,3-propane sultone in water at doses of 10, 20 or 40 mg/kg (total doses 300, 570 and 560 mg/kg, respectively) were administered to groups of 10 BD rats (the 40 mg/kg group treatment was suspended after 16 weeks due to tail vein sclerosis) (Druckrey *et* al., 1970). Three animals in the 40 mg/kg group died of tumors after 280-410 days (sarcoma of the mediastinum with right lung and kidney metastases, glial-mesodermal mixed tumor of the brain, neurosarcoma); 2/12 and 3/8 animals respectively in the 10 and 20 mg/kg groups died of tumors (10 mg/kg group: ganglioneuroma, neurocytoma; 20 mg/kg group: nephroblastoma, ileocaecal carcinoma, glial-mesodermal mixed tumor of the brain and mammary carcinoma) after 381-492 days. In the same study, a single intravenous injection of 1,3-propane sultone (150 mg/kg) induced tumors at various sites resulting in mortality within 459 days in 10/32 BD rats. Single intravenous injections of 20 or 60 mg/kg 1,3-propane sultone administered to pregnant BD rats on gestation day 15 resulted in malignant neurogenic tumors in 3/25 offspring born to the 20 mg/kg group, and in malignant tumors in 4/14 offspring (2 neurogenic tumors, 1 pancreatic tumor, 1 ovarian tumor) born to the 60 mg/kg group.

Female ICR/Ha Swiss mice (30/group) given weekly subcutaneous injections of 0.3 mg 1,3-propane sultone in 50 µl distilled water developed tumors in 21/30 mice at the injection site (1 papilloma, 7 adenoacanthomas, 12 sarcomas, 1 undifferentiated carcinoma) within 63 weeks, compared to 0/30 controls after 78 weeks (Van Duuren *et al*., 1971).

Male and female Charles River CD rats (26/sex/group) were exposed to an aqueous solution of 1,3-propane sultone by gavage twice weekly at doses of 28 mg/kg body weight for 60 weeks and 56 mg/kg for 32 weeks (Ulland *et al*., 1971; Weisburger *et al*., 1981). Control groups (32/sex) were also included; however, only 6 animals/sex were killed and necropsied at 61 weeks. Tumor types induced by 1,3-propane sultone are listed in Table 1.

Table 1: 1,3-propane sultone-induced tumor incidences in male and female CD rats

Exposure group (mg/kg)	28		56	
Sex	Male	Female	Male	Female
Tumor type				
Breast	1/26	7/26	1/26	13/26
Glioma	12/26	15/26	16/26	13/26
Ear duct	1/26	0/26	3/26	3/26
Leukemia	0/26	2/26	4/26	3/26
Intestinal adenocarcinoma	4/26	1/26	3/26	1/26
Miscellaneous	5/26	7/26	4/26	6/26

One female control died of a cerebral glioma after 33 weeks, and a pituitary chromophobe adenoma was discovered in a female control. No other control animal tumor incidences were reported.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The carcinogenicity bioassay using male and female Charles River CD rats exposed to 1,3-propane sultone by gavage (Ulland *et al*., 1971; Weisburger *et al*., 1981) demonstrated that 1,3-propane sultone induced tumors in both sexes at multiple sites; the sensitivity of both sexes was similar. The dose-response data for cerebellar malignant glioma incidence in male rats, the most sensitive site in males, was chosen as the basis for a cancer potency factor.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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PROPYLENE OXIDE

CAS No: 75-56-9

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	58.08
Boiling point	34.2°C
Melting point	-112°C
Vapor pressure	543 mm Hg @ 25°C
Air concentration conversion	1 ppm = 2.37 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 3.7 E-6 $(\mu g/m^3)^{-1}$
[Calculated by US EPA (1995) from male rat nasal cavity hemangioma/hemangio-sarcoma data (NTP,1985) using a linearized multistage procedure, extra risk.]

Oral Cancer Potency Factor: 2.4 E-1 $(mg/kg/day)^{-1}$
[Calculated by US EPA (1995) from female Sprague-Dawley rat forestomach squamous cell carcinoma tumor data (Dunkelberg, 1981), using a linearized multistage procedure, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

Theiss *et al*. (1981) conducted a retrospective cohort study of 602 active and former employees who had worked for 6 months or more in one of 8 German alkylene oxide production plants. The workers had been exposed to alkylene oxides (propylene oxide and ethylene oxide) as well as to other chemicals such as dichloropropane and epichlorohydrin. No ambient propylene oxide concentrations were reported and the study included workers employed as early as 1928; propylene oxide production did not begin until 1959. No significant difference was observed between the observed and expected numbers of cancer deaths.

Animal Studies

Exposure to propylene oxide by gavage at dose levels of 0, 15 or 60 mg/kg twice weekly for 150 weeks has been shown to induce forestomach tumors (primarily squamous cell carcinomas) in female Sprague-Dawley rats (Dunkelberg, 1982). Female NMRI mice treated with 0.1, 0.3, 1.0 or 2.5 mg propylene oxide once a week for 95 weeks via subcutaneous injection demonstrated a dose-dependent increase in injection site tumors (mostly fibrosarcomas) (Dunkelberg, 1984). Subcutaneous injection of a total dose of 1500 mg/kg propylene oxide over 325 days in rats (sex and strain not specified) resulted in the induction of injection site sarcomas (8/12 and 3/12 rats

receiving propylene oxide in oil and water vehicle, respectively) (Walpole, 1958). However, the study did not include an appropriate control group.

F344 rats and $B6C3F_1$ mice (50/sex/dose) were exposed to 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) of propylene oxide for 6 hours/day, 5 days/week for 102 weeks (NTP, 1985; Renne *et al*., 1986). In rats, positive trends were demonstrated for papillary adenomas of the nasal turbinate epithelium (males and females), thyroid gland C-cell adenomas or carcinomas (females) and keratoacanthomas (males). A significantly increased incidence of endometrial stromal polyps and sarcomas combined was noted for all doses. However, the NTP decided that only the nasal epithelial tumors were treatment-related because the other tumors were either relatively common (thyroid) or were of low incidence relative to historical controls. In mice, the low-dose group was killed due to an inadvertent overdose 19 weeks after the initial start date. New groups of low-dose mice of both sexes were started, but additional control groups were not included. Hemangiomas (males) and hemangiosarcomas (both sexes) were significantly increased at the high dose. One squamous cell carcinoma and one papilloma were observed in the nasal cavity of 2 high-dose males; nasal cavity adenocarcinomas were reported in 2 high-dose females. Although not statistically significant, historical controls have demonstrated an extremely low incidence of these tumor types. A significant dose-related trend and incidence of mammary gland adenocarcinomas was observed in high-dose females.

Cpb:WU Wistar rats (100/sex/group) were exposed to 0, 30, 100 or 300 ppm (0, 71, 238 or 713 mg/m^3) propylene oxide for 6 hours/day, 5 days/week for 123-124 weeks (Reuzel and Kuper, 1983; Kuper *et al.* , 1988). No nasal cavity tumors were observed; however, significant increases in degenerative changes and neoplasia of the olfactory and respiratory epithelium were noted in both sexes of all exposure groups. Significant increases were also found in mammary gland adenocarcinomas in high-dose females. Squamous-cell carcinomas of the nose, larynx/pharynx and trachea, and adenocarcinoma of the larynx/pharynx and lungs were reported in 5 high-dose males. Although not statistically significant, none of these tumor types were reported in control males.

Male F344 rats exposed to 0, 100 or 300 ppm propylene oxide for 7 hours/day, 5 days/week for 104 weeks displayed a significant increase in nasal epithelium hyperplasia in the high-dose group (Lynch *et al*., 1984). The incidence of adrenal pheochromocytomas was also increased.

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Studies by Dunkelberg (1981) and NTP (1985) demonstrated that oral and inhalation exposure, respectively, to propylene oxide can result in increased animal tumor incidence. In the study by Dunkelberg (1981), female Sprague-Dawley rats exposed to total average doses of 0, 2714 or 10,798 mg/kg-day propylene oxide for 150 weeks demonstrated a significant increase in forestomach squamous cell carcinoma tumor incidence (0/100, 2/50 and 19/50 for control, low-dose and high-dose animals, respectively). These data were used to calculate an oral cancer potency factor for propylene oxide.

In the NTP carcinogenicity study (1985), F344 rats and $B6C3F_1$ mice (50/sex/dose) were exposed to 0, 200 or 400 ppm (0, 475 or 950 mg/m^3) of propylene oxide for 6 hours/day, 5 days/week for 102 weeks. High-dose rats exhibited an increased incidence of nasal papillary adenomas (2/50 for males, 3/50 for females), suggesting a carcinogenic response. However, these increases were not significant when compared to controls (0/50 for both sexes), making them unsuitable for carcinogenicity risk estimation. The incidence of nasal cavity hemangiomas or hemangiosarcomas in mice was 10/50 and 5/50 in the high-dose males ($p = 0.001$) and females ($p = 0.028$), respectively. These data, from a study where adequate numbers of animals of both sexes were treated for a lifetime, demonstrate that inhalation exposure to propylene oxide results in respiratory tract carcinogenicity. The male rat hemangioma/hemangiosarcoma data was used as the basis for a inhalation unit risk factor.

Methodology

Oral Cancer Potency Factor

Transformed animal doses (0, 2.58 and 10.28 mg/kg/day) and human equivalent doses (0, 0.44 and 1.76 mg/kg-day) were calculated from the administered doses using a rat body weight of 0.35 kg, a human body weight of 70 kg, 1029 days as the length of the exposure, and 1050 days as the length of the experiment and animal lifespan. A human oral cancer potency factor of 2.4 E-1 $(mg/kg/day)^{-1}$ was calculated using the linearized multistage procedure developed by Kenneth Crump and adopted by US EPA (1980).

Inhalation Unit Risk Factor

Transformed animal doses (0, 55 and 110 mg/kg/day) were calculated from administered doses assuming 50% pulmonary absorption, 0.03 kg mouse body weight, 0.039 m^3/day as the daily inhalation volume for mice and an exposure duration and length of experiment of 103 weeks. The absorption factor is consistent with that observed for epichlorohydrin in rat respiratory tract (Stott and McKenna, 1984). Human equivalent doses were 0, 4.15 and 8.3 mg/kg/day. The transformed animal dose level was used to calculate an animal slope factor of 9.3E-4 $(mg/kg/day)^{-1}$ using the linearized multistage procedure developed by Kenneth Crump and adopted by US EPA (1980). A human unit risk factor of 3.7 E-6 $(\mu g/m^3)^{-1}$ was determined using an animal body weight of 0.03 kg, a human body weight of 70 kg and an animal lifetime of 103 weeks. US EPA has stated that the unit risk should not be used if the air concentration exceeds 3 mg/m^3, since above this concentration the unit risk may not be appropriate.

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1,1,2,2-TETRACHLOROETHANE

CAS No: 79-34-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	167.9
Boiling point	146.5ºC
Melting point	-44ºC
Vapor pressure	9 mm Hg @ 30ºC
Air concentration conversion	1 ppm = 6.87 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 5.8 E-5 (µg/m^3)$^{-1}$
Slope Factor: 2.0 E-1 (mg/kg-day)$^{-1}$
[Calculated by US EPA from NCI (1978) female mouse hepatocellular carcinoma tumor data using a linearized multistage procedure, extra risk]

III. CARCINOGENIC EFFECTS

Human Studies

Norman *et al*. (1981) studied Army personnel assigned to treat chemical warfare protective equipment with material dissolved in tetrachloroethane. Of 3859 workers assigned to this process, 1099 whites and 124 blacks had probable exposure to the solvent. No statistically significant excess cancer mortality was noted. Slight excesses were noted for leukemia (SMR = 272, based on 4 deaths) and cancer of the genital organs (SMR = 158, based on 3 deaths).

Animal Studies

Theiss *et al*. (1977) exposed groups of 20 male A/st mice to 1,1,2,2-tetrachloroethane in tricaprylin by intraperitoneal injection (3/week) at doses of 80 mg/kg body weight, 200 mg/kg or 400 mg/kg. All survivors (10, 15 and 5 at the three doses, respectively) were killed 24 weeks after the first injection. The average number of tumors/animal were not significantly increased in the treated mice (0.3, 0.5 and 1.0 at the three doses, respectively compared to 0.27 for controls). However, the poor survival of treated animals and inadequate length of observation made this study unusable for a determination of the carcinogenicity of 1,1,2,2-tetrachloroethane.

