UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION III
1650 Arch Street
Philadelphia, Pennsylvania 19103

SUBJECT: Background Information about 1,4-Dioxane: Bally TCE Site

FROM: Jennifer Hubbard, Toxicologist
Technical Support Section (3HS41)

TO: Mitch Cron, RPM
Western PA Remedial Section (3HS22)

DATE: 4/1/2003

Attached, please find miscellaneous background documentation about 1,4-dioxane, the chemical recently discovered at the Bally TCE site, for your files.

1. Demonstration of the calculation that the total child and adult cancer risk for a 30-year exposure to 6 ug/L (0.006 mg/L) is 1E-6 (6.5E-7 + 3.6E-7 = 1E-6). Exposure and toxicity assumptions were the same as indicated in my memo of 2/19/2003.

2. "Health Evaluation of 1,4-Dioxane," a thorough toxicological review prepared by ATSDR in 1996.

3. "Solvent Stabilizers: White Paper," prepared in 2001.

4. Abstracts of articles yielded as the result of a Toxline literature search (with a special focus on post-1996 articles).

I will also be retrieving some of the articles associated with these abstracts. Please let me know if you would like copies.

Attachments

Cc: Eric Johnson (3HS41; w/o attach.)
Karen Johnson (3WP32)
Lori Kier (3RC20)

DRINKING WATER EXPOSURE
SITE Baily
RECEPTOR Adult resident

ORAL EXPOSURE FROM GROUNDWATER

EQUATIONS

$$D = C \times IR \times ED \times EF / BW \times AT$$

D = ORAL DOSE (MG/KG/DAY)
C = CONCENTRATION IN WATER (MG/L)
IR = INGESTION RATE (L/DAY)
ED = EXPOSURE DURATION (YRS)
EF = EXPOSURE FREQUENCY (DAYS/YR)
BW = BODY WEIGHT (KG)
AT = AVERAGING TIME (DAYS)

$$HQ = D / RFD$$

HQ = HAZARD QUOTIENT
D = NONCARCINOGENIC DOSE (MG/KG/DAY)
RFD = REFERENCE DOSE (MG/KG/DAY)

$$CR = 1 - EXP(-CSF \times D)$$

CR = CANCER RISK
CSF = CARCINOGENIC SLOPE FACTOR (1/MG/KG/DAY)
D = CARCINOGENIC (TIME-WEIGHTED) DOSE (MG/KG/DAY)

INPUTS		ADULT RESIDENT	CHILD RESIDENT	ADULT WORKER
IR	2	2	1	1
EF	350	350	350	250
ED	24	24	6	24
BW	70	70	15	70
AT-NC	8760	8760	2190	8760
AT-C	25550	25550	25550	25550

CHEMICAL	C (MG/L)	RFD	CSF	HQ	CR
1 4-dioxane	0 006		1 1E-002	N/A	6 2E-007
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0.0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0.0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0.0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
----------				N/A	0 0E+000
TOTALS/ORAL DRINK WATER				0.0E+000	6 2E-007

DERMAL EXPOSURE FROM GROUNDWATER

EQUATIONS

INORGANICS DA = KP x CV x t x CF

DA = DOSE ABS PER UNIT AREA (MG/CM2)
KP = PERMEABILITY COEFF FROM WATER (CM/HR)
CV = CONCENTRATION IN WATER (MG/L)
t = DURATION OF EVENT (HRS)
CF = CONVERSION FACTOR (L/CM3 1E-3)

ORGANICS IF t<=t* DA = 2 x CFx FA x KP x CV x SQRT (6 x TAU x t / PI)
IF t>t* DA = KPx FA x CV x CF x [t/(1+B) + (2 x TAU x (1+3B+3B^2)/((1+B)^2))]

TAU = LAG TIME (HRS)
B = PARTITIONING CONSTANT
t* = TIME (HRS)

DAD = (DA x EF x ED x A) / (BW x AT)

DAD = DERMALLY ABSORBED DOSE (MG/KG/DAY)
A = SKIN SURFACE AREA AVAILABLE FOR CONTACT (CM2)

INPUTS		ADULT RESIDENT	CHILD RESIDENT	ADULT WORKER
A	18000	18000	6600	
EF	350	350	350	250
ED	24	24	6	24
BW	70	70	15	70
AT-NC	8760	8760	2190	8760
AT-C	25550	25550	25550	25550
t	0.2	0.2	0.33	

FOR INORGANICS, SET Do = 0. FOR ORGANICS, SET DI = 0

CHEMICAL	C (MG/L)	Di	Do	KP	t*	B	TAU	FA	t<t*	t>t*	1+B	1+3B
1,4-dioxane	0.0059286	0.00E+000	1.39E-009	3.3E-004	0.8	0.0012	0.33	1	1.39E-009	1.58E-009	1.0012	1.0036
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1
————		0.00E+000	0.00E+000						0	0	1	1

CHEMICAL	DA	RFD	CSF	HQ	CR
1,4-dioxane	1.39E-009		1.1E-002	N/A	1.3E-009
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
TOTALS/DERM DRINK WATER				0.0E+000	1.3E-009

INHALATION EXPOSURE

EQUATIONS.

kg = kH x SQRT (MW H / MW)

kg = GAS-FILM MASS TRANSFER COEFFICIENT (CM/HR)
kH = kg FOR WATER (CM/HR 3000)
MW H = MOLEC WT FOR WATER (G/MOL 18)
MW = MOLECULAR WT (G/MOL)

kl = kC x SQRT (MW C / MW)

kl = LIQUID-FILM MASS TRANSFER COEFFICIENT (CM/HR)
kC = kl FOR CARBON DIOXIDE (CM/HR 20)
MW C = MOLEC WT FOR CARB. DIOXIDE (G/MOL 44)

KL = 1 / [(1 / kl) + ((R x T) / (H x kg))]

KL = MASS TRANSFER COEFFICIENT (CM/HR)
R = GAS CONSTANT (ATM M3/MOL K 8 2E-5)
T = ABSOLUTE TEMP (K. 293)
H = HENRY'S LAW CONSTANT (ATM M3/MOL)

KaL = KL / SQRT [(T1 x US) / (TS x U1)]

KaL = ADJUSTED OVERALL MASS TRANS COEFF (CM/HR)
T1 = CALIB WATER TEMP OF KL (K)
TS = SHOWER WATER TEMP (K)
U1 = WATER VISCOSITY AT T1 (CP)
US = WATER VISCOSITY AT TS (CP)

CWD = C x CF x (1 - EXP [(-KaL x ts) / (60 x d)])

CWD = CONC LEAVING SHOWER DROPLET AFTER TIME ts (UG/L)
C = CONCENTRATION IN WATER (MG/L)
CF = CONVERSION FACTOR (UG/MG. 1E3)
ts = SHOWER DROPLET TIME (SEC)
d = SHOWER DROPLET DIAMETER (MM)

S = CWD x FR / SV

S = INDOOR VOC GENERATION RATE (UG/M3/MIN)
FR = SHOWER FLOW RATE (L/MIN)
SV = SHOWER ROOM AIR VOLUME (M3)

D = [(VR x S) / (BW x Ra x 1E6)] x Q

D = INHALATION DOSE (MG/KG/SHOWER)
VR = VENTILATION RATE (L/MIN)
BW = BODY WEIGHT (KG)
Dt = TOTAL DURATION IN SHOWER ROOM (MIN)
Ra = RATE OF AIR EXCHANGE (1/MIN)

Q = Ds + [(EXP(-Ra x Dt)) / Ra] - [(EXP(Ra x (Ds-Dt))) / Ra]

Ds = DURATION OF SHOWER (MIN)

INPUTS

T1	293	VR	14
TS	318	BW	70
U1	1 002	EF	350
US	0 596	ED	24
d	1	AT-NC	8760
ts	2	AT-C	25550
FR	20		
SV	6		
Ds	12	Q	2 4819173
Dt	20		
Ra	0 01667		

CHEMICAL	C (MG/L)	MW	H	kg	kl	KL	KaL	CWD	S	D
1,4-dioxane	0.006	88.1	4.8E-006	1356.0308	14.134107	0.2658177	0.359066	0.0713852	0.2379505	0.000007[illegible]
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0
				N/A	N/A	N/A	0	0	0	0

CHEMICAL	D	RFD	CSF	HQ	CR
1,4-dioxane	7.09E-006		1.1E-002	N/A	2.6E-008
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
----------	0.00E+000			N/A	0.0E+000
TOTALS/INHAL				0.0E+000	2.6E-008
TOTAL THIS RECEPTOR				0.0E+000	6.5E-007

RISKS BY CHEMICAL

CHEMICAL	HAZARD INDEX	CANCER RISK
1 4-dioxane	0 0E+000	6 5E-007
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0.0E+000	0 0E+000
----------	0 0E+000	0.0E+000
----------	0 0E+000	0 0E+000
----------	0.0E+000	0.0E+000
----------	0 0E+000	0 0E+000
----------	0.0E+000	0.0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0.0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0.0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0.0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
----------	0 0E+000	0 0E+000
TOTAL	0 0E+000	6 5E-007

DRINKING WATER EXPOSURE
SITE Baily
RECEPTOR Child resident

ORAL EXPOSURE FROM GROUNDWATER

EQUATIONS

$$D = C \times IR \times ED \times EF / BW \times AT$$

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EF = EXPOSURE FREQUENCY (DAYS/YR)
BW = BODY WEIGHT (KG)
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$$HQ = D / RFD$$

HQ = HAZARD QUOTIENT
D = NONCARCINOGENIC DOSE (MG/KG/DAY)
RFD = REFERENCE DOSE (MG/KG/DAY)

$$CR = 1 - EXP(-CSF \times D)$$

CR = CANCER RISK
CSF = CARCINOGENIC SLOPE FACTOR (1/MG/KG/DAY)
D = CARCINOGENIC (TIME-WEIGHTED) DOSE (MG/KG/DAY)

INPUTS		ADULT RESIDENT	CHILD RESIDENT	ADULT WORKER
IR	1	2	1	1
EF	350	350	350	250
ED	6	24	6	24
BW	15	70	15	70
AT-NC	2190	8760	2190	8760
AT-C	25550	25550	25550	25550

CHEMICAL	C (MG/L)	RFD	CSF	HQ	CR
1,4-dioxane	0.008		1 1E-002	N/A	3 6E-007
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0.0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0.0E+000
————				N/A	0.0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0.0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0.0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0.0E+000
————				N/A	0.0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
————				N/A	0 0E+000
TOTALS/ORAL DRINK WATER				0 0E+000	3 6E-007

DERMAL EXPOSURE FROM GROUNDWATER

EQUATIONS

INORGANICS DA = KP x CV x t x CF

DA = DOSE ABS PER UNIT AREA (MG/CM2)
KP = PERMEABILITY COEFF FROM WATER (CM/HR)
CV = CONCENTRATION IN WATER (MG/L)
t = DURATION OF EVENT (HRS)
CF = CONVERSION FACTOR (L/CM3 1E-3)

ORGANICS IF t<=t* DA = 2 x CFx FA x KP x CV x SQRT (6 x TAU x t / PI)
IF t>t* DA = KPx FA x CV x CF x [t/(1+B) + (2 x TAU x (1+3B+3B^2)/((1+B)^2))]

TAU = LAG TIME (HRS)
B = PARTITIONING CONSTANT
t* = TIME (HRS)

DAD = (DA x EF x ED x A) / (BW x AT)

DAD = DERMALLY ABSORBED DOSE (MG/KG/DAY)
A = SKIN SURFACE AREA AVAILABLE FOR CONTACT (CM2)

INPUTS		ADULT RESIDENT	CHILD RESIDENT	ADULT WORKER
A	6600	18000	6600	
EF	350	350	350	250
ED	6	24	6	24
BW	15	70	15	70
AT-NC	2190	8760	2190	8760
AT-C	25550	25550	25550	25550
t	0 33	0 2	0 33	

FOR INORGANICS, SET Do = 0, FOR ORGANICS, SET Di = 0

CHEMICAL	C (MG/L)	Di	Do	KP	t*	B	TAU	FA	t<t*	t>t*	1+B	1+3B
1,4-dioxane	0.006	0.00E+000	1.81E-009	3.3E-004	0.8	0.0012	0.33	1	1.81E-009	1.96E-009	1.0012	1.0036
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1
------------		0.00E+000	0.00E+000						0	0	1	1

CHEMICAL	DA	RFD	CSF	HQ	CR
1 4-dioxane	1 81E-009		1 1E-002	N/A	7 2E-010
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
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------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
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------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
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------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
------------	0 00E+000			N/A	0 0E+000
TOTALS/DERM DRINK WATER				0 0E+000	7 2E-010

INHALATION EXPOSURE

EQUATIONS

kg = kH x SQRT (MW H / MW)

kg = GAS-FILM MASS TRANSFER COEFFICIENT (CM/HR)
kH = kg FOR WATER (CM/HR: 3000)
MW H = MOLEC WT FOR WATER (G/MOL 18)
MW = MOLECULAR WT (G/MOL)

kl = kC x SQRT (MW C / MW)

kl = LIQUID-FILM MASS TRANSFER COEFFICIENT (CM/HR)
kC = kl FOR CARBON DIOXIDE (CM/HR 20)
MW C = MOLEC WT FOR CARB DIOXIDE (G/MOL: 44)

KL = 1 / [(1 / kl) + ((R x T) / (H x kg))]

KL = MASS TRANSFER COEFFICIENT (CM/HR)
R = GAS CONSTANT (ATM M3/MOL K 8.2E-5)
T = ABSOLUTE TEMP (K. 293)
H = HENRY'S LAW CONSTANT (ATM M3/MOL)

KaL = KL / SQRT [(T1 x US) / (TS x U1)]

KaL = ADJUSTED OVERALL MASS TRANS. COEFF (CM/HR)
T1 = CALIB WATER TEMP OF KL (K)
TS = SHOWER WATER TEMP. (K)
U1 = WATER VISCOSITY AT T1 (CP)
US = WATER VISCOSITY AT TS (CP)

CWD = C x CF x (1 - EXP [(-KaL x ts) / (60 x d)])

CWD = CONC LEAVING SHOWER DROPLET AFTER TIME ts (UG/L)
C = CONCENTRATION IN WATER (MG/L)
CF = CONVERSION FACTOR (UG/MG 1E3)
ts = SHOWER DROPLET TIME (SEC)
d = SHOWER DROPLET DIAMETER (MM)

S = CWD x FR / SV

S = INDOOR VOC GENERATION RATE (UG/M3/MIN)
FR = SHOWER FLOW RATE (L/MIN)
SV = SHOWER ROOM AIR VOLUME (M3)

D = [(VR x S) / (BW x Ra x 1E6)] x Q

D = INHALATION DOSE (MG/KG/SHOWER)
VR = VENTILATION RATE (L/MIN)
BW = BODY WEIGHT (KG)
Dt = TOTAL DURATION IN SHOWER ROOM (MIN)
Ra = RATE OF AIR EXCHANGE (1/MIN)

Q = Ds + [(EXP(-Ra x Dt)) / Ra] - [(EXP(Ra x (Ds-Dt))) / Ra]

Ds = DURATION OF SHOWER (MIN)

INPUTS

T1	293	VR	0
TS	318	BW	70
U1	1 002	EF	350
US	0 596	ED	24
d	1	AT-NC	8760
ts	2	AT-C	25550
FR	20		
SV	6		
Ds	12	Q	2 4819173
Dt	20		
Ra	0 01667		

CHEMICAL	C (MG/L)	MW	H	kg	kl	KL	KaL	CWD	S	D
1,4-dioxane	0 006	88 1	4 8E-006	1356 0308	14 134107	0 2658177	0 359066	0 0713852	0 2379505	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0
————				N/A	N/A	N/A	0	0	0	0

CHEMICAL	D	RFD	CSF	HQ	CR
1 4-dioxane	0 00E+000		1 1E-002	N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
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-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000
-------------	0 00E+000			N/A	0 0E+000

TOTALS/INHAL	0 0E+000	0 0E+000
TOTAL THIS RECEPTOR	0 0E+000	3 6E-007

RISKS BY CHEMICAL

CHEMICAL	HAZARD INDEX	CANCER RISK
1 4-dioxane	0 0E+000	3 6E-007
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0.0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
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————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
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————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0.0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0.0E+000	0 0E+000
————	0 0E+000	0.0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
————	0 0E+000	0 0E+000
TOTAL	0 0E+000	3 6E-007

HEALTH EVALUATION OF 1,4-DIOXANE

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INTRODUCTION

The State of Michigan, Department of Public Health (MDPH), has requested assistance from the Agency for Toxic Substances and Disease Registry (ATSDR) "in reviewing all available information related to 1,4-dioxane and the current Michigan guideline" (MDPH, 1994). MDPH asked that their letter be considered "as a formal request for a risk analysis" of 1,4-dioxane. This consultation for 1,4-dioxane presents a variety of risk assessments which all have specific assumptions regarding the carcinogenicity of 1,4-dioxane, including default assumptions, associated with them. The underlying science to support those assumptions is the primary focus of ATSDR's review. ATSDR pursued this review in the context of risk analysis, which incorporates elements of risk assessment, biomedical judgment (CEQ, 1989; ATSDR, 1993), and data specifically related to concerns identified by the State of Michigan (MDPH, 1993, 1994).

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2. Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; CASE, Computer-Automated Structure Evaluation; DMBA, dimethylbenzanthracene; GC/MS, gas chromatography/mass spectrometry; HSDB, Hazardous Substance Data Bank; HA, Health Advisory; HEAA, β-hydroxyethoxyacetic acid; IRIS, Integrated Risk Information System; IARC, International Agency for Research on Cancer; NCI, National Cancer Institute; NIOSH, National Institute for Occupational Safety and Health; NTP, National Toxicology Program; NOAEL, no-observed-adverse-effect level; NMR, nuclear magnetic resonance; PCB, polychlorinated biphenyl; RfD, Reference Dose, MDPH, State of Michigan, Department of Public Health; SAR, structure-activity relationships; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; TLC, thin-layer chromatographic; CEQ, U.S. Council of Environmental Quality; EPA, U.S. Environmental Protection Agency.

3 Key Words: consultation, 1,4-dioxane, risk analysis, risk assessment

4. This consultation reflects ATSDR's assessment of all relevant toxicological testing and information on 1,4-dioxane. It has been reviewed by scientists from ATSDR and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and has been made available for public review. Text quoted from the ATSDR Cancer Policy Framework (ATSDR, 1993) is shown in italics in the Consultation. Our conclusions are in boldface italics.

Final responsibility for the contents and views expressed in this consultation resides with ATSDR.

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In response to this request, ATSDR is not providing recommendations for a specific drinking water standard, but rather is advising the State of Michigan on the health effects of 1,4-dioxane and the issues related to risk assessment to address the public health concerns associated with exposure to 1,4-dioxane in the context of all available relevant information. The "*relevant information includes both technical data as well as science policy positions adopted by the range of organizations with programs germane to the assessment and/or regulation of carcinogens*," as noted in the Agency's Cancer Policy Framework (ATSDR 1993), which specifically addresses several of the public health concerns associated with this consultation. The Cancer Policy Framework "*is intended to serve as a framework to guide the Agency in its programs and actions regarding carcinogens and to harmonize such efforts with those of other federal agencies and relevant organizations. . . . A central theme of this Cancer Policy Framework is the use of risk analysis as an organizing construct based on sound biomedical and other scientific judgment to define plausible exposure ranges of concern rather than single numerical conclusions that may convey an artificial sense of precision. . . . As a Public Health Service agency, ATSDR places a preeminent emphasis on disease prevention.*"

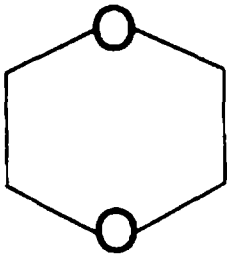
1,4-Dioxane has been classified as a substance "which may reasonably be anticipated to be a carcinogen" (NTP, 1994), placed in Group 2B as "possibly carcinogenic to humans" (IARC, 1987), and placed in Group B2 as "a probable human carcinogen" in EPA's weight-of-evidence approach (IRIS, 1994). A Lifetime Health Advisory (HA) for 1,4-dioxane has not been derived because EPA recommends that caution be exercised in assessing the risk associated with lifetime exposure to chemicals classified as Group A or Group B carcinogens (EPA, 1988a; IRIS, 1994). However, the State of Michigan is involved in a cleanup of a contaminated aquifer near Ann Arbor, Michigan (MDPH, 1994). Since 1986, the State of Michigan based risk management decisions for 1,4-dioxane in drinking water on a calculated upper bound lifetime risk to humans of developing cancer from exposure to 1,4-dioxane of 1 in 1,000,000 at a concentration of 2 μg/L (2 parts per billion, or ppb) in drinking water. However, the State of Michigan is considering an interim drinking water guideline range of 3–15 μg/L based on the risk assessment cited in IRIS (1994) (MDPH, 1993). The State of California has recently established a drinking water standard of 15 μg/L (MDPH, 1993). The range of 3–15 μg/L corresponds to upper bound lifetime cancer risks of 1 in 1,000,000 to 5 in 1,000,000.

Since ATSDR has not developed a toxicological profile for this compound, ATSDR's Division of Toxicology has developed this chemical-specific consultation for 1,4-dioxane, which is presented in a non–site-specific manner. Previously, ATSDR has suggested in a consultation that use of contaminated water should be discontinued and that site-specific information be obtained to determine the extent of contamination, and hence, the risk posed by exposure to 1,4-dioxane (ATSDR, 1986). Subsequent correspondence with the MDPH indicated that the Linearized Multistage Model was appropriate in estimating cancer risk for 1,4-dioxane (ATSDR, 1989).

In the absence of toxicological profiles, ATSDR consults relevant peer-reviewed literature, EPA documents, and on-line databases, such as TOXNET and TOXLINE (ATSDR, 1993). Accordingly, in the preparation of this chemical-specific consultation, a comprehensive search was conducted on the health effects and relevance of these health effects to humans potentially exposed to environmental levels of 1,4-dioxane. The following computerized databases were searched: MEDLINE 1965–present, TOXLINE 1964–present, CANCERLIT, Occupational Safety and Health, Water Resources Abstracts, NTIS, and EMBase (European Excerpta Medica). The computerized literature search of TOXLINE, SCISEARCH, and EMBase also included a search for Russian language articles using dioxane and its CAS No. (123-91-1) for key words. ATSDR's analysis of the Russian literature resulting from this search indicated that no information was germane to the development of this consultation regarding health guidance for 1,4-dioxane. Based upon the limited information in the Russian literature available on-line, no quantitative description is provided for human exposure. Furthermore, the animal studies described do not address mechanism of action or cancer outcomes. In addition to the computerized literature searches, several review reports were consulted, including IARC Monographs on the Evaluation of Carcinogenic Risk (IARC, 1976, 1987); Criteria for a Recommended Standard for Occupational Exposure to Dioxane (NIOSH, 1977); Final Health Advisory for *p*-Dioxane (EPA, 1988a); Evaluation of the Potential Carcinogenicity of 1,4-Dioxane (EPA, 1988c); Health and Environmental Effects Assessment for 1,4-Dioxane (Hartung, 1989); and Integrated Risk Information System for 1,4-Dioxane (IRIS, 1994). Although these secondary sources were consulted in the preparation of this consultation, all key primary studies were retrieved and reviewed. In addition, relevant studies identified in the literature search that were more recent than the studies cited in the secondary sources were retrieved and reviewed.

CHEMICAL AND PHYSICAL DATA FOR 1,4-DIOXANE

The structure of 1,4-dioxane is shown in Figure 1. Table 1 provides information on its chemical properties.



1,4-Dioxane

FIGURE 1. Structure of 1,4-dioxane.

1,4-Dioxane is used extensively as a solvent for many organic products; as an ingredient in many consumer products (e.g., paints, varnishes, cleaning and detergent preparations, cements, stains, inks, cosmetics); and as a preservative, fumigant, and deodorant, to name

some uses (IARC, 1976; NIOSH, 1977). 1,4-Dioxane is produced commercially by dehydration of ethylene glycol, by treatment of bis(2-chloroethyl) ether with alkali, by dimerization of ethylene oxide, or by heating and distilling diethylene glycol with dehydration catalysts. The technical grade product is >99.9% pure, but may contain bis(2-chloroethyl) ether as an impurity (HSDB, 1995). 1,4-Dioxane is also formed as a by-product during the manufacture of surfactants, which include shampoos and laundry detergents, and it has been found as an impurity in used ethylene glycol–based automobile antifreeze. 1,4-Dioxane is totally unrelated to the family of compounds called dioxins. 1,4-Dioxane is a natural component in some food products, such as vine-ripened tomatoes and tomato products (Chung et al., 1983), fresh shrimp (Choi et al., 1983), brewed coffee (Liardon and Ott, 1984), and fried chicken (Tang et al., 1983).

TABLE 1. Chemical Properties of 1,4-Dioxane

Property	Data	Reference
Molecular weight	88.10	
CAS registry number	123-91-1	
Description	colorless, inflammable liquid	HSDB, 1995
Melting point	11.8°C	Windholz, 1989
Boiling point	101.1°C	Windholz, 1989
Density at 20°C	1.0329	Windholz, 1989
Vapor Pressure		Verschueren, 1983
at 20°C	30 mm	
at 25°C	37 mm	
at 30°C	50 mm	
Solubility	completely miscible in water; miscible with organic solvents, aromatic hydrocarbons, oils	IARC, 1976, NIOSH, 1977, Verschueren, 1983
Henry's Law Constant	2.3×10^{-4}	Hartung, 1989
Log K_{ow}	-0.27	Hansch and Leo, 1985
Flash point	12°C	Kirk-Othmer, 1982
Ignition temperature	180°C	Kirk-Othmer, 1982
Reactivity	forms explosive peroxide in air	HSDB, 1995

POTENTIAL FOR HUMAN EXPOSURE

The principal routes of exposure are inhalation, ingestion, and dermal contact. 1,4-Dioxane can be expected to enter the environment from emissions at manufacturing sites or from its use. 1,4-Dioxane is miscible with water and is moderately volatile (IARC, 1976; NIOSH, 1977). Since 1,4-dioxane contains no functional groups susceptible to hydrolysis in the environment, it is expected to be resistant to hydrolysis in water. In addition, several investigators have found that 1,4-dioxane is resistant to microbial degradation in water and soil (Mills and Stack, 1954; Heukelekian and Rand, 1955; Ludzack and Ettinger, 1960; Sasaki, 1978; Kawasaki, 1980; Francis, 1982), but may undergo photolysis at water or soil surfaces. Moderate vaporization from water or soil would be expected. In the air, a residence time of 3.9 days was estimated based on a calculated hydroxyl radical reaction rate (Cuppitt,

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glycol with dehydration
ıtain bis(2-chloroethyl)
ı by-product during the
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ifreeze. 1,4-Dioxane is
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Reference

HSDB, 1995
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IARC, 1976. NIOSH,
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1980). Grosjean (1990) estimated a half-life of 4–20 hours for removal of 1,4-dioxane from air by reaction with hydroxyl radicals. Oxidation of 1,4-dioxane in air can lead to peroxide formation (Howard and Ingold, 1969; Malatesta and Scaiano, 1982). 1,4-Dioxane does not bind strongly to organic matter in soil (Lyman and Loreti, 1987), indicating a potential to leach readily into groundwater.

Information on the concentrations of 1,4-dioxane in groundwater, surface water, and drinking water is limited. A concentration of 1,4-dioxane of 2,100 µg/L (ppb) was reported for a drinking water well in Massachusetts (CEQ, 1981). Municipal water supplies in the United States were reported to contain 1 µg/L of 1,4-dioxane in the 1970s (Kraybill, 1978); however, the frequency of this level was not provided. In six drinking water wells near a solid waste landfill near Wilmington, Delaware, two wells were found to contain 0.1 and 0.5 µg/L 1,4-dioxane, but no 1,4-dioxane was detectable in the finished drinking water in the municipality using that well field (DeWalle and Chian, 1981). Extensive groundwater contamination (<0.01–220 mg/L or <10–220,000 µg/L) with more limited surface water contamination (<0.01–0.29 mg/L or <10–290 µg/L in a tributary creek) resulted from treatment of industrial wastewater in an unlined oxidation lagoon in Ann Arbor, Michigan (Brode and Minning, 1988). Concentrations in private wells ranged from 0.001–1 mg/L to 200 mg/L (1–1,000 µg/L to 200,000 µg/L). The concentrations of 1,4-dioxane in five wells near Circleville, Ohio, ranged from <1 µg/L to 360 µg/L after contamination of groundwater following treatment of industrial wastewater (Clark 1987a,b; Ohio EPA, 1987). 1,4-Dioxane has been observed in discharges into Lake Michigan near Chicago (Konasewich et al., 1978; Great Lakes Water Quality Board, 1986) and in the Haw River in North Carolina (Dietrich et al., 1988). Given the limited information on concentrations of 1,4-dioxane in water, further characterization of the water levels of 1,4-dioxane and possible chlorinated dioxanes in Michigan is warranted.

"*ATSDR recognizes that, at present, no single generally applicable procedure for exposure assessment exists, and, therefore, exposures to carcinogens are best assessed on a case-by-case basis with an emphasis on prevention of exposure*" (ATSDR, 1993).

HEALTH EFFECTS IN HUMANS

Information regarding health effects of 1,4-dioxane in humans is limited to inhalation and dermal exposure of volunteers or workers exposed occupationally. These data indicate that 1,4-dioxane is irritating to mucous membranes and can cause hepatic and renal effects at high inhalation concentrations. Subjects exposed to 200 or 300 ppm 1,4-dioxane for 15 minutes (Silverman et al., 1946), 1,600 ppm for 10 minutes (Yant et al., 1930), or 5,500 ppm for 1 minute (Silverman et al., 1946) complained of eye, nose, and throat irritation. Slight vertigo was also noted at 5,500 ppm. In subjects exposed to concentrations ranging from 0.7 to 2,800 ppm for unspecified durations, slight mucous membrane irritation was reported at 280 ppm, becoming more distinct at 1,400 and 2,800 ppm (Wirth and Klimmer, 1936). In a study of volunteers exposed to 50 ppm for six hours and examined by chest X-ray, electrocardiogram, respiratory function tests, blood chemistry determinations, and urinalysis, the only effect

d eye irritation (Young et al., 1977). While no subjective complaints of ...tion, or cough were reported by volunteers exposed to 1,000 ppm for five ...,000 ppm for three minutes (Fairley et al., 1934), hemorrhagic nephritis, ...lar liver necrosis, severe epigastric pain, convulsion, and coma were the major ...s found in workers who died after exposure to high concentrations (Barber, 1934, Johnstone, 1959). Examination of other workers who did not die indicated that leukocytosis and eosinophilia may have been related to 1,4-dioxane exposure (Barber, 1934). The exposures probably involved inhalation and dermal contact, but the exposure levels in the Barber (1934) study were not quantified. In one case, the worker had placed an open container of 1,4-dioxane between his feet with no ventilation while using the solvent during working hours for one week to remove glue from a table top and his hands (Johnstone, 1959). The air level of 1,4-dioxane was estimated to range from 208 ppm to greater than 650 ppm.

A few occupational epidemiological studies were conducted. In a study of 74 workers with a cumulative potential exposure of 1,840 man-years and an average duration of 25 years with estimated 1,4-dioxane exposure concentrations of 0.02–47.8 mg/m^3 (0.006–13.3 ppm), 6 of 24 current workers had evidence of the liver toxicity, as determined by serum transaminase levels (Thiess et al., 1976). The authors noted that the liver effects could have been due to ethanol consumption as all six of these workers were known as habitual alcohol drinkers. Chromosome analysis of peripheral lymphocytes in six workers revealed no differences relative to a control group. Analysis of cause of death in the 12 workers who had died revealed no increased number of cancers over those expected. Another occupational study of 165 workers exposed for at least one month during a 21-year interval to 1,4-dioxane at average concentrations ranging between 0.1 and 17 ppm and typical maximum concentrations ranging between 1.5 and 32 ppm also found no differences between observed and expected incidences of cancer (Buffler et al., 1978).

HEALTH EFFECTS IN ANIMALS

The primary purpose of this consultation is to provide an in-depth review of all available information related to 1,4-dioxane and the current Michigan drinking water guideline. While ATSDR considers this to be appropriate in this consultation regarding levels of 1,4-dioxane in drinking water supplies, exposure to volatile organic compounds in drinking water involves significant contributions from inhalation and dermal contact, in addition to the direct ingestion of contaminated water. For example, activities such as showering, bathing, and laundering can contribute to the total exposure from drinking water supplies. Exposure to volatile organic compounds in the tap water through inhalation from showering and other indoor air sources can be 1.5–6 times higher than the contribution from ingesting two liters of water per day (McKone, 1987). Therefore, the discussion of the health effects in animals exposed to 1,4-dioxane includes oral, inhalation, and dermal exposure studies.

Lethality and Systemic Toxicity

Acute oral LD_{50} values of 1,4-dioxane ranged from 5,400 to 7,300 mg/kg in rats (Laug et al., 1939; Smyth et al., 1941; Nelson, 1951; Pozzani et al., 1959); 5,900 mg/kg in mice (Laug et al., 1939); 3,300 to 4,000 mg/kg in guinea pigs (Laug et al., 1939; Smyth et al., 1941), and 2,000 mg/kg in rabbits (Nelson, 1951). In rats, mice, guinea pigs, rabbits, or dogs treated with 1,4-dioxane at lethal oral doses once by gavage or at high drinking water concentrations (5% volume per volume [v/v]) for several days, signs of anesthesia and narcosis (weakness, depression, incoordination, and coma) often preceded death, and necropsy and histological examination often revealed severe gastric, hepatic, and renal lesions (De Navasquez, 1935; Knoefel, 1935; Schrenk and Yant, 1936; Kesten et al., 1939; Laug et al., 1939; Smyth et al., 1941; Nelson, 1951; David, 1964). Treatment of male Sprague-Dawley rats by gavage with a single dose of 1,4-dioxane in saline at 0, 10, 100, or 1,000 mg/kg resulted in significant weight gain reduction at all doses, but no microscopic evidence of hepatic lesions was found (Stott et al., 1981).

In a longer-term study, administration of 1,4-dioxane in the drinking water at a high concentration (5% v/v) in rats and mice for up to 67 days resulted in the deaths of some animals of both species (Fairley et al., 1934). The 5% v/v concentration (5 mL dioxane/100 mL water or 51,645 mg/L using a density of 1.0329 g/mL) is roughly equivalent to doses of 7,230 mg/kg/day for rats and 9,812 mg/kg/day for mice using reference drinking water factors 0.14 L/kg/day in rats and 0.19 L/kg/day in mice (EPA, 1986b). Histological examination of the rats and mice that were sacrificed revealed severe lesions in the kidney (cellular degeneration in the renal cortex, casts blocking the tubules in the medullary areas, and hemorrhages and vascular congestion in the kidneys) and in the liver (cellular degeneration). Treatment of male Sprague-Dawley rats with 1,4-dioxane in the drinking water at levels (actual drinking water concentrations not reported) that provided 0, 10, or 1,000 mg/kg/day for 11 weeks resulted in a significantly increased relative liver weight and a minimal degree of centrilobular hepatocellular swelling associated with increased DNA synthesis at the 1,000 mg/kg/day dose only (Stott et al., 1981).

Several chronic studies in which 1,4-dioxane was administered to rats or mice in the drinking water described lesions in the kidney, liver, stomach, or respiratory tract. Administration of drinking water containing 1% 1,4-dioxane to adult male Wistar rats for an average of 452 days (estimated total dose of 132 g) resulted in a granular precipitate in the epithelium of the convoluted tubules and epithelial proliferation in the glomeruli of the kidneys (Argus et al., 1965). The total dose of 132 g is equal to about 584 mg/kg/day, assuming an average reference body weight of 0.50 kg for mature male Wistar rats (EPA, 1988b). In a two-year study, male and female Sherman rats were given 0.01, 0.1, or 1.0% 1,4-dioxane in the drinking water for up to 716 days (Kociba et al., 1974). The authors estimated the equivalent doses in units of mg/kg/day. Renal lesions consisted of renal tubular epithelial degeneration and regeneration, and hepatic lesions consisted of hepatocellular degeneration, necrosis, and hepatic regeneration as indicated by hepatocellular hyperplastic nodule formation at 0.1% (94 and 148 mg/kg/day for males and females, respectively) and 1.0% (1,015 and 1,599

mg/kg/day for males and females, respectively), but not at the lowest level of 0.01% (9.6 and 19 mg/kg/day for males and females, respectively). It should be noted that statistically significant increases in hepatocellular carcinomas were found in the rats at the highest drinking water concentration of 1,4-dioxane (1.0%) (see subsection on Carcinogenicity below). Therefore, the hepatocellular hyperplastic nodule formation seen in rats at the 0.1% and 1.0% concentrations might represent preneoplastic lesions.

In a study by NCI (1978), Osborne-Mendel rats were given 0, 0.5% (240 and 350 mg/kg/day in males and females, respectively), or 1.0% (530 and 640 mg/kg/day for males and females, respectively) 1,4-dioxane in the drinking water for 110 weeks. NCI (1978) calculated the equivalent doses in units of mg/kg/day based on body weight changes and water consumption data. High incidences of kidney lesions (vacuolar degeneration or focal tubular epithelial regeneration in the proximal cortical tubular epithelium, hyaline casts) were found at 0.5% in males (240 mg/kg/day) and in both sexes at 1.0% (530 mg/kg/day for males and 640 mg/kg/day for females), but not in controls. Increased incidences of liver lesions (hepatocytomegaly) compared with controls were found in females at 0.5% (350 mg/kg/day) and in both sexes at 1.0% (530 and 640 mg/kg/day in males and females, respectively). Stomach ulcers occurred in males at both doses (5/28 at 240 mg/kg/day and 5/30 at 530 mg/kg/day), compared with none in controls. Females were minimally affected, with no ulcers in controls and one each in the low- and high-dose groups. Higher incidences of pneumonia were also seen in the low- and high-dose male rats and in high-dose females rats than in the controls. Dose-related, significantly increased mortality was observed in both male and female rats at both exposure levels.

In B6C3F$_1$ mice similarly exposed for 90 weeks, NCI (1978) calculated the doses equivalent to the drinking water concentrations of 0.5% (720 and 380 mg/kg/day for males and females, respectively) and 1.0% (830 and 860 mg/kg/day for males and females, respectively). Dose-related increased mortality occurred in females (380 and 860 mg/kg/day), but not in males. Nonneoplastic lesions consisted of dose-related increased incidences of pneumonia (inflammation) and rhinitis in both sexes. The authors stated that hepatocytomegaly was commonly found in dosed mice, but the incidences were as follows: 0/49 control males, 2/50 low-dose males, 1/47 high-dose males, 1/50 control females, 7/48 low-dose females, and 0/37 high-dose females. It should be noted that treated mice had high incidences of hepatocellular tumors (see the subsection on Carcinogenicity below).

In acute and short-term inhalation studies of 1,4-dioxane in guinea pigs, rabbits, cats, rats, and mice, such effects as eye and nose irritation, narcosis, behavioral modifications, and histopathological lesions in the kidneys, liver, lungs, and brain have been observed (Yant et al., 1930; Fairley et al., 1934; Wirth and Klimmer, 1936; Gross, 1943; Goldberg et al., 1964; Frantik et al., 1994). A four-hour inhalation LC_{50} of 14,250 ppm was reported for female Carworth Farm–Nelson rats (Pozzani et al., 1959). Death and the occurrence of other effects in animals depends upon the concentration and duration of exposure, which varied from about 1,000 ppm for eight hours to 39,000 ppm for minutes.

In a two-year inhalation study, 288 male and 288 female Wistar rats were exposed to 111 ppm 1,4-dioxane for seven hours/day, five days/week (about 105 mg/kg/day) (Torkelson et al., 1974). Controls consisted of 192 males and 192 females. No treatment-related effects on activity, eye and nasal irritation, skin, respiratory distress, body weight, hematological or clinical chemistry parameters, or gross or microscopic appearance of organs and tissues were found.

A dermal LD_{50} of 7,600 mg/kg in rabbits has been reported (RTECS, 1994). Acute or subchronic dermal exposure of rabbits and guinea pigs to 1,4-dioxane has resulted in skin irritation, narcosis, and renal and hepatic lesions (Fairley et al., 1934; Nelson, 1951). However, no overt symptoms or evidence of skin irritation were observed in male COBs/Wistar rats to which 8,300 mg/kg 1,4-dioxane was applied to the unoccluded shaved skin (Clark et al., 1984).

Developmental Effects

The potential for 1,4-dioxane to induce developmental effects in the offspring of Sprague-Dawley rat dams given 0, 0.25, 0.5, or 1.0 mL/kg/day (0, 258, 516, or 1,033 mg/kg/day) by gavage on gestational days 6–15 has been studied (Giavini et al., 1985). Decreased maternal weight gain and decreased fetal weight accompanied by slight but significantly reduced sternebral ossification were observed at 1,033 mg/kg/day. No significant differences were found for the number of implantations, live fetuses, postimplantation loss, or major malformations. No effects on fertility, gestation, or development were found in OCR Swiss mice given 1,1,1-trichloroethane containing 1,4-dioxane in the drinking water that corresponded to dioxane doses of 0, 3, 10, or 30 mg/kg/day in a multigeneration study (Lane et al., 1982). Similarly, no treatment-related evidence of developmental effects was found in the offspring of Sprague-Dawley rat or Swiss Webster mouse dams that were exposed by inhalation to 1,1,1-trichloroethane containing 1,4-dioxane for seven hours/day on gestational days 6–15 (Schwetz et al., 1975). The exposure concentrations averaged 875 ppm for 1,1,1-trichloroethane and 32 ppm for 1,4-dioxane.

Carcinogenicity

The potential carcinogenicity of 1,4-dioxane has been studied in animals exposed via drinking water, inhalation, and dermal application. The carcinogenicity of dioxane has been demonstrated in animals exposed to drinking water containing 1,4-dioxane. In an early study, exposure of 26 male adult Wistar rats to 1% 1,4-dioxane in the drinking water for an average of 452 days (total dose 132 g) resulted in liver tumors (small neoplastic nodules to multifocal carcinomas) in 6 rats, and a transitional cell carcinoma of the kidney in 1 rat (Argus et al., 1965). Leukemia was found in one rat that had been treated for 387 days with a total dose of 116 g. One of nine controls developed a lymphosarcoma. The total dose of 132 g is equal to about 584 mg/kg/day and the total dose of 116 g is equal to about 599 mg/kg/day, assuming an average reference body weight of 0.50 kg for mature male Wistar rats (EPA, 1988b). Administration of 0.5% to 2% 1,4-dioxane in the drinking water to 22 male guinea pigs for 23 months (total dose of 588–623 g) resulted in gall bladder carcinomas in two guinea pigs and

hepatomas in three guinea pigs, compared with no tumors in ten controls (Hoch-Ligeti and Argus, 1970). The doses are roughly equivalent to 1,014–1,075 mg/kg/day using a reference body weight of 0.84 kg for guinea pigs (EPA, 1986b) and converting 23 months to 690 days, assuming 30 days in a month. Exposure of groups of 28–32 male Sprague-Dawley rats to drinking water containing 1,4-dioxane at concentrations of 0, 0.75%, 1%, 1.4% or 1.8% for 13 months (total doses of 104–256 g) resulted in squamous cell carcinomas in the nasal cavity of 1 rat each at 0.75% (total dose of 104 g or 444 mg/kg/day) and 1% (total dose of 142 g or about 609 mg/kg/day), and 2 rats each at 1.4% (total doses 191 and 198 g or 816 and 846 mg/kg/day) and 1.8% (total doses 213 and 256 g or 910 and 1,094 mg/kg/day) (Hoch-Ligeti et al., 1970), and hepatomas and hepatocellular carcinomas in 3 rats at 1.4% and 12 rats at 1.8% (Argus et al., 1973). In addition, incipient hepatomas (described by the investigators as nodules showing all the histological characteristics of fully developed hepatoma) developed in 4 rats at 0.75%, 9 rats at 1%, 13 rats at 1.4%, and 11 rats at 1.8% (Argus et al., 1973). One of 30 control rats developed a subcutaneous fibroma on the back of the nose. Argus et al. (1973) did not report the total doses, but the drinking water levels are probably equivalent to similar doses calculated from the data in the Hoch-Ligeti et al. (1970) study, in which 13 months was converted to 390 days and a reference body weight of 0.60 kg for mature male Sprague-Dawley rats (EPA, 1988b) was used, because the two papers appear to be separate reports of the same study. The studies discussed above contain limitations, including the use of relatively small numbers of animals, low incidences of the tumors that were not analyzed statistically, and in some cases, the use of only one dose level and the lack of dose-response data.

In groups of 60 male and 60 female Sherman rats exposed to drinking water containing 1,4-dioxane at concentrations of 0, 0.01%, 0.1%, or 1% (0, 9.6, 94, or 1,015 mg/kg/day for males, respectively, and 0, 19, 148, or 1,599 mg/kg/day for females, respectively) for 716 days, increased mortality was observed in both sexes at the high dose during the first four months (Kociba et al., 1974). The high-dose rats also had clearly depressed body weights during the duration of the study. Tumor incidences were combined for males and females and were expressed as the incidence in the effective number of rats that were alive after 12 months. Thus, the incidences of all hepatic tumors were 2/106 in controls, 0/110 at 0.01%, 1/106 at 0.1%, and 12/66 at 1.0%; the incidences of hepatocellular carcinomas were 1/106 in controls, 0/110 at 0.01%, 1/106 at 0.1%, and 10/66 at 1.0%; the incidences of nasal carcinomas were 0/106 in controls, 0/110 at 0.01%, 0/106 at 0.1%, and 3/66 at 1.0%. The increased incidences of all hepatic tumors ($p = 0.00022$) and hepatocellular carcinomas ($p = 0.00033$) were statistically significant in the high-dose rats compared with controls. For the nasal carcinomas, the p-value was 0.05491. The authors considered the hepatic and nasal tumors to be related to treatment with 1% dioxane in the drinking water.