B6C3F$_1$ mice (50 male, 50 female) were treated with technical grade (90% pure) 1,1,2,2-tetrachloroethane in corn oil by gavage 5 days/week (NCI, 1978). Low-dose and high-dose mice initially received 100 and 200 mg/kg body weight/day, respectively. Doses were increased to 150 and 300 mg/kg respectively at 18 weeks, 200 and 400 mg/kg at 21 weeks and 150 and 300

mg/kg at 26 weeks. Total duration of exposure was 78 weeks. Animals were killed 12 weeks after exposure termination. The low and high time-weighted average doses for males and females was 142 and 282 mg/kg/day, respectively. Control groups (20 male, 20 female) were left untreated or given corn oil alone for 78 weeks, and were then killed after 90 weeks. Only 1 high-dose male survived to 90 weeks, compared with 34% of the females. The incidence of hepatocellular carcinoma was positively correlated with dose level ($p<0.001$) in both male and female mice; tumor incidence in males was 1/18 for vehicle-treated controls, 13/50 for the low-dose group and 44/49 for the high-dose group. The respective tumor incidence for females was 0/19, 30/48 and 43/47.

Osborne-Mendel rats (50 male, 50 female) were treated with technical grade 1,1,2,2-tetra-chloroethane in corn oil by gavage 5 days/week (NCI, 1978). High-dose animals initially received 100 mg/kg body weight/day. In males, doses were increased to 130 mg/kg at 14 weeks, followed by 9 cycles of 4 weeks at 130 mg/kg followed by 1 week treatment-free starting at 32 weeks. In females, the dose was reduced at 25 weeks to 80 mg/kg, then followed at 32 weeks by the cyclic dosing protocol described for males (dose level 80 mg/kg). The duration of the cyclic dosing for both males and females was 45 weeks. Low-dose rats were initially exposed to 50 mg/kg/day. Doses were increased for males to 65 mg/kg at 14 weeks; doses were decreased for females to 40 mg/kg at 25 weeks. The total duration of exposure for both dose groups was 78 weeks, followed by 32 weeks without treatment. The low and high time-weighted average doses were 62 and 108 mg/kg/day for males and 43 and 76 mg/kg/day for females. Control groups (20 male, 20 female) were left untreated or given corn oil alone for 78 weeks; all surviving control and exposed animals were killed at 110 weeks. No significant increases in tumor incidence for any tumor type were noted in exposed animals. However, 2 of 49 high-dose males developed hepatocellular carcinomas and another developed a neoplastic nodule, compared with 0/20 vehicle controls.

Detailed reviews of these studies have been performed by IARC (1979) and US EPA (1980).

V. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Data from the bioassay of 1,1,2,2-tetrachloroethane by NCI (1978) was selected as the basis of a cancer potency factor because it demonstrated a dose-responsive induction of carcinogenicity after exposure to 1,1,2,2-tetrachloroethane in both sexes of a susceptible species ($B6C3F_1$ mice). Tumor incidence data from the most sensitive sex was used (hepatocellular carcinomas in females).

Methodology

The linearized multistage procedure developed by Kenneth Crump and adopted by US EPA (1980) was used to calculate a slope factor of 2.0 E-1 $(mg/kg/day)^{-1}$ from the NCI (1978) female $B6C3F_1$ mouse hepatocellular carcinoma incidence data. Calculation of the unit risk from the slope factor assumed a body weight of 70 kg and an inspiration rate of 20 m^3/day. US EPA has

stated that the unit risk should not be used if the air concentration exceeds 200 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

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THIOACETAMIDE

CAS No: 62-55-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	75.14
Boiling point	not available
Melting point	113-114 °C
Vapor pressure	not available
Air concentration conversion	1 ppm = 3.1 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.7 E-3 (µg/m^3)$^{-1}$
Slope Factor: 6.1 E+1 (mg/kg-day)$^{-1}$
[Female mouse liver tumor data (Gothoskar *et al.*, 1970), contained in Gold *et al*. (1984) database, expedited Proposition 65 methodology (Cal/EPA, 1992), with cross-route extrapolation.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of thioacetamide in humans are known to exist.

Animal Studies

Male albino rats (10/group) were exposed to thioacetamide in the diet for 18 months (Fitzhugh and Nelson, 1948). Dietary thioacetamide levels were 0, 50, 100, 250, 500 or 1000 mg/kg diet. Animals exposed to 1000 mg/kg diet thioacetamide survived for less than one month; animals exposed to 250 or 500 mg/kg diet thioacetamide also had increased mortality. One animal in the 500 mg/kg diet exposure group developed a hepatocellular carcinoma (the number of surviving animals in this group was unspecified). One animal of the 6 survivors in the 50 and 100 mg/kg diet exposure groups developed a hepatocellular adenoma. No liver tumors were observed in the control animals.

Gupta (1955, 1956) exposed 150 male and female Wistar rats to 32 mg/kg diet thioacetamide in the diet for more than 23 weeks; an untreated control group of 50 animals was included in the study. Bile duct tumors (unspecified type) were observed in 18/36 animals killed between 9 and 23 weeks; no liver tumors were noted in the control animals. Liver tumor metastases to the ovaries were noted in 4/5 animals treated for 47 weeks or longer.

Male and female Swiss mice were fed diet containing 0.03% thioacetamide for 65 weeks (89 mice total); an untreated control group was included in the study (Gothoskar *et al*., 1970).

Interim sacrifices were performed at 6, 9 and 13 months. An increased incidence of liver tumors (hepatomas) was noted in both males and females. Tumor incidence data is listed in Table 1.

Table 1. Thioacetamide-induced hepatoma incidence in male and female Swiss mice (Gothoskar *et al*., 1970)

Dose group	Average dose[1] (mg/kg-day)	Tumor incidence
male control	0	0/6
male treated	36	6/6
female control	0	0/6
female treated	39	6/7

1. Doses as reported by Gold *et al.* (1984).
2. Tumor incidences as reported by Gold *et al*. (1984).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Gold *et al.* (1984) list results from the study of thioacetamide by Gothoskar *et al.* (1970) in male and female Swiss mice. A total of 89 mice of both sexes were fed a diet containing 0.03% thioacetamide for 6, 9, 13 or 17 months. The group studied for 17 months consisted of 12 control mice (6 male and 6 female) and 13 treated mice (6 male and 7 female). Hepatomas were seen in all treated male mice, precluding estimation of the upper bound on potency in these animals. Females were slightly less sensitive; six of the seven dosed female mice developed hepatomas. Because this is the only dose-response data available in Gold *et al*., the data for the females are used to derive potency (see Table 1). The value presented here may be an underestimate, but is the best value currently available (Cal/EPA, 1992).

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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TOLUENE DIISOCYANATE
CAS No: 26471-62-5

2,4-TOLUENE DIISOCYANATE
CAS No: 584-84-9

2,6-TOLUENE DIISOCYANATE
CAS No: 91-08-7

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	174.15
Boiling point	251°C at 760 mm Hg
Freezing point	22°C (pure toluene-2,4-diisocyanate (IARC, 1985); 7.2°C (pure toluene-2,6-diisocyanate (IARC, 1985)
Vapor pressure	0.01 mm Hg at 20°C
Air concentration conversion	1 ppm = 7.12 mg/m^3 (IARC, 1985)

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 1.1 E-5 (µg/m^3)$^{-1}$
Slope Factor: 3.9 E-2 (mg/kg-day)$^{-1}$
[Male rat subcutaneous fibroma/fibrosarcoma tumor data (NTP, 1986) contained in Gold *et* al. database (1990), expedited Proposition 65 methodology (Cal/EPA, 1992)]

III. CARCINOGENIC EFFECTS

Human Studies

No epidemiological studies examining potential carcinogenic effects of 2,4- and 2,6-toluene-diisocyanate (TDI) on humans are known to exist. A case report reviewed by IARC (1985) described a 47-year old nonsmoking spray painter with a lung adenocarcinoma who had been exposed to TDI and 4,4'-methylenediphenyl diisocyanate for 15 years and had a 10-year history of lung disease thought to be caused by isocyanate exposure (Mortillaro and Schiavon, 1982).

Animal Studies

The National Toxicology Program (NTP) (1986) exposed male and female Fischer 344 344/N rats and B6C3F$_1$ mice (50/sex/exposure group) to commercial grade TDI (86% 2,4 isomer; 14% 2,6 isomer) in corn oil by gavage 5 days/week for 106 and 105 weeks, respectively. Rat exposure groups were 30 or 60 mg/kg for males and 60 or 120 mg/kg for females. Mouse exposure groups were 120 or 240 mg/kg body weight for males and 60 or 120 mg/kg for females. Vehicle control groups (50/sex/species) were included.

A dose-dependent reduction in survival occurred in treated rats; 36/50 (72%) controls, 14/50 (28%) low-dose and 8/50 (16%) high-dose males, and 36/50 (72%) controls, 19/50 (38%) low-dose and 6/50 (12%) high-dose females survived to study termination (108 weeks). A treatment-related induction of subcutaneous fibromas and fibrosarcomas was noted in males and females. The combined fibroma/fibrosarcoma incidence was 3/50 (6%) in controls, 6/50 (12%) in low-dose and 12/50 (24%) in high-dose males, and 2/50 (4%) in controls, 1/50 (2%) in low-dose and 5/50 (10%) in high-dose females. Fibromas and fibromasarcomas occurred in male and female rats with a statistically positive trend, and the incidence in both high-dose males and females was significantly greater than controls. Increased mammary gland tumor incidence in female rats was found to be significant in both the low- and high-dose groups by life table and incidental tumor analysis. The first mammary tumor was seen in an animal dying at week 84; the survival-adjusted mammary tumor incidences were 17/45 (38%) for controls, 25/36 (69%) for low-dose and 21/28 (75%) for high-dose animals. Increased incidences of pancreatic acinar cell adenomas with a statistically significant trend were observed in male rats; the incidence in the high-dose group was significantly greater than that in the controls. Pancreatic acinar nodular hyperplasia incidence was also increased in male rats in a dose-dependent manner (control, 0%; low-dose, 4%; high-dose, 8%). A statistically significant trend was noted for pancreatic islet cell adenoma incidence in both male and female rats; the incidences were significantly greater than those in the controls in both dose groups for females, and in the high-dose group for males. A significant dose-related increase in hepatic neoplastic nodule incidence in high-dose female rats was also noted.

Survival of high-dose male mice was reduced; 26/50 (52%) animals in this group were still alive at study termination (week 107) compared to 46/50 (92%) controls and 40/50 (80%) in the low-dose group. No statistically significant increase in tumor incidence was noted in treated male mice. A statistically significant positive trend was observed in the incidence of hemangiomas and hemangiosarcomas (in liver, ovaries or peritoneum), lymphomas, and hepatocellular adenomas and carcinomas in female mice. Overall hemangioma and hemangiosarcoma incidence was 0/50 in controls, 1/50 (2%) in the low-dose group and 5/50 (10%) in the high-dose group. Pairwise comparisons between the control and high-dose groups also indicated a significantly increased tumor incidence in the high-dose group. Combined hepatocellular adenoma and carcinoma incidence was 4/50 (8%) in controls, 5/50 (10%) in the low-dose group and 15/50 (30%) in the high-dose group. Tumor incidence in the high-dose group was significantly greater than in the controls. Overall lymphoma incidence was 10/50 (20%) in controls, 17/50 (34%) in the low-dose group, and 16/50 (32%) in the high-dose group; high-dose group tumor incidence was significantly greater than controls.

Male and female CD-1 mice and Sprague-Dawley CD rats (120/sex/group) were exposed to 0, 0.05 or 0.15 ppm (0, 0.36 or 1.07 mg/m^3) industrial-grade TDI (approximately 80% 2,4 isomer, 20% 2,6 isomer) by inhalation for 6 hours/day, 5 days/week, for 104 (mice), 108 (female rats) or 110 (male rats) weeks (Loeser, 1983). No treatment-induced increase in tumor incidence was noted in rats or mice. However, the rat histopathological evaluation was incomplete. Also, NTP (1986) noted that the exposure levels used corresponded to daily gavage doses of less than 1 mg/kg, and may not have been adequate doses to detect a potential carcinogenic response.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NTP carcinogenicity study (1986) demonstrated that TDI induced tumors in several species (rats and mice), in both sexes in at least one of those species, at multiple sites. The male rat subcutaneous fibroma/fibrosarcoma tumor data was chosen as the basis of a cancer potency factor because it was the most sensitive endpoint in the most sensitive of the responsive species and sexes tested.

Methodology

Expedited Proposition 65 methodology (with cross-route extrapolation) was used to derive a cancer potency factor. A unit risk factor was then calculated by OEHHA/ATES from the cancer potency factor using a reference human body weight of 70 kg and an inspiration rate of 20 m^3/day.

V. REFERENCES

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1,1,2-TRICHLOROETHANE (Vinyl trichloride)

CAS No: 79-00-5

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB (1995) except as noted)

Molecular weight	133.42
Boiling point	113.8°C at 760 mm Hg
Melting point	-36.5°C
Vapor pressure	23 mm Hg at 25°C
Air concentration conversion	1 ppm = 5.55 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.1 E-5 (µg/m^3)$^{-1}$
[Calculated by US EPA/IRIS (1980, 1994) from male mouse hepatocellular carcinoma tumor data (NCI, 1978), using a linearized multistage procedure, extra risk.]

III. CARCINOGENIC EFFECTS

Human Studies

No studies on the potential carcinogenic effects of 1,1,2-trichloroethane in humans are known to exist.

Animal Studies

The carcinogenicity of 1,1,2-trichloroethane in rats and mice was studied by the National Cancer Institute (NCI, 1978). Groups of 50 male and female B6C3F$_1$ mice (5 weeks of age) and Osborne-Mendel rats (6 weeks of age) were exposed to technical-grade 1,1,2-trichloroethane (92.7% pure, impurities unspecified) by gavage on 5 consecutive days/week for 78 weeks of a 90-91 week (mice) or 111-113 week (rats) experimental period.

Low and high dose mice received 150 and 300 mg/kg body weight, respectively, for 8 weeks, followed by 200 and 400 mg/kg, respectively, for 70 weeks, followed by 12-13 weeks without treatment, after which the experiment was terminated. The time-weighted average doses were 195 and 390 mg/kg, respectively. Untreated control and vehicle control groups were included (20 animals/sex/group).

Low and high dose rats received 35 and 70 mg/kg body weight, respectively, for 20 weeks, followed by 50 and 100 mg/kg, respectively, for 58 weeks, followed by 34-35 weeks without treatment, after which the experiment was terminated. The time-weighted average doses were 46 and 92 mg/kg, respectively. Untreated control and vehicle control groups were included (20 animals/sex/group).

No statistically significant increase in 1,1,2-trichloroethane-induced tumor incidence was noted in either male or female rats. Increases in hepatocellular carcinoma incidence were noted in all male and female mouse 1,1,2-trichloroethane-exposed treatment groups. The Fisher exact test comparing tumor incidences of dosed to control groups and the Cochran-Armitage test for positive dose-related trend indicated a highly significant association ($p < 0.001$) between hepatocellular carcinomas and 1,1,2-trichloroethane exposure. A positive dose-related association between 1,1,2-trichloroethane exposure and adrenal gland pheochromocytoma incidence in male and female mice was also indicated by the Cochran-Armitage test ($p = 0.003$ for males, $p < 0.001$ for females). Fisher exact tests confirmed these results for high dose female mice ($p = 0.006$) but not for other mouse treatment groups. Mouse tumor incidence data is listed in Table 1.

Table 1. 1,1,2-Trichloroethane-induced $B6C3F_1$ mouse tumor incidence data (NCI, 1978)

Treatment group[1] (mg/kg/day)	Time-weighted[2] average dose (mg/kg/day)	Human equivalent dose[2] (mg/kg/day)	Tumor incidence[3]
			hepatocellular carcinomas
males			
vehicle control	0	0	2/20
low dose	139	9.3	18/49
high dose	279	18.6	37/49
females			
vehicle control	0	0	0/20
low dose	139	9.3	16/48
high dose	279	18.6	40/45

1. Low and high doses: 150 and 300 mg/kg body weight, respectively, for 8 weeks, followed by 200 and 400 mg/kg, respectively, for 70 weeks, followed by 12-13 weeks without treatment.
2. Doses as reported by US EPA (1994).
3. Tumor incidences as reported by US EPA (1994).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

The NCI (1978) carcinogenicity bioassay of 1,1,2-trichloroethane indicated that 1,1,2-trichloroethane induced tumor formation in male and female $B6C3F_1$ mice. The cancer potency value is based on the dose-response data for hepatocellular carcinomas in male mice.

Methodology

Doses are time-weighted averages adjusted for frequency of exposure (5 of 7 days/week) (US EPA, 1994). Weight of the mice was assumed to be 0.033 kg. A linearized multistage procedure was used to calculate a slope factor of 1.7 E+1 $(mg/kg/day)^{-1}$ and a unit risk value of 1.6 E-5 $(\mu g/m^3)^{-1}$ from the NCI (1978) male mouse hepatocellular carcinoma incidence data. US EPA has stated that the unit risk should not be used if the air concentration exceeds 600 $\mu g/m^3$, since above this concentration the unit risk may not be appropriate.

V. REFERENCES

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2,4,6-TRICHLOROPHENOL

CAS No: 88-06-2

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	197.5
Boiling point	246°C
Melting point	69°C
Vapor pressure	0.012 mm Hg @ 25°C
Air concentration conversion	1 ppm = 8.00 mg/m^3 @ 25°C

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.0 E-5 (µg/m^3)$^{-1}$
Slope Factor: 7.0 E-2 (mg/kg-day)$^{-1}$
[Calculated from a cancer potency factor derived by RCHAS/OEHHA (CDHS, 1988)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no human carcinogenicity studies available for 2,4,6-trichlorophenol.

Animal Studies

Innes *et al.* (1969) administered 100 mg/kg body weight 2,4,6-trichlorophenol by oral gavage to two F_1 generation strains of mice, B6C3F$_1$ (C57BL/6 × C3H/Anf) and B6AKF$_1$ (C57BL/6 × AKH) (18/sex/strain) from day 7 to 28 of life, without adjusting the initial dose to account for weight gain. After 28 days, 2,4,6-trichlorophenol was added to feed at 260 ppm for 74 weeks. Surviving animals were sacrificed at 78 weeks. Survival data and tumor incidence are reported in Table 1. Incidence of tumors of all types was found to be significantly increased only among treated B6C3F$_1$ males (p=0.004; Fisher's exact test). Incidence of reticulum cell tumors was also found to be significantly increased among pooled male and female treated B6C3F$_1$ animals (p=0.005). Pairwise comparison of summary incidence data shows an increased incidence of hepatomas among treated B6C3F$_1$ females (p=0.028) and reticulum cell sarcomas among treated B6C3F$_1$ males (p=0.021). Some results of this study were published separately (Bionetics Research Laboratories, 1968).

A lifetime feeding study of 2,4,6-trichlorophenol was conducted by the National Cancer Institute in two species, B6C3F$_1$ mice and F344 rats (NCI, 1979). Rats (50/sex/group) were treated with 5,000 or 10,000 ppm 2,4,6-trichlorophenol in feed for 106-107 weeks, plus a control group of 20

rats/sex given only standard feed. Tumor incidence data are presented in Table 2. Significant increases in hematopoietic tumor (malignant lymphoma and monocytic leukemia) incidence was observed among males of both the low-dose (p=0.013) and high-dose (p=0.002) groups.

In the same study (NCI, 1979), $B6C3F_1$ mice were treated with 2,4,6-trichlorophenol in feed for 105 weeks. Male mice (50/group) were treated with 5,000 or 10,000 ppm 2,4,6-trichlorophenol. Female mice (50/group) were initially treated with diets containing 10,000 and 20,000 ppm 2,4,6-trichlorophenol; however, indications of reduced growth rate at 38 weeks led the investigators to reduce the level of compound to 2,500 and 5,000 ppm 2,4,6-trichlorophenol for the balance of the experiment, leading to time-weighted average concentrations of 5,214 and 10,428 ppm. The control group consisted of mice (20/sex) given the standard diet. Tumor incidence data are presented in Table 3. A significant increase in hepatoma incidence was observed among male mice in both treatment groups and among female mice in the high dose group (p<0.001, Fisher's exact test).

In an effort to establish whether 2,4,6-trichlorophenol may be acting as a tumor initiator, Bull *et al.* (1986) treated female SENCAR mice (30/group) with 200 mg/kg 2,4,6-trichlorophenol by several routes of exposure, including gavage, intraperitoneal injection, subcutaneous injection, and dermal application, followed by dermal application of 1.0 µg 12-o-tetradecanoylphorbol-13-acetate three time per week for 20 weeks. No skin tumors were found when survivors were examined 52 weeks after first exposure.

Table 1. Survival and tumor incidence in male and female $B6AKF_1$ and $B6C3F_1$ mice treated with 2,4,6-trichlorophenol (Innes *et al*., 1969).

		tumor incidence				
		$B6C3F_1$			$B6AKF_1$	
tumor type	treatment[1]	total	male	female	male	female
total tumors	treated	16/36	9/18[2]	7/18[3]	3/17	2/17
	control	30/166	22/79	8/87	16/90	7/82
hepatomas	treated	5/36[4]	3/18	2/18[5]	1/18	1/18
	control	17/166	17/79	0/87		
reticulum cell sarcomas	treated	6/36[6]	4/18[7]	2/18	0/18	1/18
	control	5/166	3/79	2/87		

[1] $B6C3F_1$ and $B6AKF_1$ mice were treated with 100 mg/kg body weight 2,4,6-trichlorophenol by oral gavage from day 7 to 28 of life, then fed diet containing 260 ppm 2,4,6-trichlorophenol for 74 weeks, at which time surviving animals were sacrificed.
[2] p = 0.064, Fisher's exact test.
[3] p = 0.004, Fisher's exact test.
[4] p = 0.059, Fisher's exact test.
[5] p = 0.028, pairwise comparison of summary incidence data.
[6] p = 0.005, Fisher's exact test.
[7] p = 0.021, pairwise comparison of summary incidence data.

Table 2. Tumor incidence in Fischer F344 rats treated with 2,4,6-trichlorophenol (NCI, 1979).

tumor type/ treatment[1]		tumor incidence	
		male	female
total hemato-poietic tumors	control	4/20	3/20
	low-dose	25/50[2]	11/50
	high-dose	29/50[3]	13/50
malignant lymphoma	control	1/20	0/20
	low-dose	2/50	0/50
	high-dose	0/50	2/50
monocytic leukemia	control	3/20	3/20
	low-dose	23/50[4]	11/50
	high-dose	29/50[5]	11/50

[1] F344 rats were treated with diet containing 5,000 or 10,000 ppm 2,4,6-trichlorophenol for 106-107 weeks at which time animals were sacrificed.
[2] $p = 0.019$, Fisher's exact test.
[3] $p = 0.004$, Fisher's exact test.
[4] $p = 0.013$, Fisher's exact test.
[5] $p = 0.002$, Fisher's exact test

Table 3. Hepatoma incidence in $B6C3F_1$ mice treated with 2,4,6-trichlorophenol (NCI, 1979).

treatment[1]/hepatoma type		tumor incidence	
		male	female
control	adenoma	3/20	1/20
	carcinoma	1/20	0/20
	total	4/20	1/20
low-dose	adenoma	22/49	12/50
	carcinoma	10/49	0/50
	total	32/49[2]	12/50[3]
high-dose	adenoma	32/47	17/48
	carcinoma	7/47	7/48
	total	39/47[2]	24/48[2]

[1] Male $B6C3F_1$ mice were treated with diet containing 5,000 or 10,000 ppm 2,4,6-trichlorophenol for 105 weeks, then sacrificed. Female $B6C3F_1$ mice were treated with diet containing 10,000 or 20,000 ppm 2,4,6-trichlorophenol for 38 weeks at which time diet concentrations were reduced to 2,500 or 5,000 ppm 2,4,6-trichlorophenol, respectively, until they were sacrificed at 105 weeks.
[2] $p < 0.001$, Fisher's exact test.
[3] $p = 0.059$, Fisher's exact test.

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Two studies, Innes *et al.* (1969) and NCI (1979), have been deemed adequate for the derivation of cancer potencies. Both demonstrate statistically significant increases in tumor incidence among 2,4,6-trichlorophenol exposed animal populations. Innes *et al.* (1969) show increased incidence of reticulum cell sarcomas in male $B6C3F_1$ mice and heptomas in female $B6C3F_1$ mice. The NCI (1979) study shows increased incidence of hepatomas in both male and female $B6C3F_1$ mice, and leukemia in male Fischer F344 rats. The US EPA estimate of cancer potency of 2,4,6-trichlorophenol derived from the rat study is lower than that for mice (US EPA, 1988 and below). Since selection of the potency value is made on the basis of the most sensitive species, site, and study in the absence of evidence that the data are not representative, tumor induction in $B6C3F_1$ mice has been chosen as the basis for derivation of a cancer potency value for 2,4,6-trichlorophenol.