NCI (1978) administered 1,4-dioxane in the drinking water at concentrations of 0, 0.5%, or 1.0% to groups of 35 male (0, 240, or 530 mg/kg/day) and 35 female (0, 350, or 640 mg/kg/day) Osborne-Mendel rats and groups of 50 male (0, 720, or 830 mg/kg/day) and 50 female (0, 380, or 860 mg/kg/day) B6C3F$_1$ mice for 110 weeks (rats) or 90 weeks (mice). In

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0 mg/kg/day) and 50
r 90 weeks (mice). In

rats, squamous cell carcinomas in nasal turbinates were observed at incidences of 0/33 control males, 12/33 low-dose males, 16/34 high-dose males, 0/34 control females, 10/35 low-dose females, and 8/35 high-dose females. The incidence of these tumors was statistically significant for dose-related trend and for direct comparison of the low- and high-dose males and females with controls. In addition, the incidences of hepatocellular adenomas were significantly increased in female rats, with incidences of 0/31 controls, 10/33 low-dose, and 11/32 high-dose. In mice, hepatocellular carcinomas were observed at incidences of 2/49 control males, 18/50 low-dose males, 24/47 high-dose males, 0/50 control females, 12/48 low-dose females, and 29/37 high-dose females. The incidences of hepatocellular carcinomas or adenomas were 8/49 control males, 19/50 low-dose males, 28/47 high-dose males, 0/50 control females, 21/48 low-dose females, and 35/37 high-dose females. The incidences of these tumors were statistically significant for dose-related trend and for direct comparison of the low- and high-dose males and females with controls. Thus, 1,4-dioxane induced hepatocellular adenoma in female rats, squamous cell carcinoma of the nasal turbinates in male and female rats, and hepatocellular carcinoma in male and female mice.

In a two-year inhalation study, no evidence of carcinogenicity, including hepatic or nasal carcinoma, was found in 288 male and 288 female Wistar rats that were exposed to 111 ppm 1,4-dioxane for seven hours/day, five days/week (about 105 mg/kg/day) (Torkelson et al., 1974). Controls consisted of 192 males and 192 females.

No evidence that exposure to 1,4-dioxane increased the incidence of hepatic or skin tumors was found in male C3H/HeJ Agouti mice given topical applications of 0.05 mL (50 µg) of 100% concentrations of various grades of dioxane three times/week for 78 weeks compared with ethanol controls (Perone et al., 1976).

1,4-Dioxane has been tested as a tumor initiator and as a promoter. In female Sencar mice to which 1,000 mg/kg 1,4-dioxane was administered orally, subcutaneously, or topically as an initiator followed by the promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) applied topically at 1 µg, three times/week for 20 weeks, no significant increases in the formation of papillomas were found compared with controls treated with acetone as the initiator and TPA as the promoter (Bull et al., 1986). In another initiation study, male Sprague-Dawley rats received an intraperitoneal dose of 1,4-dioxane at 881 mg/kg one day after 2/3-partial hepatectomy, followed six days later by administration of 500 ppm sodium phenobarbital in the drinking water for 49 days (Pereira et al., 1982). No increase in the number of gamma-glutamyl transpeptidase positive foci in the liver was found, indicating a lack of initiation activity. In groups of 30 male and 30 female Swiss-Webster mice to which 0.2 mL of 1,4-dioxane in acetone was applied to the clipped dorsal skin three times/week for 60 weeks, 22 males and 25 females survived (King et al., 1973). Only one skin sarcoma and one lymphoma were found, indicating that 1,4-dioxane was not a complete carcinogen under these conditions. Treatment with 50 µg of dimethylbenzanthracene (DMBA) as an initiator followed by similar application as above with 1,4-dioxane as the promoter resulted in an increased number of tumors in skin, lungs, and kidneys, and decreased the survival of the

mice to 4 of 30 males and 5 of 30 females. The skin tumor response using 1,4-dioxane as a promoter for DMBA was similar to the skin tumor response using croton oil as a promoter for DMBA, suggesting substantial promotion activity by 1,4-dioxane. In another promotion study, male Sprague-Dawley rats received an intraperitoneal dose of 30 mg/kg diethylnitrosamine as an initiator one day after 2/3-partial hepatectomy, followed by administration of 1,4-dioxane by gavage at 100 or 1,000 mg/kg/day, five days/week for seven weeks (Lundberg et al., 1987). At the 1,000-mg/kg/day dose, the number of gamma-glutamyl transpeptidase positive foci in the regenerating livers was increased, indicating promotion activity by 1,4-dioxane.

Genotoxicity and Other Biochemical Markers Related to the Mechanism of Carcinogenicity

Negative results for 1,4-dioxane were obtained in assays for reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with or without metabolic activation in several experiments at doses up to 103,000 µg/plate (Stott et al., 1981; Haworth et al., 1983; Nestmann et al., 1984; Khudoley et al., 1987). 1,4-Dioxane was negative in the absence of metabolic activation in an assay with *Photobacterium phosphoreum* M169, which detects DNA-damaging agents, DNA-intercalating agents, direct mutagens causing base substitution or frame shifts, and DNA synthesis inhibitors (Kwan et al., 1990). The assay was not repeated in the presence of a metabolic activating system. Negative results were also found for 1,4-dioxane for differential DNA repair in the *Escherichia coli* K-12 *uvrB/recA* assay at concentrations up to 1,150 mmol/L (Hellmer and Bolcsfoldi, 1992), for chromosomal aneuploidy in *Saccharomyces cerevisiae* strain D61.M (Zimmermann et al., 1985), and for mutagenicity in L5178Y mouse lymphoma cells (NTP, 1986). 1,4-Dioxane did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (Yoon et al., 1985). A weak increase in the sister chromatid exchange test without metabolic activation, but not with metabolic activation, in cultured Chinese hamster ovary cells was found for 1,4-dioxane (Galloway et al., 1987). However, negative results were obtained for chromosomal aberrations in the Chinese hamster ovary cells with or without metabolic activation. Exposure of cultured BALB/3t3 cells to 1,4-dioxane at 1.0 and 2.0 mg/mL, but not at ≤0.5 mg/mL resulted in transformations leading to the formation of foci (Sheu et al., 1988).

Using the Computer-Automated Structure Evaluation (CASE) methodology for structure-activity relationships (SAR), Rosenkranz and Klopman (1992) predicted that 1,4-dioxane would induce micronuclei in the bone marrow of rodents as a result of the $-O-CH_2-$ moiety. The authors speculated that 1,4-dioxane is genotoxic *in vivo* by an unrecognized mechanism. However, the authors stated that the $-O-CH_2-$ moiety does not seem to have intrinsic electrophilicity and a possible DNA-reactive metabolite could not be suggested; thus, they raised the possibility that the $-O-CH_2-$ moiety contributes to nongenotoxic toxicological effects of dioxane resulting in the induction of micronuclei. Another computerized SAR analysis assessed the carcinogenic potential of 1,4-dioxane using TOPKAT (version 3.0) male rat and female mouse models (Blake, 1995). Both models showed a positive influence for the $-O-CH_2-$ fragment, but the male rat model indicated that the symmetry of the molecule plays a more substantial role in its carcinogenicity than the $-O-CH_2-$ fragment. To further explore

the potential for carcinogenicity and genotoxicity of 1,4-dioxane, two of its possible metabolites, β-hydroxyethoxyacetic acid (HEAA) and 1,4-dioxane-2-one, were evaluated using these same TOPKAT male rat and female mouse models and the TOPKAT Ames mutagenicity model (Gombar, 1995). HEAA was predicted to be noncarcinogenic and nonmutagenic. However, 1,4-dioxane-2-one, the other possible metabolite, was predicted to be strongly positive in both the female mouse carcinogenicity model (predicted probability >0.84) and the Ames (*S. typhimurium*) mutagenicity model (predicted probability >0.85).

Experimental tests for micronuclei induction have been conducted with mixed results for 1,4-dioxane. In one study, a reproducible, dose-related positive increased incidence of micronucleated polychromatic erythrocytes in bone marrow cells was found in male C57Bl6 mice given single gavage doses of 1,4-dioxane at 900–3,600 mg/kg (Mirkova, 1994). Micronuclei were also induced in female C57Bl6 mice at a dose of 5,000 mg/kg, but not in male BALB/c mice at a dose of 5,000 mg/kg (female BALB/c mice not studied). Inconclusive results were obtained by two different laboratories, each of which conducted two trials in male C57Bl6 mice given three daily intraperitoneal injections of 1,4-dioxane at doses of 0, 500, 1,000, or 2,000 mg/kg/day and sampled 24 hours after the last injection (McFee et al., 1994). In the first laboratory, none of the treated groups showed statistically significant differences for micronucleated polychromatic erythrocytes compared with controls, but the percentage of polychromatic erythrocytes was significantly reduced at 2,000 mg/kg/day in the second trial only. In the second laboratory, no significant differences were found in the first trial, but a significant increase in micronucleated polychromatic erythrocytes occurred at 500 and 1,000 mg/kg, but not at 2,000 mg/kg/day, in the second trial. When mice at the first laboratory were given single intraperitoneal doses of 0, 2,000, 3,000, or 4,000 mg/kg and sampled 24 or 48 hours later, a significant increase in micronuclei induction was seen at 2,000 mg/kg after 24 hours, but no other groups showed micronuclei induction. The percentage of polychromatic erythrocytes was significantly reduced in most groups. In another study, dioxane did not induce micronuclei in the bone marrow cells of male CBA mice or male C57Bl6 mice receiving a single oral dose of 1,800 mg/kg (CBA) or 3,600 mg/kg (C57Bl6) (Tinwell and Ashby, 1994).

A number of studies have attempted to determine the mechanism(s) by which 1,4-dioxane exerts its carcinogenic effect by performing assays on markers for DNA damage, DNA synthesis, cell proliferation, or peroxisome proliferation. In cultured rat hepatocytes exposed for three hours to 0.03–30 mM 1,4-dioxane, increases in DNA strand breakage, measured by the alkaline elution assay, were observed (Sina et al., 1983). Treatment of male Sprague-Dawley rats with 1,4-dioxane in the drinking water at levels that provided 0, 10, or 1,000 mg/kg/day for 11 weeks resulted in a significantly increased relative liver weight and a minimal degree of centrilobular hepatocellular swelling at the 1,000 mg/kg/day dose (Stott et al., 1981). The hepatic lesions were accompanied by an increase in DNA synthesis in the liver, as measured by tritiated thymidine incorporation. However, no measurable DNA alkylation was found after rats were given a single dose of 1,000 mg/kg by gavage.

Furthermore, 1,4-dioxane was negative in the rat primary hepatocyte unscheduled DNA synthesis bioassay.

In another evaluation of whether 1,4-dioxane induces cancer via a cell proliferation mechanism, an *in vivo–in vitro* replicative DNA synthesis test in rat hepatocytes was used (Uno et al., 1994). Male Fischer 344 rats were given single oral doses of 0, 1,000, or 2,000 mg/kg by gavage and the incidences of replicative DNA synthesis, determined by trituated thymidine incorporation in isolated hepatocytes, and of hepatocyte viability, were determined at 24, 39, and 48 hours after dosing. An equivocal result for DNA synthesis was obtained at 24 hours with the 2,000-mg/kg dose. All other results for DNA synthesis were negative. Hepatic viability was significantly depressed at 39 and 48 hours with the 1,000-mg/kg dose and at 39 hours only with the 2,000-mg/kg dose, compared with controls. Because the results were equivocal, the experiments were repeated using doses that were 25%, 50%, and 100% of the dose at which the DNA synthesis was equivocal and the time at which the equivocal result was observed. Thus, the doses were 0, 500, 1,000, and 2,000 mg/kg, and the DNA synthesis and hepatocyte viability were assessed at 24 hours. All results of these analyses were negative.

Liver tissues from female Sprague-Dawley rats given 1,4-dioxane orally were used for the determination of hepatic DNA damage by the alkaline elution technique as a marker for genotoxic cancer initiation, of ornithine decarboxylase activity and cytochrome P-450 content as biochemical markers for tumor promotion, and of reduced glutathione content which increases susceptibility to covalent binding of reactive intermediates to macromolecules, cellular necrosis, and carcinogenesis (Kitchin and Brown, 1990, 1994; Kitchin et al., 1994). The activity of serum alanine aminotransferase was also determined. The doses were 0, 168, 840, 2,550, or 4,200 mg/kg. Statistically significant dose-related increases were found for DNA damage and cytochrome P-450 content at 2,550 and 4,200 mg/kg and for ornithine decarboxylase activity at ≥840 mg/kg. No changes in reduced glutathione content were found. Although minimal to mild vacuolar degeneration was observed in the hepatocytes of the 2,550 mg/kg–treated rats, no hepatic lesions were found in the other groups, including the high-dose group, and 1,4-dioxane had no effect on alanine aminotransferase activity.

In another study of the potential mechanism(s) of carcinogenicity of 1,4-dioxane, nasal turbinates and hepatocytes from male Fischer 344 rats treated with dioxane were examined for DNA repair as an indicator of DNA reactivity, for peroxisomal proliferation, and for cell proliferation as an indicator of promotional activity (Goldsworthy et al., 1991). Neither 1,4-dioxane nor one of its proposed metabolites, 1,4-dioxane-2-one, showed activity in the *in vitro* primary rat hepatocyte DNA repair assay when added to untreated hepatocytes in culture or when added to hepatocytes isolated from rats administered 1% (v/v) or 2% (v/v) 1,4-dioxane in the drinking water for one week to induce enzymes. In addition, administration of a single oral dose of 1,4-dioxane at ≤1,000 mg/kg or of ≤2% (v/v) 1,4-dioxane in drinking water for one week resulted in no activity in the *in vivo* hepatocyte DNA repair assay. No increase in relative liver weight or in the activity of palmitoyl CoA oxidase, an indicator of

peroxisomal proliferation, was found in rats given 1% (v/v) dioxane in the drinking water for five days. No increase in DNA synthesis, determined by tritiated thymidine incorporation, was found in the hepatocytes of rats after a single dose of 1,000 mg/kg. However, a two-fold increase in the hepatocyte labeling index was found in rats given 1% (v/v) dioxane in the drinking water for two weeks, suggesting to the investigators a role for cell proliferation in the induction of hepatocellular carcinoma. Regarding the mechanism of 1,4-dioxane–induced nasal turbinate carcinogenicity, nasoturbinate and maxilloturbinate nasal epithelial cells isolated from rats given 1% (v/v) dioxane in the drinking water for eight days followed by a single dose of ≤1,000 mg/kg by gavage showed no DNA repair activity. No significant increase in cell proliferation was found in the nasal turbinate site with the highest tumor formation rate (anterior third of the dorsal meatus) in the NCI (1978) study when rats in this study were administered 1% (v/v) dioxane in the drinking water for two weeks. Although Goldsworthy et al. (1991) noted that their protocols are generally accepted for detecting DNA repair or cell proliferation, they acknowledged the possibility that the two-week duration of exposure to 1,4-dioxane may have been insufficient for a proliferative response to be observed.

TOXICOKINETICS

Overview

The absorption of 1,4-dioxane following oral or inhalation exposure is rapid and virtually complete. Absorption after dermal exposure appears to be much less extensive. 1,4-Dioxane is widely distributed and rapidly metabolized in both humans and animals to HEAA or to its interconversion product 1,4-dioxane-2-one, both of which are rapidly and extensively excreted in the urine. Unchanged dioxane is excreted in the urine and the expired air. 1,4-Dioxane and its major metabolite show little tendency to accumulate, but metabolism to HEAA or 1,4-dioxane-2-one in rats is dose-dependent, becoming saturated at high doses, as discussed below.

Absorption

In a pharmacokinetic study, four healthy male volunteers were exposed to 50 ppm 1,4-dioxane vapor by inhalation for six hours (Young et al., 1977). The concentration of dioxane in the plasma increased rapidly to approximate levels of 1 μg/mL at 1 hour, 4.5 μg/mL at 1.5 hours, 9 μg/mL at 2 hours, and 10 μg/mL at 3 hours, after which a plateau was reached during the remainder of the exposure period, indicating that steady state was reached during the exposure period. The plasma concentration of the metabolite, HEAA, was about 2.5 μg/mL at five hours, 4 μg/mL at six hours of exposure, and peaked at 8 μg/mL at about seven hours (one hour after exposure ceased). Of the total dioxane dose, >99% was excreted in the urine as HEAA. The calculated total absorbed dose of dioxane was 5.4 mg/kg and the calculated rate was 76.1 mg/hr. To determine the amount in the body at six hours, the amount of dioxane and HEAA excreted in the urine during the six-hour exposure period was subtracted from the total dose, yielding a dose of 2.86 mg equivalent/kg at six hours. A simulation of plasma

dioxane concentrations after repeated exposures to 50 ppm dioxane for eight hours/day indicated that the peak concentration should occur at the end of each workday.

The absorption of 1,4-dioxane was also studied in male Sprague-Dawley rats after inhalation and oral exposure (Young et al., 1978). In the inhalation experiment, an absorbed dose of at least 71.9 mg/kg of 1,4-dioxane from the lungs was estimated in four rats exposed (head only) to 50 ppm dioxane vapor for six hours, based on the amounts of dioxane and HEAA excreted in the urine. These amounts were 6.8 μg of 1,4-dioxane and 21,271 μg of HEAA excreted in the urine over 48 hours. The concentration of dioxane in the plasma was 7.3 μg/mL at the end of exposure. By assuming 100% absorption from the lungs, a minute volume of 0.238 L/min was calculated.

In the oral experiment, ^{14}C-1,4-dioxane was administered to rats at single oral doses of 10, 100, or 1,000 mg/kg or multiple oral doses of 10 or 1,000 mg/kg/day for 17 days (Young et al., 1978). Data on the excretion of radioactivity in the urine and of ^{14}C-dioxane and $^{14}CO_2$ in the expired air indicate that after the single oral doses, gastrointestinal absorption of 1,4-dioxane was virtually complete within 24 hours of dosing with 10 mg/kg and within 72 hours of dosing with 100 or 1,000 mg/kg/day. After the single oral doses, 99% of the 10-mg/kg radioactive dose was excreted over 24 hours, and 86% of the 100-mg/kg dose and 76% of the 1,000-mg/kg dose were excreted over 72 hours. The percentage of expired ^{14}C-dioxane was 0.43% of the 10-mg/kg dose, 5% of the 100-mg/kg dose, and 25% of the 1,000-mg/kg dose. Excretion of $^{14}CO_2$ in the air (2–3%) or of radioactivity in the feces (0.95–2%) collected over 24 hours was not dose-dependent. Virtually complete gastrointestinal absorption of 1,4-dioxane also occurred after repeated dosing. In urine collected over 480 hours, 99% and 82% of the 10- and 1,00-mg/kg/day doses, respectively, were excreted. In the expired air, the percentage of the dose excreted as dioxane was 1% after the dose of 10 mg/kg/day and 8.86% after the 1,000-mg/kg/day dose. The percentage of the dose expired as $^{14}CO_2$ increased from 4% at the 10-mg/kg/day dose to 7% at the 1,000-mg/kg/day dose.

In rhesus monkeys to which ^{14}C-1,4-dioxane (4 μg/cm^2) in methanol or in skin lotion was applied to the unoccluded, clipped ventral surface of the forearm for 24 hours, dermal penetration was 2.3% of the applied dose in methanol and 3.4% of the applied dose in lotion, as determined from the urinary excretion of radioactivity over five days (Marzulli et al., 1981). A correction factor was used to account for radioactivity remaining in the body by measuring the five-day urinary excretion following parenteral administration. The authors, however, did not account for possible evaporation of 1,4-dioxane from the skin.

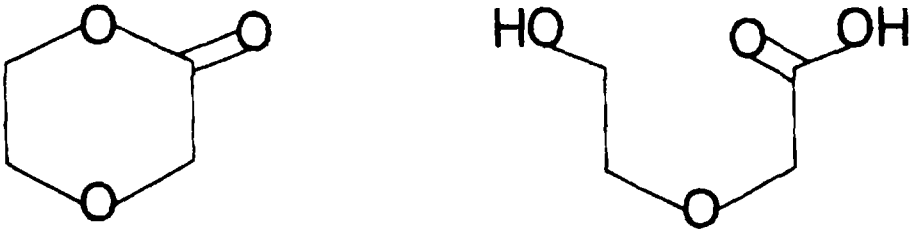
Distribution

The distribution of ^{3}H-1,4-dioxane was determined in male Sprague-Dawley rats after intraperitoneal administration of 6.97 mg/kg (Woo et al., 1977b). The radioactivity from 1,4-dioxane was widely distributed with concentrations of dioxane equivalents decreasing from 1 hour to 16 hours in the blood from 93.4 to 41.4 nmol/mL, in the liver from 59.1 to 24.2 nmol/g, in the kidney from 116.1 to 31.9 nmol/g, in the spleen from 49.6 to 30 nmol/g, in the lung from 52.2 to 23.2 nmol/g, in the colon from 56.1 to 27.7 nmol/g, and in skeletal muscle

5.3 to 28.1 nmol/g. The binding of radiolabel to macromolecules in the tissues was also ed with time. The binding of label was significantly higher in the liver, spleen, and than the other tissues. In most tissues, the binding of label increased for six hours, ed by decreases over the next ten hours; however, the binding in the lungs and kidneys ued to increase, consistent with excretion routes. Data on the subcellular distribution in revealed that most of the radiolabel was noncovalently bound in the cytosol. Covalent ng of radiolabel to macromolecules was highest in the nuclear fraction, followed by the chondrial and microsomal fractions and the whole homogenate. The binding of radiolabel acromolecules was nonspecific and not associated with DNA. No change was observed e macromolecular binding in the subcellular fractions of liver from rats pretreated with crosomal enzyme inducers, phenobarbital, PCBs, or methylcholanthrene. Furthermore, no crosomally mediated binding of radiolabel from ^{14}C- or ^{3}H-dioxane was found.

etabolism

As noted above, HEAA has been considered to be the major metabolite of 1,4-dioxane Young et al., 1977, 1978). However, a controversy exists whether 1,4-dioxane is metabolized o HEAA, which can cyclize to the 1,4-dioxane-2-one form (Braun and Young, 1977), or whether 1,4-dioxane is metabolized to 1,4-dioxane-2-one, which is readily converted to HEAA (Woo et al., 1977a, 1978). The two proposed candidate chemical structures, shown below, may readily interconvert under the chemical conditions used in the analytical work of isolation and identification, but neither of the reports (Braun and Young, 1977; Woo et al., 1977a) are definitive in the metabolite characterization. Thus, the identification of HEAA versus 1,4-dioxane-2-one as the major metabolite may depend on the analytical methods, and to date, this controversy has not been resolved.