Methodology

The multistage Doll-Armitage model polynomial was fit to tumor incidence data from Innes *et al.*(1969) and NCI (1979) (Armitage and Doll, 1954). Dosage estimates for the studies were based on food intake assumptions of 12% and 13% of body weight for male and female mice, respectively (Gold, 1984). In the NCI (1979) study, final dose values were calculated to be 1200 and 600 mg/kg-day for high- and low-dose females, and 1356 and 678 mg/kg-day for high- and low-dose males. In the Innes *et al.*(1969) study, dosage estimates were based on the method of Crouch to account for variation in dosing during the course of the experiment (Crouch, 1983). Dosage estimates were calculated to be 32.5 and 34.7 mg/kg-day for male and female mice, respectively. Using a multistage polynomial, the cancer potency was derived using the probability of dying with a tumor from a given dose and the background lifetime cancer incidence (Crump and Howe, 1984). The upper 95% confidence bound on the cancer potency was termed q_1^*. Estimates of q_1^* for tumor induction in $B6C3F_1$ mice are presented in Table 4.

Calculation of the cancer potency in animals (q_{animal}) can be made using q_1^* and the following relationship, where T is the natural lifespan of the animal (104 weeks) and T_e is the experimental duration (Innes *et al.*, T_e = 104 weeks; NCI, T_e = 78 weeks):

$$q_{animal} = q_1^* \times (T/T_e)^3$$

The resulting q_{animal} can be converted to human cancer potency (q_{human}) based on the following relationship, where bw_{animal} is the assumed body weight for the test species (Innes *et al.* (1969), bw_{animal} = 0.030 kg; NCI (1979), bw_{animal} = 0.04 kg-males and 0.035 kg-females) and bw_{human} is the assumed human body weight (70 kg):

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

Table 4. Derivation of cancer potencies from NCI (1979) and Innes *et al.*(1969).

study	tumor/group	q_1^* (mg/kg-day)$^{-1}$	q_{animal} (mg/kg-day)$^{-1}$	q_{human} (mg/kg-day)$^{-1}$	maximum likelihood estimate	LCB (95%)
NCI, 1979	hepatoma/ male	0.0017	12.1	0.021	0.016	0.004
	hepatoma/ female	0.0006	12.6	0.008	0.003	0
Innes, 1969	reticulum cell sarcoma/ male	0.035	0.035	0.47	0.2	0.05
	hepatoma/ female	0.021	0.021	0.28	0.11	0.03

LCB = Lower confidence bound.

The highest upper bound cancer potency for humans (q_{human}) was derived from the results of the Innes *et al.* (1969) study showing reticulum cell tumor induction in male $B6C3F_1$ mice. However, confidence in this value is reduced because the number of animals used in the study is small (18/group) and data were reported incompletely. Innes *et al.* (1969) and NCI (1979) both present data showing induction of hepatomas in female $B6C3F_1$ mice. However, lack of overlap between the 95% confidence bounds of the two potencies suggests there may be a greater sensitivity to this effect in the strain used by Innes *et al* (1969). Selection of a cancer potency value is made based on the most sensitive species, site, and study in the absence of evidence indicating the value is not representative (CDHS, 1985). On balance, the evidence favors neither the higher sensitivity of the Innes *et al.* (1969) study nor the high quality of the NCI (1979) study. For this reason, a method of Anderson (1983) was chosen for combining the results of these studies. The resulting cancer potency derived from the geometric mean of the four potencies shown in Table 4 is 0.07 (mg/kg-day)$^{-1}$.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.0 E-5 ($\mu g/m^3$)$^{-1}$.

V. REFERENCES

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URETHANE

CAS No: 51-79-6

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1994)

Molecular weight	89.09
Boiling point	182-184°C
Melting point	48-50°C
Vapor pressure	0.36 mm Hg @ 25°C
Air concentration conversion	1 ppm = 3.64 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor: 2.9 E-4 $(\mu g/m^3)^{-1}$
Slope Factor: 1.0 E+0 $(mg/kg\text{-}day)^{-1}$
[Calculated from a potency factor derived by RCHAS/OEHHA (CDHS, 1989)]

III. CARCINOGENIC EFFECTS

Human Studies

There are no studies available directly linking urethane exposure to induction of cancer in humans. Urethane is, however, frequently present in alcoholic beverages, particularly brandy, whisky and wine, and IARC has recognized alcoholic beverages as carcinogenic to humans (IARC, 1988). Although other compounds present in alcoholic beverages may account for this effect, urethane may be a contributor to alcohol-related increases in cancer incidence.

Animal Studies

CDHS (1989) has identified nearly 200 studies which demonstrate the carcinogenicity of urethane in animals. Below are summaries of those determined to be most relevant in the establishment of the reference cancer potency value, with emphasis on studies performed by realistic routes of exposure and in multiple doses.

Pietra and Shubik (1960) exposed male and female Syrian golden hamsters (10/sex) to drinking water containing 0.2% urethane for life. Control animals (49 male and 14 female) received plain drinking water. Animals were autopsied at death. Among exposed animals, males showed increased incidence of dermal melanotic tumors (7/10 exposed, 1/49 control; $p < 0.01$, Fisher's exact test). Male and female animals showed an increased incidence of forestomach papillomas (males: 4/10 exposed, 0/49 control; females: 6/10 exposed, 0/14 control; $p < 0.01$). Other tumors

noted in exposed animals but not control animals include single cases of thyroid adenoma and liver hemangiosarcoma in males, malignant lymphoma and bronchial adenoma in females.
Toth *et al.* (1961a) exposed Syrian golden hamsters (31 male; 30 female) to drinking water containing 0.2% urethane. Control groups of 54 male and 47 female received plain drinking water. Dosing began at 5 weeks and continued to 25 weeks at which point the drinking water urethane concentration was increased to 0.4%. At 40 weeks treatment was discontinued due to diarrhea among the animals. At 48 weeks, treatment with 0.4% urethane resumed, but was discontinued permanently at 50 weeks due to diarrhea. Survival was significantly decreased in exposed male and female hamsters. Among exposed animals, significant increases in incidence of dermal melanotic tumors (12/27 exposed males vs. 0/54 control males; 11/25 exposed females vs. 0/47 control females; $p \leq 10^{-6}$; Fisher's exact test), forestomach papillomas (22/27 exposed vs. 0/54 control, $p < 10^{-15}$, males; 18/25 exposed vs. 1/47 control; $p < 10^{-9}$, females) and carcinomas (3/27 exposed vs. 0/54 control; $p = 0.04$, males; 2/25 exposed vs. 0/47 control; $p = 0.1$, females), pulmonary adenomatosis (3/27 exposed vs. 0/54 control; $p = 0.04$, males), mammary tumors (3/25 exposed vs. 0/47 control; $p = 0.04$, females), hepatomas (3/27 exposed vs. 0/54 control; $p = 0.04$, males), and hepatic or splenic hemangiomas (5/27 exposed vs. 0/54 control; $p = 0.04$, males) were found.

Toth and Boreisha (1969) exposed Syrian golden hamsters (48 male and 52 female) to drinking water containing 0.1% urethane for life, beginning at 5 weeks of age. Control groups (100/sex) received plain drinking water. Survival was significantly decreased in exposed male and female animals. An increased incidence of dermal melanocytosis (26/49 exposed males vs. 1/88 control males; 25/41 exposed females vs. 0/79 control females; $p = 10^{-14}$; Fisher's exact test), forestomach papillomas (36/49 exposed vs. 6/88 control, $p = 10^{-15}$, males; 35/44 exposed vs. 2/84 control, $p = 10^{-20}$, females) and adenomatous polyps of the cecum (4/40 exposed vs. 0/79 control, $p = 0.01$, males; 7/33 exposed vs. 0/72 control, $p = 0.001$, females) was noted in both males and female animals. Among females an increased incidence of gall bladder papillomas, adrenal cortex carcinomas, thyroid carcinomas, ovarian carcinomas, vaginal carcinomas, and lung adenomatosis was observed ($p < 0.05$). Hemangiosarcoma incidence was increased in exposed males.

Tannenbaum *et al.* (1962) exposed Sprague-Dawley rats (15/group) to drinking water containing 0.1% urethane. Two "young" groups, one virgin females and the other males, were treated from age 7 weeks to 32 weeks. A third group of virgin females was treated for 14 weeks from age 32 weeks. Age and sex matched control groups of 15 each receiving plain drinking water were included in the study. Animals were autopsied at the time of natural death unless sacrificed when moribund. Survival was reduced in the treated groups. Incidence of Zymbal gland carcinoma was increased in treated "young" male rats (4/15 treated vs. 0/15 control, $p = 0.05$, Fisher's exact test) and female rats (3/15 treated vs. 0/15 control, $p = 0.11$). Control animals showed higher incidence of mammary tumors than treated animals, most likely because of the reduced survival of treated animals. Tumors noted among treated animals, but not control animals, include malignant lymphoma, sarcoma, and kidney tumors.

Schmähl *et al.* (1977) and Port (1976) report on exposure of rats and mice to urethane in drinking water. Tumor specific incidence data are reported by Port (1985). Male and female NMRI mice and Sprague-Dawley rats (40/sex/group) were exposed to urethane in drinking water from 8

weeks of age for their lifetime such that the daily dose rate was 0, 0.1, 0.5, 2.5, or 12.5 mg/kg body weight. Animals were given the appropriate dose in 20 ml drinking water. Animals were observed until their natural death. Among mice, significant increases in tumor incidence ($p < 0.1$ by Fisher's exact test) were found for pulmonary adenoma in males (6/40, 9/40, 14/40 in the 0.5, 2.5, and 12.5 mg/kg dose groups, respectively vs. 0/40 controls), and pulmonary adenoma (12/40 treated with 12.5 mg/kg urethane vs. 5/40 controls), pulmonary carcinoma (5/40 treated with 12.5 mg/kg urethane vs. 0/40 controls), angiosarcoma of the liver (4/40 treated with 12.5 mg/kg urethane vs. 0/40 controls), and mammary carcinoma (4/40 treated with 12.5 mg/kg urethane vs. 0/40 controls) in females. For each of these tumor types, the trend toward increased incidence was found to be dose-related ($p < 0.01$ by Mantel-Haenszel trend test). Among female rats, a significant increase in the incidence of mammary carcinoma (1/40, 2/40, 9/40 in the 0.5, 2.5, and 12.5 mg/kg urethane dose groups, respectively vs. 0/40 in the 0.1 mg/kg urethane dose group, $p = 0.0011$) and the combined incidence of mammary adenoma and carcinoma was found (2/40, 3/40, 4/40, 13/40 in the 0.1, 0.5, 2.5, and 12,5 mg/kg urethane dose groups, respectively vs. 2/40 in the 0.1 mg/kg urethane dose group, $p = 0.0016$ by Fisher's exact test). The incidence data for the untreated control animals were lost. The trend was found to be dose-related ($p < 10^{-4}$ by Mantel-Haenszel trend test).

Klein *et al.* (1962) treated 7-8 day old $B6AF_1/J$ mice (C57BL/6 female × A/J male) with 2.8 or 5.5 mg urethane in 0.05 ml 0.1% dioctylester of sodium sulfosuccinic acid by oral gavage 3 times per week for 5 weeks. Control groups for the low-dose group included both males receiving vehicle only and males receiving no treatment. Males and females receiving no treatment served as a control for the high-dose group. Survivors of the treatment period comprised the study group and ranged from 39 to 57 animals. Survival in the treated groups was significantly lower than in controls. Among animals receiving the higher dose of urethane, treated males had a higher incidence of leukemias (32/42 treated vs. 0/38 vehicle controls, $p = 10^{-13}$; Fisher's exact test), lung adenomas (42/42 treated vs. 10/38 vehicle controls, $p = 10^{-12}$) and hepatoma (4/42 treated vs. 0/38 vehicle controls, $p = 0.07$) than animals receiving vehicle alone. Among animals receiving the lower dose of urethane, males showed a higher incidence of lung adenomas (40/41 treated vs. 3/40 untreated controls, $p = 10^{-17}$), hepatoma (23/41 treated vs. 0/40 untreated controls, $p = 10^{-8}$), and leukemias (19/41 treated vs. 0/40 untreated controls, $p = 10^{-6}$) relative to untreated control animals. In the same dose group, females showed a higher incidence of leukemias (16/40 treated vs. 1/57 controls, $p = 10^{-6}$) , lung adenomas (39/40 treated vs. 9/57 controls, $p = 10^{-6}$), hepatomas (5/40 treated vs. 0/57 controls, $p = 0.01$), and forestomach papillomas (3/40 treated vs. 0/57 controls, $p = 0.07$) relative to untreated control animals.