1,4-Dioxane-2-one **β–Hydroxyethoxyacetic acid**

FIGURE 2. Structures of 1,4-dioxane-2-one and β–hydroxyethoxyacetic acid.

In some studies, HEAA has been identified in the urine of humans (Young et al., 1976, 1977) and male Sprague-Dawley rats (Braun and Young, 1977) as the major metabolite of 1,4-dioxane. Gas chromatography/mass spectrometry (GC/MS) analysis of the urine collected from five workers exposed to a time-weighted-average concentration of 1.6 ppm 1,4-dioxane for 7.5 hours at the end of the workday identified HEAA at a mean urinary concentration of 414 µmol/L and unchanged dioxane at a mean urinary concentration of 3.5 µmol/L (Young et al., 1976). The concentration of HEAA was therefore 118 times higher than the concentration of 1,4-dioxane, suggesting rapid and extensive metabolism.

In the inhalation pharmacokinetic study of four male volunteers exposed to 50 ppm 1,4-dioxane for six hours, urinary HEAA was found to account for >99% of the dose of 1,4-dioxane (Young et al., 1977). For analysis of HEAA in the urine or plasma by GC/MS, HEAA was methylated and the injection port (310°C) was filled with copper filings to catalyze the cyclization of HEAA to 1,4-dioxane-2-one. The concentration of dioxane in the plasma increased rapidly to approximately 10 µg/mL at three hours, after which a plateau was reached during the remainder of the exposure period. The plasma concentration of HEAA was about 2.5 µg/mL at five hours, 4 µg/mL at six hours of exposure, and peaked at 8 µg/mL at about seven hours (one hour after exposure ceased). The HEAA concentrations were higher than the dioxane concentrations after exposure. These data indicate that the metabolism of 1,4-dioxane begins during exposure and continues after exposure ceases. The half-life for elimination of HEAA in the urine was calculated as 2.7 hours. Metabolic clearance was 75 mL/min, suggesting that the metabolism of dioxane to HEAA increased the rate of removal of dioxane from 0.34 to 121 mL/min.

HEAA was also reported as the major metabolite of 1,4-dioxane in male Sprague-Dawley rats given a single oral dose of 1,000 mg/kg of ^{14}C-1,4-dioxane (Braun and Young, 1977). Identification techniques included: 1) two thin-layer chromatographic (TLC) systems. System 1 using *n*-butanol:acetone:water on silica gel, and System 2 using 95% ethanol water:5% ammonium hydroxide on silica gel; 2) ion-exchange column chromatography using a mobile phase of 0.001 N hydrochloric acid and measuring radioactivity by liquid scintillation counting; 3) GC using a thermal conductivity detector; 4) nuclear magnetic resonance (NMR) spectra in which samples were scanned undiluted or in hydrochloric acid solution to remove hydroxide absorption which interfered with the major metabolite absorption; and 5) GC/MS. The initial TLC analysis showed at least one major and two minor radioactivity compounds in the urine. The minor components were tentatively identified as unchanged dioxane and diethylene glycol. Chromatography of standard HEAA in TLC System 1 (neutral pH) resulted in two separate spots, one of which was HEAA and the other 1,4-dioxane-2-one. Cochromatography of HEAA with the radioactive urine from treated rats in TLC System 2 (alkaline pH) indicated that HEAA was identical with the major urinary metabolite. The presence of the two minor (15% of the radioactivity) and one major (85%) radioactive components was confirmed by ion-exchange chromatography and subsequent liquid scintillation counting. Standard HEAA and the major urinary metabolite required the same elution time. The results of NMR spectrometry of the fraction of eluant from the ion-exchange column containing the major metabolite were consistent with HEAA. Mass spectral analysis showed that HEAA, 1,4-dioxane-2-one, and the major urinary metabolite gave identical spectra consistent with 1,4-dioxane-2-one. The authors speculated that the on-column heating converted the HEAA to 1,4-dioxane-2-one. Therefore, a fraction of ion-exchange eluant containing the major metabolite was taken to dryness, redissolved in 0.1 N hydrogen chloride in methanol, and heated at 40°C for 30 minutes to form the methyl ester. After heating, excess acetic anhydride was added to remove water. GC/MS analysis of the resulting solution indicated that the metabolite was HEAA. The authors considered 1,4-dioxane-2-one to be an analytic artifact.

exposed to 50 ppm 1,4-
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nale Sprague-Dawley rats
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ess, redissolved in 0.1 N
to form the methyl ester.
GC/MS analysis of the
authors considered 1,4-

e findings of Braun and Young (1977) and Young et al. (1977), NIOSH (1977)
e following mechanism for the metabolism of 1,4-dioxane to HEAA: 1) initial
of an oxonium ion; 2) nucleophilic attack by water to open the ring, with the
the corresponding alcohol; 3) rapid reduction of the alcohol to the corresponding
d 4) rapid oxidation of the aldehyde to HEAA.

ve pharmacokinetic study in male Sprague-Dawley rats exposed to 1,4-dioxane
routes, HEAA was identified as the metabolite, and the data indicated that the
of 1,4-dioxane to HEAA became saturated as doses increased (Young et al.,
se experiments, HEAA concentrations were analyzed by GC/MS in a method by
jection port was filled with copper filings to catalyze the cyclization of HEAA to
-2-one. In one set of experiments, ^{14}C-1,4-dioxane was administered to rats at
doses of 10, 100, or 1,000 mg/kg or multiple oral doses of 10 or 1,000 mg/kg/day
. After the single oral doses, the rats excreted a decreasing percentage of the dose
as the doses increased, with 99% of the 10-mg/kg dose excreted over 24 hours
the 100-mg/kg dose and 76% of the 1,000-mg/kg dose excreted over 72 hours.
tage of expired ^{14}C-dioxane increased from 0.43% of the 10-mg/kg dose to 5% of
/kg dose to 25% of the 1,000-mg/kg dose. The dose-dependent pattern of excretion
at the metabolic pathway leading to the excretion of the major urinary metabolite
rated as the dose increased. Similar dose-dependent excretion of radioactivity in
nd of dioxane in the expired air was observed after repeated dosing. In urine
ver 480 hours, 99% and 82% of the 10- and 1,000-mg/kg/day doses, respectively,
d. In the expired air, the percentage of the dose excreted as dioxane was 1% after
10 mg/kg/day and 9% after the 1,000-mg/kg/day dose. The percentage of the dose
$^{14}CO_2$ increased from 4% at the 10-mg/kg/day dose to 7% at the 1,000-mg/kg/day
tion of dioxane in the expired breath decreased from 25% after the single dose of
g to 9% after the repeated 1,000-mg/kg/day dose. Excretion of $^{14}CO_2$ increased
7%. The decrease of expired unchanged dioxane at the high dose suggested that
sponsible for 1,4-dioxane metabolism are induced after repeated administration of
s.

e study, male rats were injected intravenously with 3, 10, 30, 100, or 1,000 mg/kg
e to determine the plasma concentrations of dioxane as a function of time (Young
8). At the low doses of 3 and 10 mg/kg, elimination of dioxane from plasma was
a half-life of 1.1 hours. At higher doses, elimination from plasma became
ely slower and biphasic with increasing dose, indicating saturation of some process
were high. Clearance rates calculated from areas under the plasma elimination
ealed that clearance decreased progressively by 92% from 3.33 mL/min at 3 mg/kg
L/min at 1,000 mg/kg. Metabolic clearance decreased from 2.82 mL/min at 10
0.17 mL/min at 1,000 mg/min, indicating saturation of metabolic conversion of
to the major metabolite. In rats given 10 or 1,000 mg/kg of ^{14}C-dioxane
usly, total excretion of dioxane in both urine and expired air amounted to 5% of the
dose and 38% of the 1,000-mg/kg dose. Excretion of HEAA in the urine accounted

for 92% of 10-mg/kg dose and 60% of the 1,000-mg/kg dose, indicating that metabolism became saturated at high doses.

In four rats exposed to 50 ppm dioxane vapor head-only for six hours, 75% of the amount of dioxane excreted in the urine over 48 hours was excreted during the six-hour exposure period (Young et al., 1978). Conversely, only 36% of the amount of HEAA excreted in the urine over 48 hours was excreted during the six-hour exposure period. HEAA accounted for >99.9% of the total urinary excretion of the inhaled dioxane.

1,4-Dioxane-2-one was reported as the major urinary metabolite in male Sprague-Dawley rats injected intraperitoneally with 1,000, 2,000, 3,000, or 4,000 mg/kg ^{14}C-1,4-dioxane (Woo et al., 1977a). The pH of the urine collected from the rats was adjusted to between 4.0 and 4.5 before analysis by GC or NMR. The gas chromatogram showed two major peaks, one with a retention time of 7 minutes corresponding to unchanged 1,4-dioxane, and the other with a retention time of 32 minutes corresponding to the major metabolite. The appearance of the metabolite peak depended upon the pH, with no peak detected when the pH of the urine was raised to >12, but with reappearance of the peak upon reacidification. The excretion of the metabolite was dose-dependent: about 450 mg/kg of metabolite at a dioxane dose of 1,000 mg/kg; about 850 mg/kg of metabolite at a dioxane dose of 2,000 mg/kg; about 1,150 mg/kg of metabolite at a dioxane dose of 3,000 mg/kg; and about 1,250 mg/kg of metabolite at a dioxane dose of 4,000 mg/kg. Thus, the excretion of the metabolite started to level off at the dose of 3,000 mg/kg. The excretion of the metabolite was maximal between 20 and 28 hours and virtually complete at 48 hours after the dioxane dose. The amount of unchanged dioxane excreted accounted for 3%, 7%, 11%, and 11% of the doses of 1,000, 2,000, 3,000, and 4,000 mg/kg, respectively. These data imply that the metabolism of 1,4-dioxane to 1,4-dioxane-2-one approaches saturation at an intraperitoneal dose of dioxane of 3,000 mg/kg. Treatment of the rats with diethylene glycol resulted in the same metabolite identified for 1,4-dioxane, which was almost entirely excreted within 16 hours, suggesting that diethylene glycol may be an intermediate metabolite of 1,4-dioxane. NMR, infrared spectrometry, and GC methods were used to identify the major urinary metabolite as 1,4-dioxane-2-one. The standard 1,4-dioxane-2-one exhibited identical NMR, infrared, and GC spectra as the dioxane metabolite. The authors noted that the identification was supported by the facts that 1,4-dioxane-2-one is a lactone with a six-membered ring, which polymerizes spontaneously to linear polymers on standing, and that 1,4-dioxane-2-one can be reversibly converted to HEAA by adjusting the pH of the solution; alkaline conditions favor the HEAA form. In a confirmatory experiment, rats were given 50 μCi ^{14}C-1,4-dioxane along with 3,000 mg/kg of unlabeled dioxane. Of the radiolabeled compounds present in the urine collected over 48 hours, 73–86% was recovered as 1,4-dioxane-2-one and the remainder was recovered as unchanged dioxane. The authors proposed three possible pathways whereby dioxane 1) is hydrolyzed to diethylene glycol, followed by oxidation of one of the hydroxyl groups; 2) is directly converted via a possible ketoperoxyl radical intermediate; or 3) undergoes α-hydroxylation, followed by the oxidation of the hemiacetal or hydroxyaldehyde intermediate. Woo et al. (1977a) acknowledged that Braun and Young (1977) reported HEAA as the major urinary metabolite, but noted that these

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hydroxyacids rarely exist as such in the pure state or in aqueous solution except in the form of salts and that the tendency of these hydroxyacids to form lactones is very strong. Interestingly, the previously discussed TOPKAT SAR analysis predicted that the 1,4-dioxane-2-one metabolite would be strongly mutagenic, but that neither 1,4-dioxane nor the HEAA metabolite would be mutagenic (Gombar, 1995). In view of the numerous reports of weak genotoxic activity for 1,4-dioxane, these TOPKAT predictions tend to support the premise of Woo et al. (1977a) that formation of the lactone metabolite (1,4-dioxane-2-one) would be much more likely than the hydroxyacid metabolite (HEAA).

In male Sprague-Dawley rats that received 3,000 mg/kg ^{14}C-1,4-dioxane intraperitoneally, the urinary excretion of 1,4-dioxane-2-one was about 300 mg metabolite/kg over 24 hours (Woo et al., 1977c, 1978). Pretreatment of rats with phenobarbital or PCBs, but not methylcholanthrene, prior to intraperitoneal dosing with 3,000 mg/kg ^{14}C-1,4-dioxane resulted in significantly increased amounts of the urinary metabolite excreted (^{14}C-1,4-dioxane-2-one determined by GC), suggesting that the metabolism of 1,4-dioxane is mediated by cytochrome P-450, rather than cytochrome P-448. The separation of ^{14}C-1,4-dioxane-2-one from the urine was achieved by alkalinizing the urine sample to pH >12 with 10% sodium hydroxide to convert the 1,4-dioxane-2-one to HEAA, which was then applied to an anion-exchange column.

1,4-Dioxane-2-one was found to be about seven times more toxic than 1,4-dioxane based on the results of intraperitoneal LD_{50} determinations in male Sprague-Dawley rats (Woo et al., 1977c, 1978). The acute intraperitoneal LD_{50} values were 790 mg/kg for 1,4-dioxane-2-one and 5,300 mg/kg for 1,4-dioxane. Pretreatment of the rats with PCBs before 1,4-dioxane treatment resulted in a lowering of the LD_{50} of 1,4-dioxane to 4,400 mg/kg. Pretreatment of the rats with phenobarbital or methylcholanthrene had no effect on the LD_{50} of 1,4-dioxane. The mixed function oxidase inhibitor, 2,4-dichloro-6-phenylphenoxyethylamine (DPNE), was found to protect the PCB-pretreated rats from the enhanced lethality of 1,4-dioxane, further indicating the involvement of mixed-function oxidases in the metabolism of 1,4-dioxane.

1,4-Dioxane itself appears to induce microsomal enzymes, as indicated by increased *in vitro* activity of hepatic aniline hydroxylase and aminopyrine N-demethylase after repeated dosing of male Sprague-Dawley rats with 1,000 mg/kg/day (Dietz et al., 1982) and by the increased *in vivo* metabolism of 1,4-dioxane after repeated dosing of rats at 1,000 mg/kg/day (Young et al., 1978). In addition, increased liver enzyme activity was observed in female Hindustan strain mice given 2,000 mg/kg 1,4-dioxane orally (Pawar and Mungikar, 1976).

Excretion and Elimination

In the pharmacokinetic study of four healthy male volunteers exposed to 50 ppm 1,4-dioxane vapor by inhalation for six hours, the plasma dioxane levels dropped linearly from a steady state concentration of about 10 µg/mL during exposure to nondetectable levels within six hours after exposure (Young et al., 1977). The half-life for elimination from plasma was 59 minutes. The data indicated a first-order, one-compartment model that did not become

saturated at 50 ppm. The plasma concentration of the metabolite HEAA was about 2.5 µg/mL at five hours, 4 µg/mL at six hours of exposure, and peaked at 8 µg/mL at about seven hours (one hour after exposure ceased), followed by a linear decrease. Of the total dioxane excreted in the urine, 90% was excreted in the six-hour exposure period, with no dioxane detected after 12 hours (6 hours after exposure). The half-life for elimination of 1,4-dioxane, calculated from urinary excretion data, which is appropriate for a one-compartment open model, was 48 minutes, showing no statistically significant difference from the half-life for elimination from plasma. Of the total dioxane dose, >99% was excreted in the urine as HEAA. Of the total HEAA excreted, 47% was excreted in the six-hour exposure period, and excretion was complete at 24 hours (18 hours after exposure). The half-life for excretion of HEAA in the urine was calculated as 2.7 hours. The investigators calculated pharmacokinetic parameters, which showed that renal clearance of HEAA was 121 mL/min, suggesting clearance by glomerular filtration, since the creatinine clearance rate was 124 mL/min. The renal clearance of dioxane was 0.34 mL/min, suggesting poor renal clearance. The metabolic clearance was 75 mL/min, suggesting that the metabolism of dioxane to HEAA increased the rate of removal of dioxane from 0.34 to 121 mL/min. A simulation of plasma dioxane concentrations after repeated exposures to 50 ppm dioxane for eight hours/day indicated that the peak concentration will occur at the end of each workday and will never be exceeded on subsequent days. Similarly, no HEAA will accumulate with repeated exposures to the same level of 1,4-dioxane.

The excretion of 1,4-dioxane was also studied in rats after inhalation, oral, and intravenous exposure (Young et al., 1978). In the inhalation experiment, four rats exposed (head only) to 50 ppm dioxane vapor for 6 hours excreted 5.1 µg of dioxane in the urine during the six-hour exposure periods and 1.7 µg dioxane in the urine over the next 42 hours. Thus, 75% of the amount of dioxane excreted in the urine over 48 hours was excreted during the six-hour exposure period. Urinary excretion of HEAA amounted to 7,613 µg during the six-hour exposure and 13,659 µg over the next 42 hours, indicating that only 36% of the amount of HEAA excreted in the urine over 48 hours was excreted during the six-hour exposure period. HEAA accounted for >99.9% of the total urinary excretion of the inhaled dioxane. The concentration of dioxane in the plasma decreased in a first-order rate manner from 7.3 µg/mL at the end of exposure to nondetectable levels at 11 hours (five hours after exposure). The half-life was one hour.

^{14}C-1,4-Dioxane was administered to rats at single oral doses of 10, 100, or 1,000 mg/kg or multiple oral doses of 10 or 1,000 mg/kg/day for 17 days (Young et al., 1978). In both experiments, the primary route of excretion was via urine, with considerably less radioactivity excreted in expired air, followed by fecal excretion. After the single oral doses, the rats excreted a decreasing percentage of the dose in the urine as the doses increased, with 99% of the 10-mg/kg dose excreted over 24 hours and 86% of the 100-mg/kg dose and 76% of the 1,000-mg/kg dose excreted over 72 hours. The percentage of expired ^{14}C-dioxane increased from 0.43% of the 10-mg/kg dose to 5% of the 100-mg/kg dose to 25% of the 1,000-mg/kg dose. Excretion of $^{14}CO_2$ in the air (2–3%) or of radioactivity in the feces (0.95–2%)

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In the same study, male rats were injected intravenously with 3, 10, 30, 100, or 1,000 mg/kg 1,4-dioxane to determine the plasma concentrations of dioxane as a function of time (Young et al., 1978). At the low doses of 3 and 10 mg/kg, elimination from plasma was linear with a half-life of 1.1 hours. At higher doses, elimination from plasma became progressively slower and biphasic with increasing dose, indicating saturation of some process. Clearance rates calculated from areas under the plasma elimination curves revealed that clearance decreased progressively by 92% from 3.33 mL/min at 3 mg/kg to 0.25 mL/min at 1,000 mg/kg. The renal clearance of dioxane was 0.032 mL/min at 10 mg/kg and 0.029 mL/min at 1,000 mg/kg, indicating reabsorption of dioxane by the kidney. Pulmonary clearance was 0.032 mL/min at 10 mg/kg and 0.055 mL/min at 1,000 mg/kg; however, this difference was not great enough to account for the large dose-dependent change in plasma clearance. Metabolic clearances decreased from 2.82 mL/min at 10 mg/kg to 0.17 mL/min at 1,000 mg/kg, indicating saturation of metabolic conversion of dioxane. In rats given 10 or 1,000 mg/kg of ^{14}C-dioxane intravenously, total dioxane excreted in the expired air was 1% of 10-mg/kg dose and 27% of the 1,000-mg/kg dose, which followed the same pattern as dioxane elimination from plasma at these doses and indicates that excretion of dioxane in expired air is a first-order process. Similar relationships were found for dioxane elimination in urine, which also indicates a first-order process. Total excretion of dioxane in the urine amounted to 4% of the 10-mg/kg dose and 11% of the 1,000-mg/kg dose. Total excretion of dioxane in both urine and expired air amounted to 5% of the 10-mg/kg dose and 38% of the 1,000-mg/kg dose. Excretion of HEAA in the urine accounted for 92% of 10-mg/kg dose and 60% of the 1,000-mg/kg dose, indicating that metabolism became saturated at high doses.

In male Sprague-Dawley rats injected intraperitoneally with 1,000, 2,000, 3,000, or 4,000 mg/kg 1,4-dioxane, the urinary excretion of the metabolite (1,4-dioxane-2-one) was dose-dependent: about 450 mg/kg of metabolite at a dioxane dose of 1,000 mg/kg; about 850 mg/kg of metabolite at a dioxane dose of 2,000 mg/kg; about 1,150 mg/kg of metabolite at a dioxane dose of 3,000 mg/kg; and about 1,250 mg/kg of metabolite at a dioxane dose of 4,000 mg/kg (Woo et al., 1977a). Thus, the excretion of the metabolite started to level off as the

dioxane dose approached 3,000 mg/kg. The excretion of the metabolite was maximum between 20 and 28 hours, and virtually complete at 48 hours after the dioxane dose. The amount of unchanged dioxane excreted accounted for 3%, 7%, 11%, and 11% of the doses of 1,000, 2,000, 3,000, and 4,000 mg/kg, respectively. In a confirmatory experiment, rats were given 50 μCi ^{14}C-1,4-dioxane along with 3,000 mg/kg of unlabeled dioxane. Of the radiolabeled compounds present in the urine collected over 48 hours, 73–86% was recovered as 1,4-dioxane-2-one and the remainder was recovered as unchanged dioxane.

RISK ASSESSMENT APPROACHES

Several risk assessments that have been performed using the Linearized Multistage Model for carcinogenicity and the threshold approach for noncancer end points are discussed below

The Office of Drinking Water of the United States Environmental Protection Agency provides Drinking Water HAs as guidance for the protection of public health (EPA, 1988a; IRIS, 1994). HAs are generally determined for one-day, ten-day, longer-term (up to seven years), and lifetime exposure if data allow. However, HAs for lifetime exposure are not determined for chemicals that are classified as Group A or Group B carcinogens. Thus, EPA has recommended one-day and ten-day HAs for 1,4-dioxane, but a longer-term HA was not calculated because of 1,4-dioxane's carcinogenic potential and because of the potential for chlorination of 1,4-dioxane in water to produce a more toxic chlorinated compound. Chlorinated dioxanes are up to 1,000 times more toxic than 1,4-dioxane alone (Woo et al., 1980). 1,4-Dioxane has been classified by EPA in Group B2, probable human carcinogen (EPA, 1988c; IRIS, 1994); therefore, a lifetime HA has not been calculated (EPA, 1988a). The one-day HA of 1,4-dioxane of 4.12 mg/L (4,120 μg/L) was calculated based on a study by Fairley et al. (1934), in which 1,4-dioxane was administered intravenously to rabbits, and the ten-day HA of 0.412 mg/L (412 μg/L) was calculated by dividing the one-day HA by ten (EPA, 1988a).