Della Porta *et al.*(1963a) exposed 5 groups of male and female CTM mice to drinking water containing 0.4% urethane in several exposure scenarios ranging from a total exposure time of 5 to 15 days. Effective group size was the number of survivors at 25 weeks for treated animals (range: 30-83 mice) and survivors at 45 weeks for controls (88 males and 99 females). Among all exposed animals there was a significant increase in the incidence of lung adenomas over control animals ($p < 10^{-8}$; Fisher's exact test). Among all exposed female mice, the incidence of lymphosarcoma was increased over controls ($p < 0.05$). Among all exposed male mice, the incidence of reticulosarcoma was increased over controls ($p < 0.04$). Other tumor types showing some significant increase ($p < 0.05$) in incidence over controls in some but not all exposure

scenarios include lymphosarcomas and Harderian gland adenomas in male mice, and mammary gland adenocarcinoma, hepatoma, and Harderian gland adenomas in female mice.

Table 1. Tumor incidence in CTM mice exposed to drinking water containing 0.4% urethane (Della Porta *et al.*, 1963a).

	A*		B		C		D		E		control	
tumor type	male	female	male	female	male	female	male	female	male	female	male	female
lung adenoma	29/36	53/63	42/56	53/83	58/71	51/68	19/45	26/48	25/30	30/39	2/88	7/99
lympho-sarcoma	12/36	17/63	14/56	13/83	14/71	15/68	8/45	7/48	2/30	10/39	4/88	5/99
reticulo-sarcoma	3/36	4/63	6/56	1/83	8/71	6/68	3/45	2/48	3/30	2/39	0/88	7/99

*Exposure scenarios: A - two 10 day exposures, separated by 10 days; B - one 10 day exposure; C - three 5 day exposures, separated by 10 days; D - two 5 day exposures, separated by 10 days; E - one 5 day exposure.

Della Porta *et al.* (1963b) conducted another study similar to that described above, but exposed CTM mice (75 male and 108 female) to drinking water containing 0.4% urethane for 10 days or two 10-day periods separated by 10 days. Control animals received plain drinking water (130 males and 120 females). Surviving animals were sacrificed at 75 weeks. The effective group size was considered the size of the group at the time of appearance of the first malignant lymphoma. Among male and female mice in both treatment groups, the incidence of malignant lymphoma was elevated over control animals (15/40 in the 20-day treatment group, 19/61 in the 10-day treatment group, vs. 4/103 controls, $p < 10^{-4}$ by Fisher's exact test). Among female mice, the incidence of mammary gland tumors was increased over controls (21/70 in the 20-day treatment group vs. 15/108 controls,$p < 0.008$; 34/83 in the 10-day treatment group vs. 15/108 controls, $p = 10^{-4}$). Other tumors observed included lung adenomas, mammary carcinomas, liver angiosarcomas, hepatomas, Harderian gland adenomas, and forestomach and skin papillomas.

Della Porta *et al.* (1967) exposed four inbred mouse strains (C57BL, C3H, C3Hf, SWR) and one hybrid mouse strain ($B6C3F_1$) to drinking water containing 0.4% urethane. Five-week old male and female animals were exposed for 15-20 days in 5- or 10-day periods separated by 10 days, and 10-day old animals were exposed five times, once every other day. The effective group size for analysis of tumor incidence was considered the initial number of animals less those dying without tumors before the 25th week for urethane-exposed animals or the 45th week for control animals. The effective group size ranged from 30 to 158 animals for animals showing significant increases in tumor incidence. Among male and female $B6C3F_1$ mice exposed for 10 days, the incidence of Harderian gland tumors (45/51 exposed vs. 3/32 control, males; 44/81 exposed vs. 0/39 control, females; $p < 10^{-10}$, Fisher's exact test) and lung adenomas (23/51 exposed vs. 7/32 control, males; 18/81 exposed vs. 4/39 control, females; $p < 0.1$) was increased. Among female $B6C3F_1$ mice alone, the incidence of thymic lymphosarcoma (10/81 exposed vs. 0/39 control; $p = 0.02$) and mammary gland adenocarcinoma (23/81 exposed vs. 1/39 control; $p = 10^{-3}$) was also increased. Among male and female C3Hf mice exposed for 15 days, the incidence of lung adenoma (45/79 exposed vs. 3/30 control, males, $p = 10^{-5}$; 46/87 exposed vs. 12/62 control, females, $p = 10^{-4}$) and Harderian gland adenoma (32/79 exposed vs. 3/30 control, males, $p = 0.001$; 25/87 exposed vs. 2/62 control, females, $p = 10^{-4}$) was increased. Among female C3Hf

mice alone, the incidence of mammary adenocarcinoma (36/87 exposed vs. 6/62 control; $p = 10^{-5}$), thymic lymphosarcoma (2/87 exposed vs. 0/39 control; $p = 0.02$), and hepatoma (29/87 exposed vs. 15/62 control; $p = 0.15$) was increased.

Innes *et al.* (1969) treated male and female $B6C3F_1$ and $B6AKF_1$ mice (24/sex) with 158 mg/kg body weight urethane (on day 7) by oral gavage from day 7 to 28 of life. Thereafter, animals were exposed to a concentration of 600 ppm urethane in their diet. Control groups (90/sex/strain) received received vehicle alone, then normal diet. Surviving animals were sacrificed and autopsied between 78 and 88 weeks of age. Significant increases in the incidence of pulmonary adenomas or carcinomas and hepatomas were observed in treated animals of both sexes and strains (see Table 2, $p < 0.05$, Fisher's exact test). The incidence of angiomas was increased in male and female $B6AKF_1$ mice ($p < 0.01$). Harderian gland adenomas were increased in $B6C3F_1$ females and $B6AKF_1$ males and females ($p < 0.01$). Lymphomas were increased in $B6AKF_1$ male mice ($p < 0.01$).

Table 2. Tumor incidence data on two strains of mice exposed to urethane by oral gavage and in drinking water (Innes, 1969).

tumor type	$B6C3F_1$				$B6AKF_1$			
	male		female		male		female	
	treated	control	treated	control	treated	control	treated	control
pulmonary adenomas or carcinomas	6/20	5/79	6/23	3/87	15/22	10/90	17/19	3/82
hepatomas	8/20	8/79	12/23	0/87	14/22	5/90	5/19	1/82
angiomas					4/22	0/90	11/19	0/82
Harderian gland adenomas			5/23	4/87	11/22	0/90	7/19	0/82
lymphomas					6/22	1/90		

Tomatis *et al.* (1972) report on a study in which urethane treatment was used as a positive control in a study of DDT's long-term health effects. Male and female CF-1 mice (60/sex) were exposed continuously to drinking water containing 0.01% urethane for 6 generations. Control animals (60/sex) were given plain drinking water. Parent generation animals were sacrificed at 140 weeks and subsequent generations at 130 weeks. Survival among animals of both sexes was reduced by urethane treatment. For statistical purposes, group size was determined by the number of animals surviving at the time of the appearance of the first tumor of any type. Comparison of groups was made by combining data from all generations. Lung tumor incidence was found to be significantly increased in urethane treated male mice (261/314 exposed vs. 157/328 controls, $p = 10^{-21}$, Fisher's exact text) and female mice (181/241 exposed vs. 124/340 controls, $p = 10^{-20}$). Among treated males, lymphoma incidence was increased (100/314 exposed vs. 79/328 controls, $p = 0.02$) and among treated female mice, osteoma incidence was increased (55/241 exposed vs. 39/340 controls, $p < 0.001$).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

Although IARC (1988) has recognized urethane as a possible human carcinogen, inadequate information relating cancer incidence to specific exposure levels precludes the development of a cancer potency value from human data. An abundant body of literature relating urethane exposure to the development of tumors in animals is available. Standard carcinogenesis models applied to the data, along with some data useful for making pharmacokinetic adjustments, permit quantitative estimates of cancer potency from the animal studies. Estimated potency values are summarized below along with the rationale for development of the reference unit risk value.

Methodology

Estimates of cancer potency from the available data on the carcinogenicity of urethane can be made based on the multistage procedure initially described by Armitage and Doll (1954). For studies in which variable dosing over time has occurred, a mathematical dosage modification was made based on the estimation procedures described by Crouch (1983) and Crump and Howe (1984). Several studies have been conducted which also permit making pharmacokinetic adjustments in the estimation of carcinogenicity. Specifically, a model has been developed describing the pharmacokinetics of urethane either administered continuously or in discrete increments (Mitchell and Gauthier Associates Inc., 1975). Urethane distribution in the body and kinetic constants for rats and mice have been determined from the studies of O'Flaherty and Sichak (1983) and Nomeir *et al.* (1989). When appropriate, a proportional correction factor was applied to the experimental dose rate to estimate the effective dose rate.

Estimates of human cancer potency (q_{human}) were estimated from derived animal values (q_{animal}) based on a scaling factor proportional to the third power of the human to experimental animal body weight ratio (bw_h and bw_a). The relationship is described as follows:

$$q_{human} = q_{animal} \times (bw_h/bw_a)^{1/3}$$

Table 3 presents the estimated human cancer potency values from animal studies in which significantly increased in tumor incidences have been found, including the species studied, most sensitive site of tumor development, the multistage procedure applied to the incidence data, and whether a pharmacokinetic adjustment was applied. For details of the methodology and assumptions made in deriving the potency, see Salmon and Zeise (1991). A measure of the "expected" or "average" value of the potency (q_1) estimated from the experimental data, termed q_{bar} , is also presented. The q_{bar} is derived when there are a large number of positive data points and the probability mass function (arithmetic mean) becomes less meaningful. It is derived by numerical computation, using the same continuous, asymptotic distribution as when deriving the upper confidence limit. The q_{bar} value is derived as follows,

$$q_{bar} = \int_0^\infty f(q_1) \cdot q_1 \, dq_1$$

with $f(q_1)$ as the frequency distribution whose log-likelihood function follows a chi-square distribution.

The selection of a cancer potency value should be made on the basis of the most sensitive site, species, and study, in the absence of evidence that such a value is not representative. The hamster studies of Pietra and Shubik (1960) and Toth *et al.* (1961a, 1969) indicate the hamster may not be as sensitive as the mouse when individual tumor sites are compared. Although the limited data available do not rule out the possibility that the hamster may be the more sensitive species, data are not available to make quantitative comparisons of hamsters and mice. This, coupled with the fact that there are extensive studies on mice, suggests the mouse urethane studies are more appropriate than hamster studies in developing a cancer potency value. Only two studies in the rat are useful for deriving cancer potency values. The Tannebaum *et al.* (1962) study showing development of Zymbal's gland tumors is of limited use since there is no supporting evidence that this site of tumor development is the most sensitive. The Schmähl *et al.* (1977) study is also of questionable value because of incomplete reporting of tumor incidence in untreated animals, in spite of showing sensitive induction of mammary tumors in female rats. In light of these limits on the studies in hamster and rats, the body of data showing tumor induction in mouse has been deemed most appropriate for the development of a cancer potency value.

Calculation of the geometric mean of q_{human} and q_{bar} values from the most sensitive sites of malignancy development in the oral mouse studies resulted in values of 0.5 and 1.4 $(mg/kg\text{-}day)^{-1}$, respectively. The geometric mean of the q_{bar} values provides an estimate of the upper 95% confidence limit on the distribution of values. Calculation of the geometric mean of q_{human} and q_{bar} values from mouse studies where the lung was the most sensitive site of malignancy development resulted in values of 0.8 and 1.9 $(mg/kg\text{-}day)^{-1}$, respectively. These mean values, coupled with the q_{human} values from the sensitive multiple dose study by Schmähl *et al.* (1977), indicate the most plausible estimate of cancer potency for urethane falls in the range of 0.6 to 3.0 $(mg/kg\text{-}day)^{-1}$. Therefore, as a reasonable estimate to the cancer potency, 1.0 E+0 $(mg/kg\text{-}day)^{-1}$ has been adopted as a cancer potency value.