The EPA also has not derived a chronic oral Reference Dose (RfD) for 1,4-dioxane because of its classification as a B2 carcinogen. EPA has performed a carcinogenicity assessment for lifetime exposure and has calculated a quantitative estimate of carcinogenic risk from oral exposure (EPA, 1988a,c; IRIS, 1994). The quantitative estimate of carcinogenic risk of 1,4-dioxane was calculated using the Linearized Multistage Model for the tumor data for squamous cell carcinoma of the nasal turbinates in male Osborne-Mendel rats exposed to 1,4-dioxane in the drinking water study by NCI (1978). The calculations result in a slope factor of 1.1×10^{-2} $(mg/kg/day)^{-1}$, a unit risk of 3.1×10^{-7} $(\mu g/L)^{-1}$, and drinking water concentrations of 300 μg/L for an upper bound lifetime cancer risk of 10^{-4} (1 in 10,000), 30 μg/L for an upper bound lifetime cancer risk of 10^{-5} (1 in 100,000), and 3 μg/L for an upper bound lifetime cancer risk of 10^{-6} (1 in 1,000,000). Previous correspondence with the MDPH indicated that the Linearized Multistage Model in estimating cancer risk for 1,4-dioxane was appropriate (ATSDR, 1989). "Even though disagreement among scientists surrounds the Linearized Multistage Model and its ability to estimate cancer risk for both genotoxic and

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...ung (1989) presented risk assessments based on all of the statistically significant tumor ...onses: hepatocellular carcinomas or adenomas in male mice, hepatocellular carcinomas in ... mice, hepatocellular carcinomas in female mice, hepatocellular carcinomas or adenomas ...e female mice, nasal carcinomas in male rats, nasal carcinomas in female rats, and ...tocellular carcinomas in female rats in the NCI (1978) study and all hepatic tumors, ...tocellular carcinomas, and nasal tumors in rats in the Kociba et al. (1974) study, using ...Linearized Multistage Model. The slope factors ranged from 3.83×10^{-5} (mg/kg/day)$^{-1}$ ...nasal carcinomas in rats in the Kociba et al. (1974) study to 1.83×10^{-2} (mg/kg/day)$^{-1}$ for ...tocellular carcinomas or adenomas in female mice in the NCI (1978) study. The drinking ...r concentrations at an upper bound lifetime cancer risk of 1 in 1,000,000 corresponding ...ese slope factors, assuming that a 70-kg human consumes two liters of water per day, are ...µg/L and 2 µg/L, respectively.

...mentioned in the Introduction, since 1986, the State of Michigan based risk management ...sions for 1,4-dioxane in drinking water using a calculated upper bound risk to humans of ...loping cancer from exposure to 1,4-dioxane of 1 in 1,000,000 at a concentration of 2 ... in drinking water. The concentration of 2 µg/L was obtained by using the Linearized ...istage Model for the tumor data for hepatocellular carcinoma or adenoma in female mice ...e NCI (1978) study. This drinking water concentration is only slightly lower than the 3 ... drinking water concentration that is obtained using the data for nasal turbinate ...noma in male rats in the NCI (1978) study in the Linearized Multistage Model, which ... calculated by EPA and appears in IRIS (1994). However, the State of Michigan is ...idering an interim drinking water guideline range of 3–15 µg/L based on the risk ...sment published in IRIS (1994) (MDPH, 1993). The range of 3–15 µg/L corresponds to ...r bound lifetime cancer risks of 1 in 1,000,000 to 5 in 1,000,000.

...ently, in attempts to take into account the pharmacokinetics of 1,4-dioxane, ...iologically based pharmacokinetic (PBPK) models have been used to predict the internal ... of 1,4-dioxane or HEAA delivered to the target organ (liver) from the doses of 1,4- ...ane in the animal bioassays. The surrogates for target doses to the liver were then utilized ...e Linearized Multistage Model to estimate the cancer risk for humans exposed to low ...s. In one such analysis, Leung and Paustenbach (1990) used the liver tumor data in rats in ...study by Kociba et al. (1974), and calculated that the dose surrogate in humans most ...y to be associated with a tumorigenic response (Maximum Likelihood Estimate or MLE) ...risk of 1 in 1,000,000 is 89 µmol/L (784 µg/L) and of 1 in 100,000 is 280 µmol/L ...68 µg/L). These MLEs are equivalent to administered doses of about 34 mg/kg/day for a ...level of 1 in 1,000,000 and 59 mg/kg/day for a risk level of 1 in 100,000. The 95% lower ...idence limits on the dose surrogate are 0.128 µmol/L (11 µg/L) and 1.28 µmol/L (113 ...L) for upper bound lifetime cancer risks of 1 in 1,000,000 and 1 in 100,000, respectively.

corresponding to administered doses of 0.08 and 0.8 mg/kg/day, respectively. Assuming lifetime drinking water consumption of 2 L/day by a 70-kg human, these doses are equal to 2.8 mg/L (2,800 µg/L) at a risk level of 1 in 1,000,000 and 28 mg/L (28,000 µg/L) at a risk level of 1 in 100,000. In another PBPK analysis, Reitz et al. (1990) calculated a risk-specific water concentration of 20,000 µg/L for upper bound lifetime cancer risk of 1 in 100,000, calculated to represent the lower 95% confidence limit on administered dose producing a lifetime increase in risk of developing liver cancer. The 20,000 µg/L concentration represented a weighted average of the four values obtained from two dose surrogates: the average area under the liver concentration/time curve and the average area under the metabolite concentration/time curve for the combined liver tumor data from male and female rats in both the NCI (1978) and Kociba et al. (1974) data and the mouse tumor data from male and female mice from the NCI (1978) study.

A threshold approach to assess the risk of 1,4-dioxane using a NOAEL (no-observed-adverse-effect level) has also been suggested. MDPH (1993) has noted that while the Office of Drinking Water of EPA does not recommend a threshold approach to derive drinking water guidelines for chemicals classified as B2 carcinogens, it has used a threshold approach for Group C carcinogens (possible human carcinogens), applying an additional uncertainty factor 10 to account for possible carcinogenicity. This approach has been used to derive a lifetime HA for atrazine (EPA, 1988d). MDPH (1993) suggested that a risk assessment for 1,4-dioxane could be based on a threshold approach (RfD) if 1,4-dioxane were classified in Group C. However, according to EPA (1986a), Group C is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. 1,4-Dioxane was carcinogenic in both sexes of at least two species of rodents; hence, the evidence in animals is sufficient to classify 1,4-dioxane in Group B. Since the evidence in humans is inadequate, 1,4-dioxane is classified as a B2 rather than a B1 carcinogen. EPA would consider modifying a classification from B2 to B1 based on a number of factors such as short-term test results and biochemical, comparative metabolism, and pharmacokinetic findings, but EPA (1986a) does not indicate any basis for reclassifying Group B2 to Group C based on whether a chemical is genotoxic or not or on pharmacokinetic considerations. Furthermore, in a recent communication, ATSDR was informed that EPA has no current plan to conduct a reevaluation of the carcinogen classification of 1,4-dioxane (EPA, 1995).

Hartung (1989) has presented a risk assessment in which the NOAEL of 9.6 mg/kg/day for hepatic and renal effects in male rats in the drinking water study by Kociba et al. (1974) is divided by an uncertainty factor of 100 (10 for interspecies variability and 10 for intraspecies variability), yielding a proposed RfD of 0.096 mg/kg/day. The corresponding drinking water concentration by a 70-kg human consuming two liters of water per day would be 3.36 mg/L (3,336 µg/L). In a similar threshold approach, MDPH (1993) multiplied the drinking water concentration of 3.36 mg/L (3,336 µg/L) by a factor of 0.20, which is often used by EPA to represent the relative source contribution (RSC) from water for lifetime HAs (EPA, 1988d), and divided the drinking water concentration by an additional factor of 10 to account for

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possible carcinogenicity, yielding a possible drinking water guideline of 67 µg/L (MDPH, 1993).

Reitz et al. (1990) also applied their PBPK analysis to a threshold approach (safety factor method). Dose surrogates from the average under the liver concentration/time curves of 257 mg•hr/L for the 0.1% drinking water level, which the authors stated was the NOAEL for tumors (the NOAEL of 0.01% for noncancer effects was not used) in the Kociba et al. (1974) study, and of 109 mg•hr/L for the 111 ppm inhalation concentration (about 105 mg/kg), which was a NOAEL in the Torkelson et al. (1974) study, were used. These dose surrogates were divided by a factor of 100, and a human exposure condition producing corresponding values of the area under the liver concentration/time curve were found. The "human virtually safe doses" of 51,000–118,000 µg/L in water were calculated.

DISCUSSION

1,4-Dioxane is used extensively as a solvent for many organic products and is an ingredient in many consumer products (IARC, 1976; NIOSH, 1977). Although technical grade 1,4-dioxane is >99.9% pure, it may contain bis(2-chloroethyl) ether as an impurity (HSDB, 1995). In the environment, 1,4-dioxane is removed from ambient air within a few days via reaction with hydroxyl radicals (Cuppitt, 1980; Grosjean, 1990). It is expected to be resistant to hydrolysis in the environment. In water and soil, it is resistant to microbial degradation (Mills and Stack, 1954; Heukelekian and Rand, 1955; Ludzack and Ettinger, 1960; Sasaki, 1978; Kawasaki, 1980; Francis, 1982) and does not bind strongly to organic matter (Lyman and Loreu, 1987), indicating a potential to leach readily into groundwater. 1,4-Dioxane has been found in groundwater (Clark, 1987a,b; Ohio EPA, 1987; Brode and Minning, 1988), in surface water (Konasewich et al., 1978, Great Lakes Water Quality Board, 1986; Dietrich et al., 1988), and in well water (CEQ, 1981; DeWalle and Chian, 1981; Brode and Minning, 1988).

As noted in the Introduction, the State of Michigan, Department of Public Health, is involved in a cleanup of a contaminated aquifer near Ann Arbor, Michigan, and has requested assistance from ATSDR in reviewing relevant information on 1,4-dioxane and the current Michigan guideline, which is 2 µg/L in drinking water based on a calculated upper bound risk to humans of developing cancer from exposure to 1,4-dioxane of 1 in 1,000,000 (MDPH, 1994). Because 1,4-dioxane has been classified as a probable human carcinogen (Group B2) by EPA, the Office of Drinking Water of EPA has not recommended a lifetime HA as a guideline for drinking water. EPA's risk assessment of 1,4-dioxane is based on the carcinogenicity with drinking water concentrations of 3 µg/L at an upper bound lifetime cancer risk of 1 in 1,000,000, 30 µg/L at an upper bound lifetime cancer risk of 1 in 100,000, and 300 µg/L at upper bound lifetime cancer risk of 1 in 10,000. The State of Michigan is considering adopting a drinking water guideline of 3–15 µg/L based on the EPA drinking water concentration of 3 µg/L for an upper bound lifetime cancer risk range of 1 in 1,000,000 to 5 in 1,000,000 (MDPH, 1993).

Three major issues are related to the risk assessment of 1,4-dioxane:

1. ***The contention that toxic and carcinogenic effects of 1,4-dioxane occur at doses at which the metabolism of 1,4-dioxane becomes saturated, leading to an increased body burden of 1,4-dioxane. This issue has also led to questions regarding whether a threshold approach for the risk assessment of 1,4-dioxane is more appropriate.***

2. ***Whether or not 1,4-dioxane possesses any genotoxic activity and, hence, whether 1,4-dioxane possesses some initiation activity in addition to its demonstrated promotion activity.***

3. ***Whether chemicals that are carcinogenic via a genotoxic mechanism should be treated differently than chemicals that are carcinogenic via an epigenetic mechanism, such as inducing cell proliferation. Some scientists consider nongenotoxic carcinogens to possess a threshold for carcinogenicity and question the appropriateness of applying low-dose extrapolation models, such as the Linearized Multistage Model.***

Each of these issues is discussed in detail below.

Saturation of 1,4-Dioxane Metabolism

Some investigators contend that cancer and noncancer toxic effects of 1,4-dioxane occur only at doses at which the detoxifying metabolism becomes saturated. Pharmacokinetic studies, discussed above in the Toxicokinetics section and summarized below, indicate that ***the metabolism of 1,4-dioxane becomes saturated as doses of 1,4-dioxane increase. However, the level at which the metabolism becomes saturated and whether the metabolism represents a detoxifying mechanism have not been resolved.***

Pharmacokinetic studies of 1,4-dioxane have been performed in humans exposed by inhalation to 50 ppm for six hours (Young et al., 1977) and in rats treated orally by gavage at single doses or at repeated daily doses up to 1,000 mg/kg, by inhalation to 50 ppm for six hours, or by intravenous injection at doses up to 1,000 mg/kg (Young et al., 1978). These studies indicate that 1,4-dioxane is rapidly and extensively absorbed from the lungs and the gastrointestinal tract, and is extensively metabolized to a product that is rapidly excreted in the urine. Unchanged dioxane is excreted in the urine and expired air. 1,4-Dioxane and its major urinary metabolite showed little tendency to accumulate after single or repeated exposure. The kinetics of plasma clearance and urinary and expiratory excretion of dioxane and its urinary metabolite in rats in the pharmacokinetic study by Young et al. (1978) indicated that metabolism of dioxane to its major urinary metabolite started to become saturated at doses ≥100 mg/kg.

Young et al. (1978) stated that the correlation of the dose-dependent fate of dioxane with the results of toxicological studies in rats supports a conclusion that there is an apparent threshold

e toxic effects of dioxane which coincides with saturation of the metabolic pathway for toxification. As discussed above in Health Effects in Animals, toxic effects of dioxane s first seen at doses ≥94 mg/kg/day in rats exposed via drinking water. However, ***a roversy exists regarding the form of the major urinary metabolite as it is produced in . This controversy has ramifications regarding whether the metabolism represents a ifying mechanism or whether the metabolite is more toxic than 1,4-dioxane. It also s questions regarding doses at which the metabolism of 1,4-dioxane becomes rated.***

e investigators have identified HEAA in the urine of humans (Young et al., 1976, 1977) male Sprague-Dawley rats (Braun and Young, 1977) as the major urinary metabolite. wever, other investigators have identified 1,4-dioxane-2-one as the major urinary abolite in male Sprague-Dawley rats (Woo et al., 1977a,c, 1978). HEAA and 1,4-dioxane-ne are readily interconvertible depending on pH and/or temperature, and the identification the metabolite may depend on the conditions used in the analysis (see *Metabolism* in xicokinetics section, p. 17). HEAA is the predominant form at alkaline pH. Woo et al. 977a, 1978) maintain that 1,4-dioxane-2-one is the form that is produced *in vivo* and creted in the urine. On the other hand, Braun and Young (1977) maintain that HEAA is the m that is produced *in vivo* and excreted in the urine. Woo et al. (1977a) acknowledged that raun and Young (1977) reported HEAA as the major urinary metabolite, but noted that these ydroxyacids rarely exist as such in the pure state or in aqueous solution except in the form of lts and that the tendency of the hydroxyacids to form lactone is very strong. It is reasonable assume that methylating the urinary sample, as was done by Braun and Young (1977) and oung et al. (1977, 1978), would stabilize the urinary metabolite in the methylated-HEAA rm to the extent that high temperatures and copper catalysis were required to cyclize the EAA to 1,4-dioxane-2-one during the GC/MS analytical method. No additional studies to solve which form of the metabolite is produced *in vivo* were identified in the literature.

The identification of the* in vivo *form of the metabolite is important regarding whether the metabolism represents a detoxifying mechanism or whether the metabolite is more toxic than 1,4-dioxane. No information was located on the toxicity of HEAA, but Young et al. (1978) considered the metabolism of 1,4-dioxane to represent a detoxifying mechanism, because doses at which saturation of metabolism of 1,4-dioxane began to occur (≥100 mg/kg) in rats were similar to the doses at which toxic effects (≥94 mg/kg/day) were observed in rats in the Kociba et al. (1974) study. On the other hand, Woo et al. (1978) determined that 1,4-dioxane-2-one was about seven-fold more toxic than 1,4-dioxane based on intraperitoneal LD_{50} determinations. In addition, Woo et al. (1978) noted that while the toxic effects and carcinogenicity of 1,4-dioxane-2-one have not been studied, a number of saturated and unsaturated lactones are carcinogenic, indicating a potential for 1,4-dioxane-2-one likewise to be carcinogenic. This possibility is supported by the TOPKAT SAR analyses that predict that both 1,4-dioxane and its 1,4-dioxane-2-one metabolite would be carcinogenic (Blake, 1995; Gombar, 1995). In addition, it is interesting to note that although 1,4-dioxane itself was not predicted to be mutagenic, the 1,4-dioxane-2-one metabolite was predicted to be a mutagen

(Gombar, 1995), thereby providing a plausible explanation and support for the weak genotoxic activity variously reported for 1,4-dioxane.

Both Young et al. (1978) and Woo et al. (1977a) demonstrated that metabolism of 1,4-dioxane to its major metabolite becomes saturated as the dose of 1,4-dioxane increases. Based on plasma clearance and excretion data, Young et al. (1978) found that the percentage of HEAA started to decrease at 100 mg/kg and declined more at 1,000 mg/kg in rats that were treated with gavage doses of 1,4-dioxane. However, Woo et al. (1977a) found that as the intraperitoneal dose of 1,4-dioxane in rats increased from 1,000 to 4,000 mg/kg, the amount of 1,4-dioxane-2-one excreted in the urine started to level off at a dose of 3,000 mg/kg. The difference in the dose levels at which the metabolism of 1,4-dioxane appears to become saturated in these studies may have been influenced by the route of administration. Oral dosing with 1,4-dioxane appears to result in virtually complete absorption by the gastrointestinal tract, suggesting that the differences are not due to absorption differences. A first-pass phenomenon to the liver would be expected for both the oral and the intraperitoneal routes; however, whether the first-pass to the liver would occur to the same extent for the two routes is not known. No additional studies were located in the literature to resolve these discrepancies. Thus, ***the dose at which the metabolism of 1,4-dioxane becomes saturated remains in question.***

The contention of Young et al. (1978) that the toxic effects and carcinogenicity of 1,4-dioxane occur only at doses at which the metabolism becomes overwhelmed does not take into account the fact that the rats in the pharmacokinetic study received single bolus doses via gavage while the animals in the toxicity and carcinogenicity studies received 1,4-dioxane in the drinking water daily for their lifespans. Thus, while Young et al. (1978) reported that a bolus dose of 100 mg/kg 1,4-dioxane may saturate the metabolic process, a drinking water concentration of 0.1% (equivalent to a dose of about 100 mg/kg/day, which the animals would receive gradually over a day every day of their lifetimes as they drink the water) would not saturate the metabolism, but could lead to cumulative toxicity. Furthermore, the *in vitro* activities of hepatic aniline hydroxylase and aminopyrine N-demethylase increased after repeated dosing of rats with 1,000 mg/kg/day 1,4-dioxane (Dietz et al., 1982), and the *in vivo* metabolism of 1,4-dioxane increased after repeated oral dosing of rats at 1,000 mg/kg/day (Young et al., 1978), suggesting that enzymes responsible for the metabolism of 1,4-dioxane are induced after repeated administration. In addition, Woo et al. (1977a) found that the amount of the metabolite excreted in the urine leveled off at intraperitoneal doses ≥3,000 mg/kg, which are much higher than the doses at which toxic effects (≥94 mg/kg/day) and carcinogenicity (≥240 mg/kg/day) were observed in rats, mice, and guinea pigs in the studies by Argus et al. (1965, 1973), Hoch-Ligeti and Argus (1970), Hoch-Ligeti et al. (1970), Kociba et al. (1974), and NCI (1978). Furthermore, Woo et al. (1978) demonstrated that 1,4-dioxane-2-one is more toxic than 1,4-dioxane based on the intraperitoneal LD_{50} values.

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***Dioxane has been tested for genotoxic effects in numerous systems with mostly negative
ts, but a few positive results suggest that 1,4-dioxane may be weakly genotoxic. While
mber of studies have attempted to determine the mechanism (genotoxic or epigenetic)
which 1,4-dioxane exerts its carcinogenic effects, the mechanism remains unknown and
be novel.***

discussed in the Health Effects sections, negative results of 1,4-dioxane were obtained in
ys for reverse mutation in five strains of *Salmonella typhimurium* with or without
abolic activation (Stott et al., 1981; Haworth et al., 1983; Nestmann et al., 1984,
udoley et al., 1987); in an assay with *Photobacterium phosphoreum* (Kwan et al., 1990),
differential DNA repair in the *Escherichia coli* (Hellmer and Bolcsfoldi, 1992); for
romosomal aneuploidy in *Saccharomyces cerevisiae* (Zimmermann et al., 1985); and for
tagenicity in L5178Y mouse lymphoma cells (NTP, 1986). 1,4-Dioxane did not induce
x-linked recessive lethal mutations in *Drosophila melanogaster* (Yoon et al., 1985). An
ccupational epidemiological study found no evidence that 1,4-dioxane caused chromosomal
berrations in peripheral lymphocytes of six workers (Thiess et al., 1976). Negative results
ere obtained for chromosomal aberrations in the Chinese hamster ovary cells with or
thout metabolic activation (Galloway et al., 1987). However, a weak increase in the sister
romatid exchange test without metabolic activation, but not with metabolic activation, was
und in cultured Chinese hamster ovary cells. In addition, exposure of cultured BALB/3t3
lls to 1,4-dioxane resulted in transformations leading to the formation of foci (Sheu et al.,
988).