A unit risk value based upon air concentrations was derived by OEHHA/ATES using an assumed human breathing rate of 20 m^3/day, 70 kg human body weight, and 100% fractional absorption after inhalation exposure. The calculated unit risk value is 2.9 E-4 $(\mu g/m^3)^{-1}$.

Table 3. Cancer potency estimates from oral studies in animals (adapted from CDHS (1989)).

study/tumor	species/strain	sex	model*	q_{human} (95 %) (mg/kg-day)$^{-1}$	q_{bar} (mg/kg-day)$^{-1}$
Pietra (1960)	hamster/ Syrian G		MST		
skin melanotic tumor		M		0.19	0.11
forestomach papilloma		M		0.11	0.060
forestomach papilloma		F		0.18	0.094
Toth (1961a)	hamster/Syrian G		AD		
forestomach papilloma		M		0.13	0.091
forestomach papilloma		F		0.15	0.11
Toth (1969)	hamster/Syrian G		MST		
forestomach papilloma		M		0.10	0.077
forestomach papilloma		F		0.20	0.15
Tannenbaum (1962)	rat/Sprague-Dawley		MPK		
Zymbal gland carcinoma		M		0.12	0.061
Schmähl (1977)	rat/Sprague-Dawley		WPK		
mammary gland carcinoma		F		0.83	0.48
Toth (1961b)	mouse/Swiss		APK		
lung adenoma		M		3.8	3.0
lung adenoma		F		3.6	2.9
lymphoma		M		0.30	0.18
lymphoma		F		0.46	0.25
Tannenbaum (1962)	mouse/		APK		
lung alveolar cell tumor	DBA	M		0.9	0.61
mammary gland carcinoma	DBA	F		1.2	0.90
lung adenoma	DBA	M		0.4	0.29
lung adenoma	C3H	F		0.4	0.28
Klein (1962)	mouse/$B6AF_1$		APK		
lung adenoma		M		0.85	0.54
lung adenoma		F		0.76	0.48
leukemia		M		0.090	0.071
leukemia		F		0.10	0.066
Della Porta (1963a)	mouse/CTM		APK		
lung adenoma		M		0.62	0.17
lung adenoma		F		0.60	0.12
Della Porta (1963b)	mouse/CTM		APK		
malignant lymphoma		M		0.55	0.17
mammary gland		F		0.50	0.12
Della Porta (1967)	mouse/		APK		
Harderian gland tumor	$BC3F_1$	M		0.88	0.66
Harderian gland tumor	$BC3F_1$	F		0.32	0.25
Harderian gland tumor	C3Hf	M		0.22	0.15
Harderian gland tumor	C57BL	M		0.32	0.25
Harderian gland tumor	C57BL	F		0.23	0.19
mammary gland carcinoma	C3Hf	F		0.23	0.16
lung adenoma	C3H	M		0.18	0.13
lung adenoma	SWR	M		0.94	0.67
lung adenoma	SWR	F		1.0	0.76

Table 3. Cancer potency estimates from oral studies in animals (continued) (adapted from CDHS (1989)).

study/tumor	species/strain	sex	model*	q_{human} (95 %) (mg/kg-day)$^{-1}$	q_{bar} (mg/kg-day)$^{-1}$
Innes (1969)	mouse/		MPK		
liver hepatoma	$B6C3F_1$	M		0.40	0.23
liver hepatoma		F		0.61	0.27
lung adenoma	$B6AKF_1$	M		0.78	0.51
lung adenoma		F		1.5	0.99
Tomatis (1972)	mouse/CF-1		MPK		
lung adenoma		M		0.90	0.75
lung adenoma		F		0.67	0.55
Schmähl (1977)	mouse/NMRI				
lung adenoma		M	WPK	3.0	1.7
lung carcinoma		M	MPK	0.85	0.55
lung adenoma		F	WPK	1.9	-
lung carcinoma		F	MPK	0.56	0.12
			W1PK	3.0	1.7

*MST- multistage; APK - Armitage-Doll model; MPK - multistage with pharmacokinetic adjustment; WPK - Weibull time-dependent with pharmacokinetic adjustment; W1PK - Weibull linear in dose time-dependent model with pharmacokinetic adjustment.

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TECHNICAL SUPPORT DOCUMENT FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS
APPENDIX A

TOXICITY EQUIVALENCY FACTORS FOR POLYCHLORINATED DIBENZO-p-DIOXINS AND DIBENZOFURANS

Introduction

The Office of Environmental Health Hazard Assessment (OEHHA) cancer potency value for 2,3,7,8- tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) was determined as part of the Toxic Air Contaminant Program and approved by the Scientific Review Panel and the Air Resources Board in 1986 (CDHS, 1986). To evaluate the cancer risk due to exposure to samples containing mixtures of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), California Toxicity Equivalency Factors (CTEFs) were developed and adopted (CDHS, 1986). These factors were based on rodent cancer bioassay data on 2,3,7,8-TCDD and a mixture of hexaCDDs and assumptions about the relative potency of other PCDDs and PCDFs that had not undergone cancer bioassays. Since 1986, another TEF scheme was developed during an international symposium (NATO/CCMS, 1988a,b), and it has been adopted by US EPA (US EPA, 1989) and the Department of Toxic Substances Control (DTSC) (DTSC, 1992). The international scheme, referred to as ITEFs, is based on experimental cancer and noncancer data for many 2,3,7,8-PCDDs and 2,3,7,8-PCDFs and on the assumption that the mechanism of all PCDD/PCDF-related biologic effects are based on initial binding to a specific protein, the Ah receptor. Because the ITEF scheme incorporates more experimental data from cancer and noncancer studies for more PCDDs/PCDFs than does the CTEF scheme, the replacement of the CTEFs by the ITEFs is appropriate for use in risk assessment. This approach also increases uniformity among Cal/EPA guidelines.

Background

PCDDs and PCDFs belong to a series of tricyclic aromatic hydrocarbons, in which the middle ring contains one (PCDF) or two (PCDD) ring oxygens. On each of the other two rings, four sites are available for substitution (eight sites total). There are 75 possible chlorinated PCDD congeners and 135 possible chlorinated PCDF congeners. (Rabbe *et al*., 1979). Congeners of PCDD and PCDF which contain chlorine in the same position are referred to as homologues. For example, 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF) is a homologue of 2,3,7,8-TCDD.

The original public health concern about the PCDDs/PCDFs was the result of high toxicity of 2,3,7,8-TCDD. In particular, the concern about the carcinogenicity of 2,3,7,8-TCDD led to the development of a cancer potency by the California Department of Health Services (CDHS), for this congener (CDHS, 1986). Additional studies showed, however, environmental samples containing 2,3,7,8-TCDD contained other congeners which were also toxic (NATO/CCMS, 1988a,b; US EPA, 1989). The toxic and biologic responses to the PCDDs/ PCDFs are varied and include carcinogenicity, immunotoxicity, reproductive toxicity, thymic atrophy, decreased body

weight gain, increased cytochrome P450-dependent activity, cell proliferation and liver damage. The current working hypothesis for the mechanism of the origin of the disease state associated with exposure to PCDD/PCDF is the required binding of the PCDD or PCDF congener to a specific receptor protein (the Ah receptor) followed by the expression of various endpoints (CDHS, 1986; NATO/CCMS, 1988a,b; US EPA, 1989). While continued research on the toxicities associated with each of the 210 congeners, including dose-response assessments, would lead to important toxicologic information, the cost and time would lead to delays in addressing the public health concerns associated with exposures to these mixtures. Hence, a means for expressing exposure related health risk of PCDD/PCDF mixtures needs to be developed in the absence of a complete data base.

Toxicity Equivalency Factors

Toxicity equivalency factors (TEFs) are numerical factors that express the toxicity of an individual PCDD or PCDF relative to the toxicity of TCDD, the highly toxic and best studied among the 210 congeners. TEFs are used in risk assessment to calculate the potential for health effects from a mixture of PCDDs and PCDFs. The total "2,3,7,8-TCDD" equivalents - referred to as TCDD equivalents - in a sample (e.g. air, soil, food) is estimated by multiplying the concentration of each congener in the sample by its appropriate TEF and summing all TCDD equivalents. The total TCDD equivalents (TEQ) is then used in conjunction with a cancer potency or reference exposure level to estimate cancer risk or noncancer hazard index, respectively.

Although analytical methods are currently available to reliably quantify the amount of the various congeners in a sample, not all congeners of PCDD and PCDF possess equal biologic activity. Such differences may be a reflection of different toxicokinetic properties. For example, congeners that lack the 2,3,7,8-configuration of chlorine groups, do not appear to bioaccumulate, as do the 2,3,7,8-congeners. Within the group of 2,3,7,8-congeners, biologic activity is variable, and this property is probably due to differences in dose-response relationships. A basic premise of the TEF methodology is the presence of a common biologic end-point or in the case of multiple end-points, a common mechanism of action. A second assumption is additivity of effects. These assumptions are inherent in all TEF-schemes, and the accuracy of all TEF-schemes will be affected by situations where such assumptions are not applicable.

California TEFs (CTEFs)

TEF schemes for PCDDs and PCDFs have been developed or adopted by many governmental institutions throughout the industrialized world (NATO/CCMS, 1988). Among the schemes was one developed by the CDHS, based on carcinogenicity data (CDHS, 1986) and adopted for use in the California Toxic Air Contaminant Program and in the California Air Toxics "Hot Spots" Program (CAPCOA, 1992). This scheme is referred to as the CTEF. Due to lack of data on the 2,3,7,8-penta- and hepta- congeners of PCDD, the carcinogenic potencies of the penta-congeners were considered equal to that of TCDD (1.0) and that of the hepta-congeners equal to that of hexaCDD (0.03), relative to 2,3,7,8-TCDD. The 2,3,7,8-PCDFs were considered equal in cancer

potency to their PCDD homologues. The potencies of the octa-congeners of PCDD and PCDF were assumed to be zero, based on the evidence available at the time, that the octa-chlorinated compounds did not produce characteristic toxicity following short-term exposure.

International TEFs (ITEFs)

The ITEF scheme was the result of an international conference, convened for the purpose of reaching a consensus for a uniform TEF scheme based on available whole animal non-cancer and cancer data, short term and in vitro data (NATO/CCMS, 1988a,b). To incorporate the results from many studies, the ITEF scheme used the assumption that all effects are initiated by the interaction of a PCDD or PCDF congener with a specific receptor protein, the Ah receptor. The rationale for this assumption comes from analyses in which biologic endpoints (i.e. body weight loss, thymic atrophy, *in vivo* enzyme induction) were found to be highly correlated with known Ah receptor associated effects (e.g. increased cytochrome P450-dependent enzyme activity in vivo and binding affinities). The ITEF scheme focuses on those congeners that are preferentially absorbed and accumulated in mammalian tissue over a long period of time and exhibit a similar spectrum of toxicities as 2,3,7,8 TCDD, i.e. PCDDs/PCDFs that in which positions 2-,3-,7-, and 8- are substituted by chlorine. Unlike the CTEF scheme, the octa-congeners are included in the ITEF scheme, because of a study in which rats exposed to OCDD, exhibited 2,3,7,8,-TCDD-like non-cancer toxicities after a 13-week exposure (Couture *et al*., 1988). This study was not available at the time the CTEFs were developed.

The choice of an ITEF for each 2,3,7,8-PCDD/PCDF congener was based on a synthesis of data from cancer studies, long-term toxicity studies, subchronic effects including thymic atrophy and body weight loss, acute toxicity studies and receptor binding and enzyme induction. Greater weight was given to results from long-term studies, but information of short-term studies was also considered. In the absence of long-term studies, data from short-term whole animal and/or *in vitro* studies were used. A specific formula was not applied to the various data, but rather the final individual ITEF was based on the professional judgment of the aggregate data available for the individual congener.

The basis for the ITEF scheme has been extensively reviewed by US EPA (US EPA, 1989) and the California Department of Toxic Substances Control (DTSC, 1992). These agencies concluded that the ITEF scheme was superior to the CTEF scheme because of the larger, more inclusive data base. The US EPA and the DTSC each adopted the ITEF scheme for use in risk assessment activities as an interim procedure which is expected to be updated as more information becomes available.