A computerized SAR analysis using TOPKAT to assess the carcinogenic potential of 1,4-
ioxane indicated that both the male rat and female mouse models showed a positive
influence for the -O-CH_2- fragment, but the male rat model indicated that the symmetry of the
molecule plays a more substantial role in its carcinogenicity than the -O-CH_2- fragment
(Blake, 1995). 1,4-Dioxane was predicted to induce micronuclei in the bone marrow of
rodents as a result of the -O-CH_2- moiety using the CASE methodology for SAR (Rosenkranz
and Klopman, 1992). For additional discussion on the role of the -O-CH_2- fragment, see the
Genotoxicity subsection in the Health Effects in Animals section above. Experimental tests
for micronuclei induction in mice have been conducted with mixed results, with positive
results by Mirkova (1994), inconclusive results by McFee et al. (1994), and negative results
by Tinwell and Ashby (1994). As discussed by Ashby (1994), the question of whether 1,4-
dioxane is genotoxic is important due to its unexpected induction of nasal tumors in rats,
since only overtly genotoxic (electrophilic) chemicals had been reported to induce tumors in
nasal tissues. Since the data on micronuclei induction by 1,4-dioxane are extensive and
inconsistent, Ashby (1994) notes that it is not always possible to categorize a chemical as
either unequivocally positive or negative in a genotoxicity assay. Thus, ***Ashby (1994) states
that the CASE prediction of activity in the micronucleus assay needs to be validated, and he
supports the conclusion of Kitchin and Brown (1990) that 1,4-dioxane is a weakly
genotoxic chemical and a strong promoter.***

A number of studies have attempted to determine the mechanism (i.e., genotoxic or epigenetic) by which 1,4-dioxane exerts its carcinogenic effect by performing assays on markers for DNA damage, DNA synthesis, cell proliferation, or peroxisome proliferation. Increases in DNA strand breakage were found in cultured rat hepatocytes (Sina et al., 1983). An increase in DNA synthesis, but no DNA alkylation, was found in the livers of male rats given 1,4-dioxane in the drinking water at a level that provided 1,000 mg/kg/day for 11 weeks (Stott et al., 1981). Furthermore, since 1,4-dioxane was negative in the rat primary hepatocyte unscheduled DNA synthesis bioassay, the author stated that ***its cytotoxic effects at carcinogenic dose levels and the lack of genotoxicity suggested that 1,4-dioxane induces tumors by a nongenetic mechanism, perhaps by inducing cell proliferation.***

In another evaluation of cell proliferation, an equivocal result for DNA synthesis in rat hepatocytes was obtained after the rats were treated with 2,000 mg/kg 1,4-dioxane by gavage (Uno et al., 1994). Hepatic viability was significantly depressed at 1,000 and 2,000 mg/kg. The authors could not explain the reason that 1,4-dioxane, a known hepatocarcinogen, failed to induce replicative DNA synthesis in this study, but they suggested that ***1,4-dioxane may exert its hepatocarcinogenicity only in initiated cells.***

Statistically significant increases were found for DNA damage and for cytochrome P-450 content and ornithine decarboxylase activity in the livers of female Sprague-Dawley rats treated with 1,4-dioxane (Kitchin and Brown, 1990, 1994; Kitchin et al., 1994). However, no evidence for cytotoxicity was found. Therefore, hepatic DNA damage was observed without cytotoxicity, suggesting a potential for initiation of cancer by 1,4-dioxane (Kitchin and Brown, 1990; Kitchin et al., 1994). The results found for ornithine decarboxylase and cytochrome P-450 also suggested a potential for 1,4-dioxane as a promoter (Kitchin and Brown, 1990; Kitchin et al., 1994). ***Thus, the authors considered 1,4-dioxane to be a weak genotoxic carcinogen in addition to being a strong promoter.***

In another study of the potential mechanisms of carcinogenicity of 1,4-dioxane, neither 1,4-dioxane nor one of its proposed metabolites, 1,4-dioxane-2-one, showed activity in the *in vitro* primary rat hepatocyte DNA repair assay (Goldsworthy et al., 1991). Furthermore, 1,4-dioxane produced no activity in the *in vivo* hepatocyte DNA repair assay, no increase in relative liver weight or in the activity of palmitoyl CoA oxidase, an indicator of peroxisomal proliferation, and no increase in DNA synthesis in rat hepatocytes. However, a two-fold increase in the hepatocyte labeling index was found in rats given dioxane in the drinking water for two weeks, suggesting a role for cell proliferation in the induction of hepatocellular carcinoma. Regarding the mechanism of 1,4-dioxane–induced nasal turbinate carcinogenicity, nasoturbinate and maxilloturbinate nasal epithelial cells isolated from rats given dioxane showed no DNA repair activity. No significant increase in cell proliferation was found in the nasal turbinate site with the highest tumor formation rate in the NCI (1978) study when rats in this study were administered 1% (v/v) dioxane in the drinking water for two weeks. Although the protocols used by Goldsworthy et al. (1991) are generally accepted for detecting DNA repair or cell proliferation, these authors acknowledged the possibility that the two-week

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novel mechanism for carcinogenicity of 1,4-dioxane is supported by a study comparing get organs of carcinogenicity for mutagenic and nonmutagenic chemicals (Gold et al., 93). This study evaluated 351 carcinogens and concluded that many mutagens and nonmutagens are carcinogenic in rodents at the maximum tolerated dose, and that compared nonmutagens, mutagens are more likely to be carcinogenic, more likely to induce tumors at ere than one site, and are more likely to be carcinogenic in more than one species. ecording to this conclusion, one might predict that 1,4-dioxane would behave like a utagen since it induces cancer in rats, mice, and guinea pigs and more than one tumor site s identified (see Carcinogenicity subsection above). In addition, in the NCI (1978) study, 4-dioxane produced statistically significant increases in tumor incidences in both sexes of and mice at both dose levels (Haseman and Lockhart, 1994). Gold et al. (1993) noted that % of the chemicals that are carcinogenic in rodents are not mutagenic in *S. typhimurium* d postulated that administration of near-toxic doses can stimulate cell division; mitogenesis reases rates of mutagenesis and thus carcinogenesis. However, as noted above, ***data garding the mechanism(s) by which 1,4-dioxane induces its carcinogenic effects are consistent, suggesting to many of the investigators an as yet unknown mechanism. deed, Williams (1992) lists 1,4-dioxane as unclassified in a discussion of DNA reactive rsus epigenetic (promoting, endocrine-modifying, immunosuppressant, cytotoxic, or roxisome proliferator) carcinogens.***

conclusion, the mechanism(s) by which 1,4-dioxane exerts its carcinogenic effects mains in question.

echanistic Considerations for Risk Assessment

e relationship between mutagenicity and carcinogenicity is an important issue regarding k assessment since some investigators contend that nongenotoxic carcinogens should be ated differently than genotoxic carcinogens (Benigni, 1990). In an analysis of 116 rcinogens and 35 potential tumor sites for male and female rats and male and female mice, e chemical classification based on tumorigenicity (Cluster 1 for tumors in one sex and one ecies to Cluster 4 for tumors in both sexes and both species) was compared with Ames say (*S. typhimurium*) results. According to this definition, dioxane falls in Cluster 4 and was gative in Ames assays. The analysis indicated that a significant association for tumor tterns with the Ames test resulted only for Cluster 4. The patterns of sites actually induced y chemicals do not show a significant difference between Ames-positive and Ames-negative hemicals. Some compounds are likely to act according to both genotoxic and nongenotoxic mechanisms, depending on the experimental conditions and tissues affected, and pure promoters probably do not exist, since almost all are weakly carcinogenic at high doses. The author questioned whether the Ames test is a satisfactory measure of genotoxicity and concluded that ***classifying carcinogens as primary (genotoxic) and secondary***

(nongenotoxic) for risk assessment purposes is theoretical and speculative, and not sufficiently supported by scientific knowledge.

Tennant (1993) proposed that ***the genetic basis of cancers induced by nonmutagens involves heritable changes in the regulation of gene expression.*** That is, some cancers represent diseases of transcription arising from errors in transcriptional regulation, and some chemicals can elicit such changes independent of their capacity to stimulate cell proliferation. Chemically induced cell proliferation may be essential for the clonal amplification of transcriptionally altered cells. Thus, the ability of a chemical to interfere specifically with some process of transcription may distinguish this class of nonmutagenic carcinogens from both other nonmutagens, and from carcinogenic mutagens.

Given the limited knowledge about mechanisms of carcinogenesis that relate to the need to deal with human disease and prevention, Lijinsky (1990) disagrees with assertions that the ability to assess human cancer risks from exposure to nongenotoxic carcinogens is less than the corresponding ability to assess risks from genotoxic carcinogens. Since experimental determination of a safe dose at which no increase in cancer risk to a large population of humans is not possible, ***the existence of a threshold is a theoretical concept for both genotoxic and nongenotoxic carcinogens. The risk is great that assumptions about carcinogenicity mechanism are wrong, given the incomplete understanding of the process.***

As noted in the Cancer Policy Framework (ATSDR, 1993), *"Carcinogens may work through mechanisms that directly alter the genome (genotoxic), or through mechanisms that indirectly involve the genome (epigenetic). Currently, it is assumed that many or most carcinogens are characterized by the absence of a threshold in eliciting a tumorigenic response. However, the presence or absence of a threshold for one step in the multistage process of carcinogenesis does not necessarily imply the presence or absence of a threshold for other steps or the entire process. . . . Under such circumstances, ATSDR evaluates the relevance of the animal data to humans on a case-by-case basis with a view towards extending its assessment effort beyond the dominant paradigm of carcinogenesis (i.e., initiation, promotion, and progression)."*

Irrespective of the possible mechanism of action by which 1,4-dioxane or any chemical induces its carcinogenic effects, such information would not be used as a basis to reclassify 1,4-dioxane from a Group B2 carcinogen to a Group C carcinogen (EPA, 1986a).

CONCLUSIONS

In summary,

- ***The hepatic, renal, and neurological systems are the major targets of 1,4-dioxane's noncancer toxicity.***
- ***Drinking water studies in rodents have shown that high doses are associated with increased incidences of liver and nasal turbinate tumors.***

The exact mechanism by which 1,4-dioxane exerts its carcinogenic effect is unknown, but the studies reviewed indicate that 1,4-dioxane is weakly genotoxic and is a strong tumor promoter. It has been proposed that 1,4-dioxane exerts its carcinogenic effect by an unknown and possibly novel mechanism.

- ***Pharmacokinetic studies indicate that the metabolism of 1,4-dioxane becomes saturated as doses increase, but the doses at which metabolism becomes saturated and whether the metabolism represents a detoxifying mechanism are not clear.***

- ***Given the current classification of 1,4-dioxane as a Group B2 carcinogen, ATSDR considers EPA's approach to the risk assessment for 1,4-dioxane to be appropriate and notes that this corresponds to a range of 3–300 μg/L at upper bound lifetime cancer risks of 1 in 1,000,000 to 1 in 10,000.*** ATSDR further notes that the range of 3–300 μg/L encompasses most of the alternate risk assessment approaches.

ATSDR's (ATSDR, 1993) qualitative conclusions regarding carcinogenicity involve a narrative weight-of-evidence approach, which relies upon the Department of Health and Human Services' most recent Annual Report on Carcinogens (NTP, 1994). Conclusions of the International Agency of Research on Cancer (IARC, 1987), EPA's Guidelines for Carcinogen Risk Assessment (EPA, 1986a), and the Occupational Safety and Health Administration (OSHA, 1980) are also considered and presented, as appropriate. A substance is determined to be carcinogenic if any of these agencies classify it as "known," "probable," "possible," or "reasonably anticipated to be a carcinogen." 1,4-Dioxane is classified by NTP (1994) as a substance "which may reasonably be anticipated to be a carcinogen," by IARC (1987) as "possibly carcinogenic to humans" (Group 2B), and by EPA (IRIS, 1994) as "a probable human carcinogen" (Group B2). ***Such classifications are made irrespective of whether a chemical has been shown to be genotoxic. It is significant that the independent assessments by NTP, IARC, and EPA come to similar conclusions regarding the carcinogen classification of 1,4-dioxane. Similar to its 1989 conclusion, "ATSDR has found no information in the scientific literature that would contraindicate the IARC and EPA findings" (ATSDR, 1989) or in the conclusions presented subsequently by NTP and EPA.***

As noted in ATSDR's previous communication with MDPH (ATSDR, 1989), "historically, neither EPA nor ATSDR have separated the use of the Linearized Multistage Model according to the two basic classes (i.e., genotoxic and epigenetic) of chemical carcinogens. Moreover the Linearized Multistage Model has been used to assess human cancer risk for exposure to other epigenetic carcinogens such as benzene, trichloroethene, tetrachloroethene, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), and tetrachlorodibenzodioxin (TCDD). Several of these chemicals are classified as promoters. Dioxane appears also to act as a promoter, a weak genotoxin, and a cytotoxin." Since dioxane has been shown to cause cancer in both sexes of at least two species of

rodents, a risk assessment approach that fails to properly reflect the human carcinogenic potential may not be protective of public health.

ATSDR recognizes that significant uncertainties regarding the carcinogenicity of 1,4-dioxane remain. These include the mechanism of action, the potential for carcinogenicity in humans, and the relevance of results at high doses to low-dose exposure. In addition, the protection of susceptible populations (e.g., those with chronic medication use, existing chronic disease, or genetic variance), the possibilities that chlorination of 1,4-dioxane in the drinking water may lead to chlorinated compounds more toxic than 1,4-dioxane, that 1,4-dioxane may be contaminated with bis(2-chloroethyl) ether, a more potent carcinogen, and that 1,4-dioxane may interact with other water contaminants leading to potentiation of the toxicity, are serious concerns.

"Although ATSDR recognizes the utility of numerical risk estimates in risk analysis, the Agency considers these estimates in the context of the variables and assumptions involved in their derivation and in the broader context of biomedical opinion, host factors, and actual exposure conditions" (ATSDR, 1993). ***To the extent that exposure and mechanistic assumptions underlying the EPA approach diverge from actual drinking water exposures to, and toxicity of, 1,4-dioxane, actual risk may vary. Thus, the final risk management decision should rest with the State of Michigan, based on relevant standards and criteria as well as anticipated human exposures.***

While the primary concern for exposure to 1,4-dioxane in this consultation involves drinking water, the contribution of exposure from water should also take into consideration the possibility of inhaling 1,4-dioxane vapors that might be generated from such activities as showering. Such activities as showering, bathing, and laundering in 1,4-dioxane-contaminated water will also contribute to dermal contact. ***As noted on page 6 in the Health Effects in Animals section, exposure to volatile organic compounds in the tap water through inhalation from showering and other indoor air sources can be 1.5–6 times higher than the contribution from ingesting two liters of water per day (McKone, 1987).*** If the liver is the major site of metabolism of 1,4-dioxane, and this metabolism represents a detoxifying mechanism, the contribution of inhalation or dermal exposure to the total toxicity may be of greater concern since first-pass to the liver would not occur, resulting in other potential target organs being exposed to the parent compound. *"The actual parameters of environmental exposures must be given careful consideration in evaluating the assumptions and variables relating to both toxicity and exposure"* (ATSDR, 1993). In the absence of actual values for estimating total exposure (information on inhalation rate, water consumption, food consumption, life span, body weight, and other factors depending on the route of exposure), ATSDR frequently uses default estimates including those described by EPA (EPA, 1986b, 1988b), recognizing that significant uncertainty is associated with the use of such default values.

In addition to the foregoing conclusions of the consultation, ATSDR recommends that the risk management of 1,4-dioxane reflect the health implications of the following: a) the average daily intake of 1,4-dioxane from dietary sources; b) given daily intake, the added body burden from nondietary sources from different environmental media (water, air, soil); c) the present worst-case scenario based on available monitoring and dietary data and average intake expected from all sources; d) the risk reduction to be expected from percentile reduction in the 1,4-dioxane concentration from nondietary source exposure due to remediation activities; and e) potential economic and health impacts.

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SOLVENT STABILIZERS

WHITE PAPER

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4.0 TOXICOLOGY OF 1,4-DIOXANE AND APPLICABLE REGULATORY STANDARDS

Availability of ample toxicological data is critical to the determination of the degree to which 1,4-dioxane, 1,3-dioxolane and other solvent stabilizers pose a threat to drinking water quality. Because regulatory standards for 1,4-dioxane do not yet include a Federal Maximum Contaminant Level, state government environmental officials and scientists have used various federal advisory levels or performed their own risk assessments to establish state advisory levels. The result has been a spectrum of professional opinion among toxicologists in different states, and also within states. For example, California uses a drinking water advisory level of 3 ug/L for 1,4-dioxane, while published and peer reviewed journal articles recommend a standard on the order of 1,200 ug/L using physiology-based models. The flexible nature of California's advisory level make these two determinations more similar than it first appears, yet regulatory agencies have employed strict cleanup standards at solvent release and other industrial waste sites closer to 3 ug/L due to the finding that 1,4-dioxane is listed as a probable human carcinogen. The following sections summarize regulatory standards, and salient information from the toxicology literature for 1,4-dioxane summarizing studies of its carcinogenicity and toxicity. The determination of site cleanup standards for 1,4-dioxane from health risk assessments is also discussed.

4.1 Drinking Water Standards

WATER QUALITY CRITERIA and GUIDELINES FOR PROTECTION OF HUMAN HEALTH FROM SOLVENT STABILIZER COMPOUNDS (compiled in March 2001)

1,4-DIOXANE

Jurisdiction	Guideline	Application	Reference
Massachusetts	50 µg/L	Guideline	Anastas 1988
Florida	5 ug/L	Drinking water standard	US EPA 1993
Maine	70 ug/L	Drinking water standard	US EPA 1993
Michigan	85 ug/L	Drinking water standard	Michigan DEQ, 2001
California	3 ug/L	Drinking water action level	Cal-EPA DHS, 2001
North Carolina	7 ug/L	Drinking water action level	US EPA 2001

EPICHLOROHYDRIN

Jurisdiction	Guideline	Application	Reference
California	4.5 ug/L	Prop 65 Regulatory Level; No significant risk level for carcinogens	CDWR 1997
United States	Zero	MCLG – maximum contaminant goal for carcinogens is zero	CFR 40(1)141.50

TETRAHYDROFURAN

Jurisdiction	Guideline	Application	Reference
New York	50 µg/L	Guidance value	NYSDEC 1998
Massachusetts	1300 µg/L	Guideline	Anastas 1998
Michigan	230 µg/L	Drinking water standard	US EPA 1993
New Hampshire	156 µg/L	Drinking water standard	US EPA 1993
Wisconsin	50 µg/L	Drinking water standard	US EPA 1993

1,3-Dioxolane – none found

The California Action Level is not a regulated limit for which testing must be performed. The California Department of Health Services (DHS) explains its Action Levels as follows:

> *If a contaminant exceeds its Action Level in drinking water, the (DHS) recommends that the utility inform its customers and consumers as soon as is feasible about the presence of the contaminant, and its potential for adverse health effects. If the concentration of a contaminant for which no MCL has been established and for which the Action Level is*

based on cancer risk is detected at concentrations 100 times the Action Level, DHS recommends the well be taken out of service.

Action Levels for contaminants considered carcinogens [including 1,4-dioxane], correspond to a theoretical lifetime risk of up to one excess case of cancer in a population of 1,000,000 people—the 10^{-6} de minimis risk level. (In that population, approximately 250,000-300,000 cases of cancer would be anticipated to occur naturally.) A level 100 times greater corresponds to a theoretical lifetime risk of up to one excess case of cancer in 10,000 people (i.e., 10^{-4} risk), the upper value of the 10^{-6} to 10^{-4} risk range typically allowed by regulatory agencies. If the action level for a carcinogen is a concentration corresponding to a risk greater than 10^{-6}, the recommendation for source removal remains at the 10^{-4} level.

The risk calculation used to determine DHS Action Levels follows the conventional 70 kg body weight model, 2 liters per day consumption, with the carcinogen slope factor (CSF) for 1,4-dioxane as 0.011 mg/kg/day, resulting in the health-based limit at the 10^{-6} risk level as 0.003 mg/L. A reference dose (RfD) and a maximum contaminant level (MCL) has not been established for 1,4-dioxane.

4.2 Human health data

Little data is available for human exposure to 1,4-dioxane. One account of acute exposure includes reports of five cases of fatal poisoning in men working in a textile factory who inhaled excessive amounts of 1,4-dioxane. Symptoms were irritation of the upper respiratory passages, coughing, irritation of eyes, drowsiness, vertigo, headache, anorexia, stomach pains, nausea, vomiting, uremia, coma, and death. Autopsy revealed congestion & edema of lungs and brain, and marked injury of liver and kidney. Death was attributable to kidney injury. Blood counts showed no abnormalities other than considerable leukocytosis. Exposure levels for these cases are unknown and investigators consider it debatable whether this was an instance of chronic or acute exposure (Clayton, et al, 1982).

1,4-dioxane & beta-hydroxyethoxyacetic acid (HEAA – a metabolite of 1,4-dioxane) were found in urine of plant personnel exposed to time-weighted average concentrations of 1.6 ppm dioxane for 7.5 hours. Average concentrations of dioxane HEAA in urine were 3.5 and 414 micro-moles/L, respectively (Young, et al, 1976).

No adequate epidemiological data were available to assess the carcinogenicity of 1,4 dioxane to humans. (Anonymous, 1990).

A physiologically based pharmacokinetic model (PBPK model) was developed for a lactating woman to estimate the amount of chemical that a nursing infant ingests for a given nursing schedule and maternal occupational exposure. Human blood/air and milk/air partition coefficients (PCs) were determined for 1,4-dioxane and 18 other VOCs. Milk/blood PC values were above 3 for carbon tetrachloride, TCA, perchloroethylene (PCE), and 1,4-dioxane. In a simulated exposure of a lactating woman to a threshold limit value concentration of an individual chemical, only PCE and 1,4-dioxane exceeded the U.S. Environmental Protection Agency non-cancer drinking water ingestion rates for children. Very little data exists on the pharmacokinetics of lactational transfer of volatile organics. (Fisher et al, 1997).

IARC and the National Toxicology Program (NTP) stated that variability in the mutagenicity test results with TCE might be due to the presence of various stabilizers used in TCE which are mutagens (e.g. epoxybutane, epichlorohydrin).

4.2.1 Occupational Exposure

Most occupational exposure limits are for the inhalation pathway. Exposure limits for breathing vapors of 1,4-dioxane has bearing on water quality as it may limit the concentration that can be distributed in water

systems. Volatile organic compounds may be inhaled while showering, dishwashing, or other household uses of water.

The National Occupational Hazard Survey estimates that 334,000 workers are potentially exposed to 1,4-dioxane, 100,000 of whom are exposed as a result of dioxane contamination of TCA. OSHA estimates that 466,000 workers are potentially exposed (Sittig, 1985).

The Permissible Exposure Limit (PEL) for 1,4-dioxane is 100 ppm as an 8-hour Time Weighted Average (TWA 360 mg/m^3 – skin designation) (Code of Federal Regulations, 1998). The PEL was raised from the 1989 OSHA PEL TWA of 25 ppm (90 mg/m^3), skin designation, although the lower PEL is still enforced in some states (NIOSH, 1997). The Threshold Limit Value for 1,4-dioxane is 25 ppm as an 8-hour Time Weighted Average (TWA), skin, (ACGIH, 1998)

The National Institute of Occupational Safety and Health (NIOSH) recommends that dioxane be regulated as a potential human carcinogen (NIOSH, 1997). NIOSH usually recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration. The NIOSH Recommended Exposure Limit for a thirty minute period lists a ceiling value of 1 ppm (3.6 mg/m^3).