Comparison of CTEF and ITEF Schemes

Based on the assumption that the PCDD/PCDF induced biologic effects result from an interaction between a congener and the Ah receptor, the carcinogenicity driven CTEFs may be compared to the ITEFs based on non-cancer and cancer end points. The CTEF and ITEF schemes are outlined in Tables 1 and 2. Table 1 describes, qualitatively, the features of the two methodologies. Included in Table 2 are the ranges of values associated with the many end-points

for each congener in the ITEF scheme. TEFs for two major noncancer toxicity endpoints, teratogenicity and immunotoxicity, are presented in Table 3. An important feature of this table is the relatively high toxicity of the 2,3,4,7,8-pentaCDF, based on teratogenicity (TEF = 0.1) and immunotoxicity (TEF = 0.8).

A comparison of the CTEF and ITEF schemes (Table 2) shows the CDHS to ITEF ratios are variable. For example, the CTEF/ITEF for 1,2,3,7,8-pentaCDF is 20, whereas the same ratio for the 2,3,7,8-hexaCDD and hexaCDF congeners is 0.3. In each case, the CTEF was based on an assumed equivalence of carcinogenicity, whereas the ITEF was based on experimental data from cancer and noncancer studies. For the octa-congeners of PCDD and PCDF, the ITEF value is 0.001 whereas no TEF was developed for the CTEF scheme. Although the ITEF = 0.001 is small, its use in the ITEF scheme recognizes a heretofore unknown toxicity property of the octa congeners.

The ultimate use of a TEF scheme is to estimate the TEQ level in a sample. Therefore, a comparison of TEQs in various environmental samples, as estimated by the CTEF and ITEF schemes, is of interest. In Table 4, the TEQs, present in seven contaminated samples, are compared by the CTEF and ITEF methodologies. The results suggest that where differences occur, they are less than 10-fold and appear to be due largely to differences in the TEFs for the PCDFs, in particular the tetra- and penta-congeners. When studying the results in Table 4, the reader should keep in mind the ITEF scheme was developed from a much larger data base than the CTEFs. The CTEF scheme also assumes the 2,3,7,8-penta congeners are equivalent to 2,3,7,8-TCDD, the 2,3,7,8-hepta-congeners are equivalent to the 2,3,7,8-hexa-congeners, and the PCDFs are equivalent to their PCDD homologues. In the ITEF schemes, such assumptions are not made but are based on available information.

Public Health Impact

Currently, two schemes, the CTEFs and the ITEFs, are in use in the State of California for risk assessment of PCDD/PCDF contaminated samples. The CTEF scheme was incorporated into the Hot Spots Risk Assessment Guidelines (CAPCOA, 1993), while the ITEF scheme was adopted by the DTSC (DTSC, 1992). The ITEF scheme incorporates more data on congener specificity and multiple end-points. The use of multiple endpoints is important for PCDD- and PCDF-induced toxicities, because the evidence is clear that exposure to this class of compounds leads to many responses that may be related by a similar mechanism of action, i.e. initial binding to the Ah receptor. Hence, the ITEF scheme provides a more complete picture of the relative toxicity of the various congeners than does the CTEF scheme. Since the TEFs are applied to carcinogenic and noncancer evaluations in risk assessment, the ITEF scheme is more appropriate than the CTEF scheme.

The results of the two schemes are relatively consistent. Although the CTEF scheme sometimes results in TEQs up to 4-times greater than the ITEF scheme, the differences in the TEQs are generally within the uncertainties of the estimated carcinogenicity or noncancer toxicity of

2,3,7,8-TCDD. Consequently, the impact using the ITEFs in place of the CTEFs to estimate PCDD/PCDF exposure related risk, will be minimal.

The user of any TEF scheme should not consider such a methodology as definitively precise analysis for PCDD/PCDF related adverse health effects. A TEF scheme is an instrument that is useful for estimating health risks but it contains uncertainties shared by all risk assessment methodologies. Furthermore, as research results become available, changes in our understanding of the basis of PCDD/PCDF related health effects may result in changes to the TEF scheme (see e.g. US EPA, 1989; Maronpot *et al*., 1993; DeVito and Birnbaum, 1995).

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Table 1

FEATURES OF THE CTEF AND ITEF METHODOLOGIES

	CTEF	ITEF
Congeners of Concern	2,3,7,8-	2,3,7,8-
Available Data	Tetra-, Hexa-	Tetra-, Penta-, Hexa-, Hepta- Octa-
Biologic Endpoint	Carcinogenicity	Acute,chronic toxicity, carcinogenicity
Application	Assess mixtures for cancer & noncancer risk	Assess mixtures for cancer & noncancer risk

Table 2

TOXICITY EQUIVALENCY FACTORS [a]

DIBENZO-p-DIOXINS & DIBENZOFURANS

(relative to 2,3,7,8-TCDD)

COMPOUND	CONGENERS	DHS - TEF[b]	I-TEF[c]	Obs. TEF Toxicity[d]	Obs. TEF AHH Ind. cell[d]	Obs. TEF AHH Ind. animal[d]
Dioxins						
Mono-, Di-, Tri-CDDs		0	0			
TCDD	2,3,7,8- others	(1.0) 0	(1.0)	(1.0)	(1.0)	(1.0)
PeCDD	2,3,7,8- others	1.0 0	0.5 0	0.05 - 0.6	0.1	0.006 - 0.01
HxCDD	2,3,7,8- others	0.03 0	0.1 0	0.02 - 0.2	0.1	0.008 - 0.05
HpCDD	2,3,7,8- others	0.03 0	0.01 0			0.003
OCDD		0	0.001		0.0002	0.0006
Dibenzfurans						
Mono-, Di-, Tri- CDFs		0	0			
TCDF	2,3,7,8- others	1.0 0	0.1 0	0.02 - 0.2	0.006	0.02 - 0.09
PeCDF	1,2,3,7,8- 2,3,4,7,8- others	1.0 1.0 0	0.05 0.5 0	0.02 - 1.0 0.05 - 0.8	0.003 - 0.05 0.1 - 0.2	0.03 - 0.06 0.3 - 1.4
HxCDF	2,3,7,8- otheres	0.03 0	0.1 0	0.01 - 0.2	0.01 - 0.02	0.04 - 0.5
HpCDF	2,3,7,8- others	0.03 0	0.01 0			
OCDF		0	0.001			

a. Endpoints include inhibition of body weight gain, thymic atrophy, hepatic arylhydrocarbon hydroxylase activity, ethoxyresorufin (sic) deethylase activity, lethality, teratogenicity, immunotoxicity, carcinogenicity.
b. CDHS (1986). Endpoint is carcinogenicity.
c. NATO/CCMS (1988) - adopted by USEPA (1989) and CTSCP (1991-draft)
d. NATO/CCMS (1988) - taken from Table 8, p.35.

Table 3

TEFs for PCDF CONGENERS BASED ON NON-CANCER

***IN VIVO* ED_{50} VALUES**

(relative to 2,3,7,8-TCDD)

	Endpoints	
Congeners	Teratog enicity	Immuno toxicity
2,3,7,8-TCDD	(1.0)	(1.0)
2,3,7,8-tetraCDF	0.05	0.2
1,3,6,8-tetraCDF		0.0007
2,3,4,7,8-pentaCDF	0.1	0.8
1,2,3,7,8-pentaCDF	0.03	
2,3,7,8,-tetraCDF	0.05	0.2
1,2,3,7,9-pentaCDF		0.003
1,2,3,4,7,8-hexaCDF	0.01	

a. Calculated from data presented in Table 5 (NATO/CCMS, 1988).

Table 4

A COMPARISON OF CTEF- AND ITEF- BASED TCDD EQUIVALENTS IN PCDD/PCDF MIXTURES FOUND IN SELECTED SAMPLES,

	TCDD Equivalents (CTEF / ITEF)[a]		
Source of Contamination	PCDDs	PCDFs	PCDDs + PCDFs
Metal Recovery Fly Ash[b]	1.1	4.0	3.9
PCB Soot Fire[c]	1.6	1.5 - 4.2[d]	1.5 - 4.1[d]
MSW - ESP Dust[c]	0.85	1.8 - 3.5[d]	1.5 - 2.4[d]
Contaminated Soil[e]	1.0	2.2	1.7
Ground Beef[f]	1.09	1.4	1.4
Soft Cream Cheese[f]	1.2	1.8	1.4
Haddock[f]	1.0	4.5	2.6

a. The TCDD equivalents are calculated by multiplying the concentration of ezch congener by its CTEF or ITEF and summing values for PCDDs only, PCDFs only, and PCDDs + PCDFs.

b. from Harnly *et al*., (1992).

c. from USEPA (1989).

d. The chemical analyses of the penta-PCDFs did not distinguish between 1,2,3,7,8- and 2,3,4,7,8-PCDF, to which different ITEFs have been assigned from DTSC (1991).

e. from DTSC (1991).

f. from Schecter *et al*., (1994).

TECHNICAL SUPPORT DOCUMENT FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS

APPENDIX B

TOXIC AIR CONTAMINANT DOCUMENTS

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TECHNICAL SUPPORT DOCUMENT FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS

APPENDIX C

International Agency for Research on Cancer (IARC) and U.S. Environmental Protection Agency (US EPA) Carcinogen Classifications

International Agency for Research on Cancer (IARC) Carcinogen Classifications (IARC, 1987)

Group 1: The agent is carcinogenic to humans.

This category is used only when there is sufficient evidence of carcinogenicity in humans.

Group 2

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as agents for which, at the other extreme, there are no human data but for which there is experimental evidence of carcinogenicity. Agents are assigned to either 2A (probably carcinogenic) or 2B (possibly carcinogenic) on the basis of epidemiological, experimental and other relevant data.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B: The agent is possibly carcinogenic to humans.

This category is generally used for agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

Agents are placed in this category when they do not fall into any other group.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is evidence suggesting lack of carcinogenicity in humans together with evidence suggesting lack of carcinogenicity in experimental animals. In some circumstances, agents for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

U.S. Environmental Protection Agency (US EPA) Carcinogen Classifications (US EPA, 1986)

Group A: Human Carcinogen

This group is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer.

Group B: Probable Human Carcinogen

This group includes agents for which evidence of human carcinogenicity based on epidemiologic studies is "limited," and also includes agents for which the weight of evidence of carcinogenicity based on animal studies is "sufficient." The group is divided into two subgroups. Usually, Group B1 is reserved for agents showing limited evidence of carcinogenicity from epidemiologic studies. It is reasonable, for practical purposes, to regard an agent with "sufficient" evidence of carcinogenicity in animals as if it presented a carcinogenic risk to humans. Therefore, agents for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies would usually be categorized under group B2.

Group C: Possible Human Carcinogen

This group is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence, e.g., (a) a malignant tumor response in a single well-conducted experiment that does not meet conditions for sufficient evidence, (b) tumor responses of marginal statistical significance in studies having inadequate design or reporting, (c) benign (not malignant) tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) responses of marginal statistical significance in a tissue known to have a high or variable background tumor rate.

Group D: Not Classifiable as to Human Carcinogenicity

This group is generally used for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

Group E: Evidence of Noncarcinogenicity for Humans

This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

The designation of an agent as being Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

REFERENCES

International Agency for Research on Cancer (IARC) 1987. Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volumes 1 to 42 In: IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Supplement 7. IARC, Lyon, France, pp. 31-32.

U.S. Environmental Protection Agency (US EPA) 1986. Guidelines for Carcinogen Risk Assessment, Federal Register 45 FR 79318.

TECHNICAL SUPPORT DOCUMENT FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS

APPENDIX D

Asbestos Quantity Conversion Factors

The unit risk factor for asbestos is listed in this document in units of 100 PCM fibers/m^3 [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$] and in units of µg/m^3 [6.3 E-2 (µg/m^3)$^{-1}$]. The value listed in the Toxic Air Contaminant (TAC) document for asbestos (CDHS, 1986) was 1.9 E-4 (100 PCM fibers/m^3)$^{-1}$. However, emitted asbestos quantities reported to the various Air Quality Districts under the requirements of the Air Toxics "Hot Spots" Information and Assessment Act of 1987 (Health and Safety Code (HSC) Section 44300 et seq. and as amended by Statutes 1992, Chapter 1162) are in units of pounds/year and maximum pounds/hour. Therefore, the original TAC unit risk value has been converted using a factor of 0.003 µg asbestos = 100 asbestos fibers which has been derived from information published by US EPA (1985). The number of asbestos fibers associated with a given mass of asbestos can vary appreciably. Also, US EPA (1985) has stated that this conversion factor is the geometric mean of measured relationships between optical fiber counts and mass airborne chrysotile in several published studies, the range of the conversion factor between the different studies is large (0.0005 - 0.015 µg asbestos/100 asbestos fibers), and carries with it an appreciable uncertainty. Use of the unit risk factor listed in the asbestos TAC document [1.9 E-4 (100 PCM fibers/m^3)$^{-1}$], wherever possible, will result in a more precise risk estimation. Additionally, the unit risk factor expressed in units of (µg/m^3)$^{-1}$ may change if a conversion factor with less uncertainty is developed, or may be eliminated if asbestos quantity reporting requirements render use of a unit risk factor expressed in units of (µg/m^3)$^{-1}$ unnecessary.