1,3-dioxolane

Human exposure is thought to be limited to production workers involved in the manufacture of 1,3-dioxolane, the production of polyacetals (plastics), or the use of dioxolane as a chemical intermediate. Industrial hygiene monitoring of production and polyacetal manufacturing areas at a major production facility indicated that worker exposure levels are low. Over several years, of monitoring, data from 91 measurements of air concentrations showed an average level of 0.29 ppm and values ranged from 0 to 1.6 ppm.

4.3 Animal Laboratory Studies

The following summaries of toxicity and carcinogenicity studies will be of greatest interest to toxicologists and other scientists engaged in health risk assessments.

4.3.1 Toxicity

- dogs given dioxane orally over a period of 9 days died after a total consumption of about 3 g/kg, with severe liver & kidney damage (ACGIH, 1986)
- kidney and liver injury occurs in rabbits and guinea pigs after repeated dermal application (Doull et al, 1980).

Various studies with 1,4-dioxane identified:

- oral LD50 of 5.66 g/kg in mice
- oral LD50 of 5.17 g/kg in rats
- oral LD50 of 3.90 g/kg in guinea pigs
- inhalation LC50 for rats was estimated to be 14,250 ppm
- dermal LD50 for rabbits of 7.6 g/kg
- 1,4-Dioxane is absorbed through skin, causing kidney and liver injury in rabbits and guinea pigs following repeated topical application of 20 and 10 drops of 80% dioxane/day for 14 weeks. (Shell Oil, 1980).

4.3.2 Carcinogenicity

The International Agency for Research on Cancer classifies 1,4-dioxane as a probable human carcinogen ('B2'). The basis provided for this classification of carcinogenicity is 1) evidence in humans: inadequate; 2) evidence in animals: sufficient; 3) evidence for activity in short-term tests: inadequate (IARC, 1976). The animal evidence cited is the induction of nasal cavity and liver carcinomas in multiple strains of rats, liver carcinomas in mice, and gall bladder carcinomas in guinea pigs (US EPA, 2000c).

Willhite et al (1999) note the limitations of the quantitative risk assessment techniques employed to derive preliminary drinking water standards. Animal studies note a non-linear nature of exposure to 1,4-dioxane, with toxic and tumorogenic effects occurring only after saturation of the uptake and elimination systems for the animals studied. The US EPA linearized multi-stage procedure relies on body surface area procedures that do not work well for interspecies scaling of dose. Willhite et al (1999) advocate a physiological based pharmacokinetic (PBPK) model, and Reitz et al (1990) used a PBPK model to determine that a more appropriate drinking water standard may be on the order of 1.2 mg/L rather than 0.003 mg/L, the current California Action Level.

The following summaries highlight key studies on the carcinogenicity of 1,4-dioxane in laboratory animal tests[3].

Goldsworthy et al (1991) summarizes several studies as follows (summaries of individual studies follow):

> *Several long-term studies with 1,4-dioxane have shown it to induce liver tumors in mice, and nasal and liver tumors in rats when administered in amounts from 0.5 to 1.8% in the drinking water (Argus et al. 1965; Kociba et al. 1974; National Cancer Institute, 1978). In order to examine potential mechanisms of action, chemically-induced DNA repair (as an indicator of DNA reactivity) and cell proliferation (as an indicator of promotional activity) were examined in nasal turbinate epithelial cells and hepatocytes of male Fischer-344 rats treated with dioxane. Neither dioxane nor 1,4-dioxane-2-one, one of the proposed metabolites, exhibited activity in the in vitro primary rat hepatocyte DNA repair assay, even from cells that had been isolated from animals given either 1 or 2% dioxane in the drinking water for 1 week to induce enzymes that might be responsible for producing genotoxic metabolites. No activity was seen in the in-vivo hepatocyte DNA repair assay in animals given a single dose of up to 1000 mg/kg dioxane or up to 2% dioxane in the drinking water for 1 week. Treatment of rats with 1.0% dioxane in the drinking water for 5 days yielded no increase in liver/body weight nor induction of palmitoyl CoA oxidase, indicating that dioxane does not fit into the class of peroxisomal proliferating carcinogens. The percentage of cells in DNA synthesis phase (S-phase) was determined by administration of 3H-thymidine and subsequent quantitative histoautoradiography. The hepatic labeling index (LI) did not increase at either 24 or 48 h following a single dose of 1000 mg/kg dioxane. The LI did increase approximately two-fold in animals given dioxane in the drinking water for 2 weeks. No DNA repair was seen in either nasoturbinate or maxilloturbinate nasal epithelial cells isolated from animals treated with 1% dioxane in the drinking water for 8 days followed by a single dose of up to 1000 mg/kg dioxane by gavage 12 h before sacrifice. Reexamination of the nasal passages of male rats in archived material from the NTP bioassay (National Cancer Institute 1978), revealed that the primary site of tumor formation was the anterior third of the dorsal meatus. The location of these tumors supports the proposal that inhalation of dioxane-containing drinking water may account for the site specificity of these nasal lesions. In vivo studies showed no increase relative to controls in cell proliferation at the site of highest tumor formation in the nose in response to 1.0% dioxane in the drinking water for 2 weeks. Thus, repair-inducing DNA adduct formation, peroxisomal proliferation in the liver, and short-term induction of cell proliferation in the nose do not appear to be involved in tumor formation by dioxane. There may be a role of dioxane-induced cell proliferation in the formation of the liver tumors. However, the quantitative relationships between induced cell proliferation and tumorogenic potential have yet to be established.* (Goldsworthy, et al, 1991).

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[3] the toxicology information listed is selected verbatim from the sources, and presented for the convenience of those readers experienced in the development of Health Risk Assessments. The author is not a toxicologist and has not evaluated the quality or validity of the studies cited.

- *A bioassay of 1,4-dioxane for possible carcinogenicity was conducted by administering the test chemical in drinking water to Osborne Mendel rats and B6C3F1 mice at concentrations of either 0.5% or 1.0% (v/v) in drinking water. The rats were dosed for 110 weeks and the mice for 90 weeks. In rats, the incidence of squamous cell carcinomas of the nasal turbinates was statistically significant. In both male and female mice, the incidence of hepatocellular carcinomas was statistically significant ($p < 0.001$). 1,4-Dioxane induced hepatocellular adenomas in female Osborne Mendel rats. 1,4-Dioxane was carcinogenic in both sexes of rats, producing squamous cell carcinomas of the nasal turbinates, and in both sexes of B6C3F1 mice, producing hepatocellular carcinomas* (NCI, 1978).

- *Liver tumors, ranging from small neoplastic nodules to multifocal hepatocellular carcinomas in 6 of 26 male Wistar rats given 1% 1,4-dioxane in drinking water for 63 weeks (total dose 130 g). One rat developed a transitional-cell carcinoma of kidney pelvis, and one developed leukemia. There was also one lymphosarcoma in 9 control animals* (Argus et al, 1965).

- *60 male and 60 female Sherman rats given 0, 0.01, 0.1 or 1% 1,4-dioxane in drinking water for 716 days At the highest level, 10 developed hepatocellular carcinomas, 2 developed cholangiomas, and 3 developed squamous-cell carcinomas of the nasal cavity. One rat receiving 1,4-dixoane at the 0.1% level developed hepatocellular carcinoma. No statistically significant increases in incidence of tumors were seen in rats given the two lower dose levels* (Kociba et al, 1974). *This study did not report the tumor incidences for male and female rats separately.*

- *4 groups of 28 to 32 male Sprague-Dawley rats were given 0.75, 1.0, 1.4 or 1.8% ... in drinking water for 13 months (total dose 104-256 g/rat). One rat receiving 0.75%; one receiving 1.0%; two receiving 1.4%; and two receiving 1.8% developed nasal cavity tumors. These were mainly squamous-cell carcinomas, with adenocarcinomas in 2 cases. Liver cell tumors developed in 3 rats receiving 1.4%, and subcutaneous fibroma developed in 12 rats receiving 1.8% 1,4-dioxane compared to one in thirty among control animals* (Argus et al, 1973; Hogh-Ligeti et al, 1970).

- *22 male guinea pigs received drinking-water containing 0.5 to 2% 1,4-dioxane over 23 months (total dose, 588-623 g/animal). Two animals had carcinomas of the gall bladder, and 3 had hepatomas. No liver tumors were reported in 10 untreated controls* (Hogh-Ligeti and Argus, 1970).

- *Rats given 1.0 or 0.1% 1,4-dioxane in drinking water for 4 to 24 months showed renal tubular and hepatocellular degeneration, necrosis and regeneration. Rats ingesting 1.0% had increased incidence of liver tumors and nasal carcinomas* (Kociba, et al, 1975).

- *1,4-dioxane induced liver neoplasms after chronic ingestion of cytotoxic dosages in rats. Treatment of rats with tumorigenic dose levels of 1,4-dioxane (1 g/kg/day) in drinking water for 11 weeks resulted in a 1.5 times increase in hepatic DNA synthesis. Cytotoxicity was not detected in rats dosed orally with non-tumorigenic levels of 1,4-dioxane (10 mg/kg/day). Alkylation of hepatic DNA and DNA repair was not detected in rats dosed orally with 1 g ^{14}C-1,4-dioxane/kg. 1,4-dioxane did not elicit a positive response in Ames bacterial mutagenicity or Williams hepatocyte DNA repair in vitro assay. The lack of genotoxic activity of 1,4-dioxane and its cytotoxicity at tumorigenic dose levels suggest a non-genetic mechanism of liver tumor induction in rats* (Stott et al, 1981).

The following discussion on the applicability of laboratory animal cancer bioassay data to the potency of 1,4-dioxane in humans reveals inherent limitations to the extrapolation methods employed in conventional risk assessments:

> *A cancer bioassay conducted in 1974 (Kociba et al.) indicated that rats given drinking water containing dioxane at a dose of 1184 mg increased incidence of liver tumors. Applying the linearized multistage extrapolation model to these data, the administered dose estimated to present a human cancer risk of 1 in 100,000 (10^{-5}) was 0.01 mg. This estimate assumed that humans were about 5.5 times more sensitive than rats on a mg/kg basis. However, this approach did not consider that the metabolism of dioxane is saturable at high doses. Based on experience with similar chemicals, it is known that the conventional risk extrapolation method may overestimate the most likely human cancer risk.*

In order to determine more accurately the likely human response following lifetime exposure to dioxane, a physiologically based pharmacokinetic (PB-PK) model was developed. The objective of this study was to establish a quantitative relationship between the administered dose of dioxane and the internal dose delivered to the target organ. Using this PB-PK model, and assuming that the best dose surrogate for estimating the liver tumor response was the time-weighted average lifetime liver dioxane concentration, the cancer risk for humans exposed to low doses of dioxane was estimated. The dose surrogate in humans most likely to be associated with a tumorigenic response of 1 in 100,000 is 280 micro-mol/L, equivalent to an administered dose of about 59 mg lower confidence limit on the dose surrogate at the same response level is 1.28 micro-mole/L, equivalent to an administered dose of 0.8 mg. Traditional approaches based on the administered doses in the rodent bioassay, if uncorrected for metabolic and physiological differences between rats and humans, will overestimate the human cancer risk of dioxane by as much as 80-fold. (Leung H-W, 1990).

1,3-dioxolane

Dioxolane demonstrates a low order of acute toxicity to mammals by the oral, inhalation, and dermal routes. Genotoxicity has been evaluated using multiple *in vitro* and *in vivo* experimental procedures covering both mutation and chromosome aberration. The weight of evidence indicates lack of significant genotoxic properties. Adverse reproductive effects are absent at dosage levels below maternally toxic doses. Dioxolane is not a specific developmental toxin. (Dioxolane Manufacturers Consortium, 2000).

4.3.3 Teratogenicity and Reproductive Effects

- *The teratogenic potential of the industrial solvent 1,4-dioxane was evaluated in rats. The compound was administered to pregnant Sprague Dawley rats on gestation days 6 to 15 by gavage in doses of 0, 0.25, 0.5, or 1.0 mL/kg/day. Food consumption and weight gain of the dam were followed. Rats were killed on gestation day 21. Females in the highest dose group had slightly lower weight gains compared to controls, both during treatment and later. Compared with controls, dioxane did not induce variations in the number of implantations, live fetuses, or resorptions, but the average weight of live fetuses from dams treated with 1 ml/kg/day was significantly less than controls. Mean fetal weight in this group was 3.6 g, compared to 3 8 g for controls. The frequency of major malformations remained within normal limits for all groups, and no deviations were found regarding minor anomalies and variants when compared with controls. However, with the highest dioxane dose, a significant retardation was found in the development of the sternum* (Giavini et al, 1985).

1,3-dioxolane

- *Tests provide evidence of genotoxic activity of dioxolane (Przybojewska B et al, 1984). Application of 1.3-Dioxolane to rats in drinking water resulted in decreased maternal body weights and increased number of stillborn pups, decreased survival of pups, and decreased numbers of pups* (Industrial BIO-TEST Labs, Inc., 1975).

    - *1,3-dioxolane was evaluated in Salmonella tester strains TA98, TA100, TA1535, TA1537 and TA1538 (Ames Test), both in the presence and absence of added metabolic activation. 1.3-Dioxolane did not produce a reproducible positive response in any tester strain with or without metabolic activation* (Goodyear, 1979).

4.4 Ecotoxicity of 1,4-dioxane and 1,3-dioxolane

- A report describing acute and chronic toxicity of 1,4-dioxane to fathead minnows, (*Pimephales promelas*), noted acute effects at concentrations of 10,000 mg/L; the highest no-observed-adverse-effect level was 6000 mg/L.
- An LC 50 was developed for bluegill sunfish (*Lepomis macrochirus*) as 10,000 ppm in a 96 hour static bioassay in fresh water at 23 °C (Verschueren ,1983).
- An LC 50 was developed for inland silverside fish (*Menidia beryllina*) as 6,700 ppm in a 96 hour static bioassay in synthetic seawater at 23 °C (Verschueren ,1983).

A calculated Log Bioconcentration Factor was determined to be -0.44. 1,4-Dioxane is not expected to bioconcentrate in fish and other aquatic organisms (Hansch et al, 1985; Howard 1990).

1,3-dioxolane

Dioxolane has been found to have a low order of toxicity to typical aquatic environmental species. A 96-hour LC_{50} static renewal study using bluegill with daily renewal of test solution to prevent loss due to volatilization recorded no mortality, with a resultant No Observed Effects Concentration of 95.4 mg/L (Dioxolane Manufacturers Consortium, 2000).

4.5 Site Cleanup Standards for 1,4-dioxane

Cleanup standards for 1,4-dioxane and other solvent stabilizers have not been widely established for solvent release sites. Where standards have been established, target concentrations vary by state and by site. If a contaminant is detected that does not have established Maximum Contaminant Levels or Maximum Contaminant Level Goals (e.g., 1,4-dioxane), EPA will evaluate available standards and information, such as California Department of Health Services drinking water action levels, to identify a relevant and appropriate standard for the contaminant (US EPA, 2000b).

Cleanup levels for the Gelman Sciences Site in Washtenaw County, Michigan, have been raised on two occasions following re-evaluation of toxicological data and performance of health risk assessments. When the contamination was first discovered in 1985, the generic residential cleanup criterion was 3 parts per billion (ppb) for groundwater and 60 ppb for soils. In June 1995, the State of Michigan amended the Natural Resources and Environmental Protection Act, and the generic residential cleanup criteria was increased to 77 ppb for groundwater and 1,500 ppb for soils. In June 2000, the Michigan Department of Environmental Quality adopted the US EPA methodology for calculating risk-based cleanup criteria, which resulted in the cleanup standards being raised to 85 ppb for groundwater, and 1,700 ppb for soils. The concentration of 1,4-dioxane in surface water considered by DEQ as safe for human contact and the environment is 2,800 ppb (Michigan DEQ, 2000).

A health risk assessment performed for 1,4-dioxane in groundwater by Blasland Bouck and Lee suggested that 38 ug/L would be an appropriate cleanup level for a Florida Gulf Coast shallow aquifer (Alonso, 2001).

The discharge limit for 1,4-dioxane in an NPDES permit for discharge of treated groundwater from various areas impacted by the release at Gelman Sciences was initially proposed at 60 ug/L. Although the residential cleanup criteria was raised to 77 ug/L, public comment was considered and allowable limits for 1,4-dioxane were reduced to 10 ppb as a monthly average with 30 ppb as a daily maximum. This permit was later contested by Gelman Sciences, asking for a daily maximum of 100 ug/L, and by local citizens, asking for the limit to be lowered to 3 ug/L.

In Spartanburg, South Carolina, the effluent limit set for 1,4-dioxane in a NPDES[4] permit for a polyester plant was 30 ug/L (McGrane, 1997).

[4] National Pollution Discharge Elimination System

5.0 TREATABILITY OF 1,4-DIOXANE – TECHNOLOGIES AND ENERGY COSTS

The discovery of 1,4-dioxane at cleanup sites has often occurred well after site characterization and remedial design is complete, making implementation of effective remedial measures for 1,4-dioxane cumbersome. Possible presence of 1,4-dioxane has not been investigated at the majority of solvent release sites. This is due to the relatively recent development of the laboratory methods necessary to detect 1,4-dioxane at concentrations less than 100 ug/L, and the recent and increasing awareness that the halogenated solvents are not the only contaminant of concern at solvent release sites.

Conventional treatment systems have been ineffective at removing 1,4-dioxane to site cleanup levels or drinking water advisory limits in the case of well-head treatment. Advanced oxidation processes have proven effective at removal of 1,4-dioxane, and progress is being made at developing engineered bioreactors, phytoremediation, and other techniques for treatment of 1,4-dioxane. The monitored natural attenuation approach to solvent contamination is unlikely to achieve degradation of 1,4-dioxane or 1,3-dioxolane.

5.1 Ability of Conventional Pump and Treat Technologies to Remove 1,4-dioxane

Very low K_{OC} values and Henry's Law constant for 1,4-dioxane makes carbon adsorption and air stripping inefficient treatment processes for 1,4-dioxane. At a groundwater treatment facility in El Monte, California, a liquid granular activated carbon treatment system consisting of two 20,000-pound carbon vessels and treating 500 gallons per minute of solvent-contaminated groundwater was ineffective at reducing influent 1,4-dioxane concentrations at 14 ug/L to the treatment target of 3 ug/L (Bowman et al, 2001). In the City of Industry, California, 1,4-dioxane concentration in influent at an air stripper designed to remove 1.2 mg/L chlorinated solvents at 70 gallons per minute was measured at 610 ug/L, while 1,4-dioxane in effluent was measured at 430 ug/L (Bowman et al, 2001).

Because the most common conventional groundwater treatment technologies employed for treating contamination by chlorinated solvents are ineffective at removing 1,4-dioxane and other solvent stabilizer compounds, many existing treatment systems are likely to be discharging or reinjecting unmitigated amounts of 1,4-dioxane. In the San Gabriel Basin Baldwin Park Operable Unit, the following adjustments to treatment technologies were made following the discovery of the presence of 1,4-dioxane, and two rocket fuel contaminants:

GROUNDWATER TREATMENT TECHNOLOGIES AT BPOU, AZUZA, SAN GABRIEL VALLEY, CA	
Original Cleanup Plan	**Updated Cleanup Plan (after finding 1,4-dioxane)**
Use air stripping or carbon treatment to remove VOCs from the groundwater.	Use same technologies to remove VOCs. Also use UV oxidation to remove 1,4-dioxane.

Source: US EPA, 1999a.

Distillation is physically viable, but the relatively high boiling point (101°C) makes this approach uneconomical for most applications. Distillation is used to remove high concentrations of 1,4-dioxane from process wastewater effluent in the manufacture of polyester fiber (McGrane, 1997).

Chlorination of dioxane has been attempted, and found to optimally break down dioxane at 75°C and pH 5.2. Chlorination byproducts, however, are from 12 to 1,000 times more toxic than 1,4-dioxane (Woo et al, 1980). This raises questions as to whether 1,4-dioxane subjected to chlorination in drinking water supply wells and at municipal wastewater treatment plants may lead to distribution or discharge of toxic byproducts.

Conventional activated sludge and other common municipal wastewater treatment technologies have also proven ineffective at removing 1,4-dioxane (see Section 5.6, Lyman et al, 1982;Klecka and Gonsior, 1986; Abe, 1999). This has implications for the viability of the use of reclaimed municipal wastewater for groundwater recharge, which may contain 1,4-dioxane.

5.2 Advanced Oxidation Processes

The remedial technology most commonly employed in the removal of 1,4-dioxane from groundwater ex-situ is advanced oxidation processes (AOP), often in combination with ultraviolet light. AOP processes include ultraviolet light with ozone, hydrogen peroxide with ultraviolet light, ozone and hydrogen peroxide in combination, and Fenton's Reagent (hydrogen peroxide and ferrous iron).

Ultraviolet light causes release of hydroxyl radicals from hydrogen peroxide added to influent contaminated water. The hydroxyl radicals react with 1,4-dioxane to oxidize the molecule to harmless reaction products (water, carbon dioxide, and residual chloride). The decay of 1,4-dioxane by UV-oxidation in a laboratory study generated several intermediates identified and quantified as aldehydes (formaldehyde, acetaldehyde, and glyoxal), organic acids (formic, methoxyacetic, acetic, glycolic, glyoxylic, and oxalic acids) and the mono- and diformate esters of 1,2-ethanediol (ethylene glycol). (Stefan and Bolton, 1998).

In the presence of hydroxyl radicals produced by direct photolysis of hydrogen peroxide, 1,4-dioxane decays rapidly following first order kinetics with a rate constant of $k = (8.7 \pm 0.4) \times 10^{-3}\ s^{-1}$ (much higher than that determined for the direct photolysis of dioxane, $(6.4 \pm 0.3) \times 10^{-5}\ s^{-1}$). Within the first five minutes of UV irradiation, almost 90% of the initial concentration of 1,4-dioxane was depleted, while four major primary reaction intermediates, 1,2-ethanediol mono and diformate esters, formic acid, and methoxyacetic acid were generated. These byproducts undergo further oxidative degradation initiated by hydroxyl radicals, leading to glycolic and acetic acids, and finally to oxalic acid as the end product. As these reactions progress, pH has been measured to drop from 5 to 3.25 within the first 12 minutes, then slowly to a minimum of 3.12 within 25 minutes, and gradually increases to 4.2 by the end of the 60-minute UV irradiation period (Stefan and Bolton, 1998).

Dioxane is characterized as a very weak absorber of ultraviolet light; direct photolysis is not expected. In experiments studying the decay products of dioxane in UV-oxidation, 1 mM 1,4-dioxane and 15mM hydrogen peroxide were exposed to UV light in the 200 to 400 nm wavelength range. Hydrogen peroxide absorbed 50% of the UV light entering the Rayox reactor while dioxane absorbed only 0.15% (Stefan and Bolton, 1998).

Stefan and Bolton (1998) found that for their particular configuration, the removal of dioxane itself requires 46 kWh/kg of carbon in the contaminant mass, however the removal of the residual total organic carbon follows zero order kinetics in two stages, requiring higher electrical energy input, about 1500 kWh/kg in the first five minutes, followed by 418 kWh/kg for the next twenty minutes.