REFERENCES

California Department of Health Services (CDHS) 1986. Report to the Air Resources Board on Asbestos. Part B. Health Effects of Asbestos. Epidemiological Studies Section, Berkeley, CA.

U.S. Environmental Protection Agency (US EPA) 1986. Airborne Asbestos Health Assessment Update. EPA/600/8-84/003F, Office of Health and Environmental Assessment, Washington, DC.

TECHNICAL SUPPORT DOCUMENT (TSD) FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS
APPENDIX E

US EPA IRIS INHALATION UNIT RISK AND ORAL CANCER POTENCY FACTORS FOR CHEMICALS LISTED IN THE TSD

Chemical	IRIS inhalation unit risk $(\mu g/m^3)^{-1}$	IRIS oral cancer potency factor $(mg/kg\text{-}day)^{-1}$
Acetaldehyde	2.2E-6	NA
Acrylamide	1.3 E-3	4.5 E+0
Acrylonitrile	6.8 E-5	5.4 E-1
Aniline	1.6 E-6	5.7 E-3
Arsenic	4.3 E-3	1.5 E+0
Asbestos	2.3 E-1 (fibers/ml)	NA
Benzene	8.3 E-6	2.9 E-2
Benzidine	6.7 E-2	2.3 E+2
Benzo[a]pyrene	NA	7.3 E+0
Benzyl chloride	NA	1.7 E-1
Beryllium	2.4 E-3	4.3 E+0
Bis(2-chloroethyl) ether	3.3 E-4	1.1 E+0
Bis(chloromethyl)ether	6.2 E-2	2.2 E+2
1,3-Butadiene	2.8 E-4	NA
Cadmium (and compounds)	1.8 E-3	NA
Carbon tetrachloride	1.5 E-5	1.3 E-1
Chloroform	2.3 E-5	6.1 E-3
Chromium (hexavalent)	1.2 E-2	NA
3,3'-Dichlorobenzidine	NA	4.5 E-1
1,4-Dioxane	NA	1.1 E-2
Epichlorohydrin	1.2 E-6	9.9 E-3
Ethylene dibromide	2.2 E-4	8.5 E+1
Ethylene dichloride	2.6 E-5	9.1 E+2
Formaldehyde	1.3 E-5	NA
Hexachlorobenzene	4.6 E-4	1.6 E+0
Hexachlorocyclohexanes (technical grade)	5.1 E-4	1.8 E+0
Hydrazine	4.9 E-3	3.0 E+0
Methylene chloride	4.7 E-7	7.5 E-3
Nickel compounds	2.4 E-4	NA
N-Nitroso-n-dibutylamine	1.6 E-3	5.4 E+0
N-Nitroso-N-methylethylamine	NA	2.2 E+1
N-Nitrosodi-n-propylamine	NA	7.0 E+0
N-Nitrosodiethylamine	4.3 E-2	1.5 E+2
N-Nitrosodimethylamine	1.4 E-2	5.1 E+1
N-Nitrosodiphenylamine	NA	4.9 E+3
N-Nitrosopyrrolidine	6.1 E-4	2.1 E+0
Pentachlorophenol	NA	1.2 E-1
Polychlorinated biphenyls (highest risk and persistence)	NA	2.0 E+0
(low risk and persistence)	1.0 E-4	4.0 E-1
(lowest risk and persistence)	NA	7.0 E-2

US EPA IRIS INHALATION UNIT RISK AND ORAL CANCER POTENCY FACTORS FOR CHEMICALS LISTED IN THE TSD (CONTINUED)

Chemical	IRIS inhalation unit risk $(\mu g/m^3)^{-1}$	IRIS oral cancer potency factor $(mg/kg\text{-}day)^{-1}$
Propylene oxide	3.7 E-6	2.4 E-1
1,1,2,2-Tetrachloroethane	5.8 E-5	2.0 E-1
1,1,2-Trichloroethane (vinyl trichloride)	1.6 E-5	5.7 E-2
2,4,6-Trichlorophenol	3.1 E-6	1.1 E-2

TECHNICAL SUPPORT DOCUMENT FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS
APPENDIX F

HOT SPOTS CANCER UNIT RISK VALUES WHICH DIFFER FROM CORRESPONDING US EPA IRIS CANCER UNIT RISK VALUES

Chemical		Source	Hot Spots Unit Risk $(\mu g/m^3)^{-1}$	IRIS Unit Risk $(\mu g/m^3)^{-1}$	HS/IRIS Ratio
Acetaldehyde		TAC	2.7 E-6	2.2 E-6	1.2
Acrylonitrile		RCHAS-S	2.9 E-4	6.8 E-5	4.3
Arsenic (inorganic)	(inhalation)	TAC	3.3 E-3	4.3 E-3	0.8
Asbestos		TAC	6.3 E-2	7.7 E-3	8.2
			1.9 E-4#	2.3 E-5#	
Benzene		TAC	2.9 E-5	8.3 E-6	3.5
Benzidine		RCHAS-S	1.4 E-1	6.7 E-2	2.1
Bis(2-chloroethyl) ether		RCHAS-S	7.1 E-4	3.3 E-4	2.2
Bis(chloromethyl)ether		RCHAS-S	1.3 E-2	6.2 E-2	0.2
1,3-Butadiene		TAC	1.7 E-4	2.8 E-4	0.6
Cadmium (and compounds)		TAC	4.2 E-3	1.8 E-3	2.3
Carbon tetrachloride		TAC	4.2 E-5	1.5 E-5	2.8
Chloroform		TAC	5.3 E-6	2.3 E-5	0.2
Chromium (hexavalent)		TAC	1.5 E-1	1.2 E-2	12.5
3,3'-Dichlorobenzidine		RCHAS-S	3.4 E-4	1.3 E-4	2.6
1,4-Dioxane		RCHAS-S	7.7 E-6	3.1 E-6	2.5
Epichlorohydrin		RCHAS-S	2.3 E-5	1.2 E-6	19.2
Ethylene dibromide		TAC	7.1 E-5	2.2 E-4	0.3
Ethylene dichloride		TAC	2.2 E-5	2.6 E-5	0.8
Formaldehyde		TAC	6.0 E-6	1.3 E-5	0.5
Hexachlorobenzene		RCHAS-S	5.1 E-4	4.6 E-4	1.1
Hexachlorocyclohexanes (technical grade)		RCHAS-S	1.1 E-3	5.1 E-4	2.2
Methylene chloride		TAC	1.0 E-6	4.7 E-7	2.1
Nickel compounds		TAC	2.6 E-4	2.4 E-4	1.1
N-Nitroso-n-dibutylamine		RCHAS-S	1.1 E-1	1.6 E-3	68.8
N-Nitrosodiethylamine		RCHAS-S	1.0 E-2	4.3 E-2	0.2
N-Nitrosodimethylamine		RCHAS-S	4.6 E-3	1.4 E-2	0.3
N-Nitrosodiphenylamine		RCHAS-S	2.6 E-6	1.4 E-6	1.9
Pentachlorophenol		RCHAS-S	5.1 E-6	3.4 E-5	0.2
2,4,6-Trichlorophenol		RCHAS-S	2.0 E-5	3.1 E-6	6.5

Footnotes #: $[100 \text{ PCM fibers}/m^3]^{-1}$

Source Key

TAC Toxic Air Contaminant document, Office of Environmental Health Hazard Assessment (OEHHA)
RCHAS-S Standard Proposition 65 document, OEHHA
RCHAS-E Expedited Proposition 65 document, OEHHA

Note: The TSD Unit Risk and Cancer Potency Factors Table includes 13 US EPA IRIS cancer unit risk values.

TECHNICAL SUPPORT DOCUMENT FOR DESCRIBING AVAILABLE CANCER POTENCY FACTORS
APPENDIX G

PROCEDURES FOR REVISITING OR DELISTING CANCER POTENCY FACTORS BY THE PROGRAM OF ORIGIN

Toxic Air Contaminant documents

Submissions of new scientific information pertaining to Toxic Air Contaminant (TAC) risk assessments should be made to the Air Resources Board (ARB) at the following address:

Air Resources Board
Executive Officer
P.O. Box 2815
Sacramento, CA 95812

The submission process, as approved by the ARB Scientific Review Panel (SRP) on December 12, 1989, is described below.

Scientific Review Panel Process For Evaluation And Response To Submittals Of New Scientific Information As Evidence For Review Of Toxic Air Contaminant (TAC) Risk Assessments

I. STATEMENT OF NEED

It is anticipated that submittal of information pertaining to a toxic air contaminant (TAC) risk assessment could result in a request from the Chairperson of the ARB, for the SRP to provide a formal evaluation and recommendation. A procedure is needed for the SRP to process the submittal and evaluation of such information. The following elements have been identified by the SRP for inclusion in such a procedure:

- Screening submittals of new scientific evidence
- Performing SRP/DHS analysis of newly submitted scientific evidence to determine the need to review an original (TAC) risk assessment

II. PROCESS

A. Screening Submittals Of New Scientific Evidence

To prevent a misuse of valuable SRP time and resources, the submittal of new scientific evidence should first be screened by the staff of the ARB and DHS to determine whether the material contains the necessary elements to warrant the SRP's attention. The screening criteria shall include the following:

1. The submittal shall describe specifically what in the original risk assessment will be qualitatively and/or quantitatively changed. At a minimum, the following three points shall be addressed:

    a. Does the new evidence, if accepted, change the determination of the health effects of the compound? If so, how?

    b. Does the new evidence, if accepted, change the threshold determination adopted by the Board and contained in the regulation? If so, how?

    c. Does the new evidence, if accepted, change the potency which was the basis of the original risk assessment? If so, how?

4. The Panel would review the leadperson's evaluation along with supporting material and recommend to the ARB Chairperson, through the SRP Chairperson, whether on the basis of the submitted material a review of the original risk assessment is warranted.

Proposition 65 listings

No formal process has been implemented at this time for revisiting Proposition 65 documents or for delisting listed chemicals. A draft version of the document "Mechanisms For Removing Chemicals From The Proposition 65 List Based On Findings Made By "The State's Qualified Experts" has been released for public comment; copies of the draft document can be requested by contacting the address listed below. This document can also be obtained from the Office of Environmental Health Hazard Assessment (OEHHA) Web site at http://www.calepa.cahwnet.gov/oehha. New scientific information relevant to Proposition 65 listed chemicals should be sent to the Proposition 65 Implementation Program at the following address:

Office of Environmental Health Hazard Assessment
Proposition 65 Implementation Program
PO Box 942732
Sacramento CA 94234-7320
(916) 445-6900

US EPA IRIS listings

The information contained in Section II (Carcinogenicity Assessment for Lifetime Exposure) of the IRIS chemical listings files represents a consensus opinion of US EPA health scientists representing the Program Offices and the Office of Research and Development. From 1985 to 1995, the corresponding consensus body was referred to as the Carcinogen Risk Assessment Verification Endeavor Work Group, or CRAVE. The consensus process involves interpreting the scientific literature applicable to health effects of a chemical, and using established methodologies to develop values for carcinogenic slope factor and unit risk. The products of this work, summarized in IRIS and elaborated in chemical-specific support documents, have been subject to US EPA's peer review policy since its issuance in 1994. It is US EPA policy that as

new scientific information becomes available, US EPA will review it, as appropriate, and revise IRIS files accordingly. Interested parties should contact the National Center for Environmental Assessment, Cincinnati, OH (Telephone 513-569-7254; FAX 513-569-7159; email RIH.IRIS@epamail.epa.gov).

Air Toxicology and Epidemiology Section cancer potency values
Pesticide and Environmental Toxicology Section cancer potency values

No formal process has been developed for revisiting cancer potency values developed by the Air Toxicology and Epidemiology Section (ATES) or the Pesticide and Environmental Toxicology Section (PETS) of OEHHA. New scientific information relevant to risk assessments performed by either of those sections should be sent to the following address:

Office of Environmental Health Hazard Assessment
Air Toxicology and Epidemiology Section
(or) Pesticide and Environmental Toxicology Section
2151 Berkeley Way, Annex 11
Berkeley, CA 94704