Ozonation of many synthetic organic compounds has been shown to enhance their biodegradability. Ozone is a strongly selective oxidant. Advanced oxidation processes utilize hydroxyl radicals, which are much stronger oxidants, non-selective, and have reaction rate constants often 9 orders of magnitude greater than ozone for the same organic compounds (Fahataziz and Ross, 1977; McGrane, 1997).

An evaluation of the effectiveness of the oxidant combination of ozone and hydrogen peroxide found that biodegradation of 1,4-dioxane was enhanced following oxidation. Neither ozone nor hydrogen peroxide alone readily oxidized 1,4-dioxane. The optimum peroxide/ozone molar ratio lies within the range of 0.5 to 1.0 for most industrial wastewaters. Below this range, less than the stoichiometric amount of hydrogen peroxide is added, precluding efficient conversion of ozone to hydroxyl radicals. Above this

range, hydrogen peroxide may increase scavenging by hydroxyl radicals without increasing oxidation efficiency, or cause excessive residual hydrogen peroxide concentrations in effluent. Competition for oxidants during advanced oxidation was observed from bicarbonate alkalinity, which scavenges hydroxyl radicals, and also from other synthetic organic compounds, including 1,3-dioxolane. Anaerobic pretreatment of industrial wastewaters containing 1,4-dioxane may be effective at reducing the net chemical oxidant demand (Adams, et al, 1994; McGrane, 1997).

Safarzadeh, et al, (1997) compared visible-range UV photolysis of ferrioxalate in the presence of hydrogen peroxide for treatment efficiency of tank bottom waters including 1,4-dioxane, and found the UV/ferrioxalate/H_2O_2 process significantly more efficient than either the UV/H or UV/Fe(II)/H_2O_2 (UV-Fenton) processes, by a factor of 3 to 30.

Example Applications of Advanced Oxidation Processes for 1,4-Dioxane Removal from Groundwater

Applied Process Technologies Inc. (APT) has developed an advanced oxidation process proven effective at removal of 1,4-dioxane from high-volume flows containing elevated concentrations of chlorinated solvents, at line pressures without ultraviolet light. APT's HiPOx™ system meters hydrogen peroxide at about 7 ppm through an injection system, while introducing ozone at about 9%. The performance of this system has been studied at two groundwater treatment facilities in the San Gabriel Basin (southern California), and proven effective at removal or 1,4-dioxane and reduction of chlorinated solvents. Installation of HiPOx™ units ahead of conventional treatment systems such as liquid granular activated carbon will significantly extend the life of the carbon vessels by reducing influent concentrations of VOCs. The advanced oxidation process employed in APT's HiPOx™ units is *p*H dependent, therefore treatment of air stripper of carbon vessel treatment system effluent is not viable, because *p*H variations from acid addition or other scale control measures will impair system performance (Bowman, et al, 2001).

Calgon Carbon markets a medium-pressure peroxide UV oxidation system that does not use ozone, thereby avoiding formation of undesirable bromates. Capital costs for a system installed in La Puente, California were approximately $135,000, with operating costs estimated at $50/acre-foot in a normal power market for a 2,500 gpm drinking water treatment system with peroxide addition at 5 mg/L for removal of low concentration 1,4-dioxane and NDMA (nitrosodimethylamine, a contaminant of liquid rocket fuel). In another Calgon installation, a 170 gpm system for 110 ug/L 1,4-dioxane and a treatment target of 2 ug/L cost $150,000 to install, and about 50 cents per 1,000 gallons to operate. Calgon markets the Rayox® reactor system to handle non-adsorbable, non-strippable organic compounds such as 1,4-dioxane, NDMA, PAH's, pentachlorophenol and other phenols. In another installation at a chemical manufacturing facility in Salisbury, North Carolina, three 90 kW Rayox reactors were installed to treat up to 615 gallons per minute of water contaminated with 1,4-dioxane up to 2.5 mg/L, reducing concentrations to less than 10 ug/L (99.96% destruction), at a cost of about 75 cents per thousand gallons. (Calgon Carbon, 2001, Drewery, 2001)

Hydrogeochem, of Tucson, Arizona, markets another variation of the UV-oxidation system for 1,4-dioxane treatment. Hydrogeochem has developed low pressure UV-oxidation systems for a site at which perchlorate, NDMA, and 1,4-dioxane are contaminants. They have also developed tools to optimize concentrations and flow rates to minimize energy costs. For a drinking water system in La Puente, CA (San Gabriel Basin Water Authority) operating at 600 gallons per minute, a system that reduced 1,4-dioxane from 8 ug/L to 2 ug/L is operated at a cost of 19 cents per 1,000 gallons, and cost $240,000 to install. Success of this technology is dependent on water clarity. UV light with a transmittance of 254 nanometers is used, and should have 90% penetration for optimal performance. Nitrate interferes with UV light transmittance, even in turbidity-free water (Kuhn, 2001).

A team of engineers from Blasland, Bouck, and Lee presented this account of their experience at successfully designing and operating a UV-oxidation treatment system for 1,4-dioxane (Alonso, 2001):

A printed circuit board plant in Tampa, Florida, used degreaser tanks for preparing printed circuit boards Leaks from the tanks steadily released solvent and still bottoms including TCE and TCA. Remedial investigations and treatment system design by previous investigators did not initially look for or account for 1,4-dioxane, nor did regulatory orders require it. The solution to remove 1,4-dioxane was a system provided by Calgon Carbon Oxidation Technologies. Initial 1,4-dioxane concentrations in extracted groundwater are less than 20 ug/L, however treated effluent in Florida may not exceed 5 ug/L, the Florida drinking water standard. The system is designed with four 30 kW units in series. Capital cost was about $200,000, with life-cycle cost expected to be about $1.8 million. While capital costs are considered similar to conventional stripping and polishing systems, realized operating costs for UV-oxidation are considerably higher. The peroxide feed solution, a 50% mixture, costs $0.35 per pound. UV lamps are $3,000, and since they burn with a surface temperature of about 2000° F, they are short-lived and must be replaced three times per year. System controls require frequent inspection and adjustment, as slight variations in flow, mixture, or other interrelated parameters may cause treatment targets to be missed or lamps to overheat.

5.3 Potential for Biodegradation of 1,4-dioxane and 1,3-dioxolane

There has not yet been a peer-reviewed publish account of documented biodegradation of 1,4-dioxane under ambient in-situ conditions, and research completed to date suggests indigenous soil bacteria do not possess the metabolic ability to biodegrade ethers. Enhanced biodegradation in ex-situ engineered bioreactors, or by isolation, culturing, and introduction of specific microbe strains capable of metabolizing cyclic ethers in the presence of specific cometabolites and nutrients, remains promising.

Biodegradation of 1,4-dioxane and 1,3-dioxolane in-situ is not presently considered a viable remediation option. The ether bond is a highly stable linkage and not readily biodegraded under ambient conditions (Zenker et al, 2000). No data were located which suggest biodegradation is an important fate process of 1,3-dioxolane in soil or water under ambient conditions. The biochemical oxygen demand of 1,4-dioxane was found to be negligible after twenty days of observation, and no biodegradation of dioxane was observed in cultures of sewer microorganisms exposed for one year at 100 to 900 mg/L. Dioxane concentrations up to 300 mg/L had no adverse effect on the performance of activated sludge (Klecka and Gonsior, 1986).

Cultures of naturally occurring organisms have been reportedly isolated that are capable of biodegradation of 1,4-dioxane under controlled conditions (Adams, et al, 1994).
Using microorganisms acclimated to a mixed domestic and industrial wastewater with a dioxane concentration of 1,080 mg/L and a total organic carbon of 5,200 mg/L, 44% removal of dioxane was observed after 44 days (Roy et al, 1994). This microbial population was also shown to be capable of degrading pure 1,4-dioxane in the absence of other industrial wastes or organic matter. For initial concentrations of 150, 300, and 670 mg/L 1-4,dioxane, reductions of 100%, 67.5%, and 49.5% were obtained, respectively. The biodegradation of pure 1,4-dioxane in batch reactors appears to result in the formation of toxic byproducts, inhibiting biologic activity after a threshold reduction is obtained (Roy et al, 1994).

Mycobacterium vaccae reportedly catabolize 1,4-dioxane less than 50% when incubated at 30°C for 48 hours on a rotary shaker and using propane as a substrate. M. vaccae were not able to use dioxane as a sole source of carbon to support growth (Burback and Perry, 1993).

In soil microcosm studies of 1,4-dioxane and tetrahydrofuran, no biodegradation of either compound was exhibited when incubated under ambient conditions. When incubated at 35° C, however, complete biodegradation of both compounds occurred in soil previously exposed to 1,4-dioxane, and to which phosphorous and trace minerals were added. Biodegradation of 1,4-dioxane in these studies depended on elevated incubation temperatures and the presence of tetrahydrofuran (Zenker et al, 1999).

In pure culture, an actinomycete was found to degrade 1,4-dioxane at a rate of 0.33 mg of dioxane per minute per milligram of protein. The strain CB1190 was isolated from a dioxane contaminated sludge sample after first enriching the culture with yeast extract and tetrahydrofuran, and incubating the culture aerobically. Strain CB1190 was the first reported pure culture demonstrating sustained growth on 1,4-dioxane as a sole carbon and energy source. In three replicate samples, 60% of carbon from dioxane was converted to CO_2. No other organic byproducts or other intermediates accumulated in the medium, suggesting complete metabolism. CB1190 was tested on other ethers, with the fastest growth rate found for tetrahydrofuran, and no growth found on 1,3-dioxolane and MtBE. Direct enrichments of CB1190 were unsuccessful; early enrichments in the isolation process appeared to be cometabolizing 1,4-dioxane in the presence of tetrahydrofuran (Parales et al, 1994).

Biodegradation of 1,4-dioxane in a laboratory scale fluidized bed reactor was studied using the propane oxidizing bacterium ENV425 acclimated to methyl tert butyl ether (MtBE) (Vainberg, et al, 1999.) After 4 months of acclimation to MTBE, an influent concentration of 8 mg/L 1,4-dioxane was added, and following an additional month of operation, more than 60% of the influent concentration of 1,4-dioxane was removed during a 2 hour hydraulic residence in the reactor.

Research performed at Clemson University confirmed that microorganisms capable of metabolizing 1,4-dioxane under controlled aerobic wastewater treatment conditions could be cultured (Sock, 1993). McGrane (1997) confirmed bacteria could degrade 1,4-dioxane in the presence of tetrahydrofuran using an innoculum or return-activated sludge from four industrial waste treatment processes, all of which had been historically exposed to 1,4-dioxane, in a submerged attached growth air-lift reactor. Cultures of 1,4-dioxane degrading bacteria were developed that proved capable of degrading 1,4-dioxane in the absence of tetrahydrofuran, and eventually in the absence of residual organic carbon (McGrane, 1997).

5.4 Innovative In-Situ Treatment Technologies and 1,4-dioxane

Fenton's Reagent

Fenton's reagent has been used in the mineralization of 1,4-dioxane in process wastewater, however chemical costs and reaction time requirements limited the feasibility of this process (McGrane, 1997). No published work was found documenting in-situ use of Fenton's Reagent to eliminate 1,4-dioxane in groundwater.

Phytoremediation

Phytoremediation, the use of vegetation for remediating contaminated soil and groundwater, has been investigated for its suitability for removal of 1,4-dioxane in groundwater. Hybrid poplar cuttings (*Populus deltoides X nigra*, DN 34, Imperial Carolina) removed 23 mg/L 1,4-dioxane rapidly, at 54± 19% within 9 days. Phytoremediation was also determined to effectively remove 1,4-dioxane from soil, with only 18.8 ± 7.9% of the initially spiked concentration remaining after 15 days. In both hydroponic experiments for groundwater remediation and soil experiments, 76 to 83% of the dioxane taken up by poplars were transpired from leaf surfaces to the atmosphere, where it can be readily dispersed and photo-degraded. The poplar cuttings used in this study did not exhibit visible toxic effects when subjected to water contaminated with 1,4-dioxane. Phytoremediation is considered a relatively inexpensive treatment alternative, costing 10 to 50% of conventional treatment technologies such as soil excavation, and providing a more aesthetically pleasing appearance to the contaminated site (Aitchison et al, 2000).

Effectiveness of phytoremediation is limited to shallow groundwater settings where contamination is confined to a limited depth within the root zone of poplar trees. Long-term stabilization of contaminated soil for which excavation and stockpiling is otherwise required is another viable application for phytoremediation. For low-flow groundwater treatment regimens, above-ground hydroponic treatment systems may also be a viable solution for 1,4-dioxane removal.

5.5 Treatability of 1,4-dioxane and 1,3-dioxolane in POTWs

Dioxane is essentially immune to biodegradation by microorganisms under conditions normally present in conventional industrial and municipal biotreatment processes. No significant aerobic biodegradation was achieved by microorganisms acclimated to municipal wastewater, soils, or to other synthetic organic chemicals. Dioxane is also not amenable to biodegradation under anaerobic conditions (Adams, et al, 1994).

Treated effluent from a wastewater treatment plant serving several apartment complexes in Japan was found to contain an average of 0.25 mg/person/day. Sources of dioxane in households discharging to the treatment plant were presumed to be shampoos, and liquid dishwashing and laundry soaps, which contain from 0.2 to 0.56 mg/L dioxane (Abe, 1999).
1,4-Dioxane exhibited a negligible biological oxygen demand in two activated sludge experiments and the compound has been classified as relatively non-degradable (Lyman et al, 1982). Abe (1999) found that dioxane in domestic wastewater was not significantly removed at a treatment plant which used an activated sludge process, supporting the general understanding that dioxane is a recalcitrant compound, relatively immune to biodegradation under ambient conditions. The biochemical oxygen demand of dioxane was found to be negligible after twenty days of observation, and no biodegradation of dioxane was observed in cultures of sewer microorganisms exposed for one year at 100 to 900 mg/L (Klecka and Gonsior, 1986).

1,4-Dioxane was detected at 1 ug/L in effluents from the North Side and Calumet sewage treatment plants on the Lake Michigan basin (Konasewich, et al, 1978). 1,3-Dioxolane was qualitatively detected in 4 samples of final effluents taken from 3 publicly owned treatment works (POTWs) in Roselle, Danville, and Decatur, Illinois (Ellis et al, 1982).

Recycled wastewater used for groundwater recharge should be tested for 1,4-dioxane to ensure this practice isn't introducing a highly mobile and recalcitrant contaminant to the aquifer.

CONCLUSIONS AND RECOMMENDATIONS: IMPLICATIONS FOR SOLVENT CLEANUP SITES

Where solvents have been released from spills, leaks, and dumping, particularly at facilities whose operational use of TCA extends for decades and where groundwater contamination by TCA is extensive, the presence of 1,4-dioxane should be expected. Accordingly, site investigations and remedial designs that have failed to account for this contaminant are incomplete and should be revisited with at least sampling and analysis for 1,4-dioxane in treatment system influent and effluent, in the core of the plume, and at the sentinel wells beyond the leading edge of the plume.

The consequence of finding 1,4-dioxane in groundwater, treatment system effluent, recycled wastewater, or water supply wells is made somewhat ambiguous by the lack of a legal standard for human health and other beneficial uses of groundwater. Cleanup criteria are currently issued at restrictive levels, while some toxicologists believe that physiological based pharmaco-kinetic models support higher limits.

Much work remains to characterize the patterns of occurrence and migration of 1,4-dioxane and other stabilizers, to develop federal maximum contaminant levels, and to refine treatment technologies to effectively remove these contaminants from groundwater.

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Introduction

Industrial solvents used in degreasing, electronics, metal finishing, fabric cleaning, and many other applications are commonly formulated with additives to enhance their performance. These additives, known as *solvent stabilizers*, serve to prevent solvent breakdown and to inhibit reactions that may degrade solvent properties. Many solvent stabilizer compounds are present at volumetrically inconsequential proportions to be considered significant for solvent release site investigation and cleanup. One ether stabilizer, 1,4-dioxane, has been included with 1,1,1-trichloroethane (TCA, also called methyl chloroform) in mixtures at 2 to 8% by volume, and has proven to be a contaminant of concern at solvent release sites. Other solvent stabilizer compounds may also be problematic. The industrial applications in which solvents are used, such as cold vapor degreasing, tend to increase the proportion of some stabilizers in condensate relative to the host solvent. Once these waste residuals are spilled, leaked, or dumped to the subsurface, 1,4-dioxane tends to be refractory to the biotransformation of TCA, resulting in further increases in the relative proportion of stabilizers.

Solvent stabilizer compounds have thus far received relatively little attention from regulatory caseworkers and remedial project managers at solvent release sites. 1,4-dioxane was not detectable at low concentrations in a standard laboratory scan for chlorinated solvents, and Maximum Contaminant Levels have not been established for this compound. This may explain why solvent stabilizer compounds are not routinely analyzed in groundwater at solvent release sites, or included in the cleanup objectives of regulatory orders. It is only within the past few years that improvements to laboratory methods for 1,4-dioxane have made it possible to obtain reliable detections at concentrations comparable to other volatile organic compounds. Familiarity with solvent stabilizer compounds can aide in site investigation, remedial design, forensic investigations, and water supply management.

California's regulatory guidance for 1,4-dioxane is a Department of Health Services Drinking Water Action Level (3 ug/L). 1,4-dioxane is listed as a Class II-B probable human carcinogen, and is known to damage the kidneys. 1,3-dioxolane, an alternative stabilizer for TCA, has similar physical and chemical properties to 1,4-dioxane (see Section 2.1, below); however, it is not listed as a US EPA Clean Water Act Priority Pollutant.

1,4-dioxane is not significantly removed by conventional pump and treat technologies (air stripping and carbon adsorption), and is generally resistant to biodegradation. Advanced oxidation processes, the primary available treatment technology successful in removing 1,4-dioxane from groundwater, is expensive and energy-intensive.

This report summarizes information obtained on solvent stabilizers from an extensive literature review, and presents the nature and use of solvent stabilizers, how they behave in the subsurface, a description of laboratory analytical techniques, a summary of toxicological information for solvent stabilizer compounds, and a survey of the effectiveness and costs of available treatment technologies. Calculations of expected migration rates are contrasted with case study examples. Implications for solvent release site remediation, forensic investigations, and groundwater basin management are also discussed.

1.0 SOLVENT STABILIZERS

Chlorinated solvents sold for use in metal cleaning, degreasing, electronics, and textile cleaning applications require solvent stabilizer compounds to ensure proper performance in the intended application. Without these compounds, solvents tend to break down in the presence of light, heat and oxygen, or react with acids and metal salts.

1.1 Purpose of Solvent Stabilizers

Addition of solvent stabilizers is necessary to supply solvents with acid acceptors, metal inhibitors, and antioxidants.

During the degreasing process, both solvents and oils can decompose and produce strong acids. These acids, usually hydrochloric acid, can corrode the parts being cleaned and the cleaning equipment itself. Acid acceptors react with and chemically neutralize trace amounts of hydrochloric acid formed during degreasing operations. Acid acceptor compounds are either neutral (epoxides) or slightly basic (amines), and react with hydrochloric acid, forming an alcohol in the process (Archer, 1984). If left unneutralized, hydrochloric acid can cause solvent degradation.

Metal inhibitors deactivate metal surfaces and complex any metal salts that might form. Metal stabilizers are Lewis bases that inhibit solvent degradation reactions in the presence of a metal and its chloride (e.g. aluminum and aluminum chloride). The inhibitor either reacts with the active aluminum site, forming an insoluble deposit, or complexes with aluminum chloride, preventing degradation of the solvent.

Antioxidants reduce the solvent's potential to form oxidation products (Archer, 1984). Antioxidants suppress the free radical chain decomposition reaction of unsaturated solvents by forming stable resonance hybrids and slowing the propagation step of auto-oxidation (Joshi et al, 1989).

1.2 Solvent Compositions and Stabilizer Packages

TCE and TCA require both metal inhibitor and acid acceptors, while TCE also requires an antioxidant (Archer 1996). Perchloroethylene (PCE) is relatively stable and requires only minor amounts of acid inhibitors for degreasing operations, but no metal inhibitors (Keil, 1978). Methylene chloride (MC) is also quite stable, requiring less than 0.1% acid inhibitors by volume.

Producers of chlorinated solvents emphasize the stability of their products in their marketing literature. For example: "NEU-TRI™ solvent [a TCE formulation] is highly stabilized for vapor degreasing. Its unique combination of stabilizers makes it especially effective for long-term use. The stabilizer system prevents the build-up of acid in the degreaser and also protects against metal corrosion and reaction in the solvent." (Dow Chemicals, 2001).

Composition of 1,1,1-Trichloroethane
Uninhibited (unstabilized) TCA may react with aluminum to produce aluminum chloride, 2,2,3,3-tetrachlorobutane, 1,1-dichloroethylene; and hydrogen chloride. Adequate metal inhibitors can prevent TCA-aluminum reactivity and allow the solvent to be used in aluminum metal-cleaning applications (Archer, 1979).

The solvent stabilizer packages added to commercially available TCA vary with grade and producer. Actual compositions are difficult to obtain because the formulas are proprietary. Viewing Material Safety Data Sheets (see Table 1.1), a general sense can be obtained for the variation of solvent composition and the inclusion of stabilizer compounds in the formulation. Several producers of TCA now use 1,3-

dioxolane instead of 1,4-dioxane, and some (Great Western Chemical) advertise their product as "Dioxane Free". Many current applications of TCA list 1,3-dioxolane as the stabilizer present at the greatest weight fraction, for example 3% in a cleaning solvent, 3% in "electrical grade silicon bulk", 2-3% in a tire-cleaning solvent, and 3% in a brake-cleaning solvent (Cornell University, 2001 a,b,c,d; Alonso, 2001)

One producer, Occidental Chemical, lists TCE as present in its formulation of TCA, but no weight fraction is specified. All of the MSDS referenced in Table 1.1 were obtained from the Internet in 2001; older formulations may have used different proportions, and discussions with solvent producers provide an anecdotal basis for greater amounts of these additives in past decades (Mertens, 2000; HSIA, 2000). The multitude of synonyms and trade names for the chemicals added to solvents as stabilizers and inhibitors can lead to confusion for non-chemists. Table 1.2 summarizes synonyms of the more common solvent stabilizers.

Table 1.1 Composition of 1,1,1-Trichoroethane from Material Safety Data Sheets

Compound	Fischer	Vulcan	J.T.Baker	PPG	UnoCal Chem	Occ. Chem.	GW Chem.
TCA	95%	>95%	96-100%	95 %	96-98%	96 –97 5%	95%
Nitromethane						0.2 –0.5%	
1,2-butylene oxide		<0.5%	< 0.5%				
1,4-dioxane	~5%		< 3%	+	0-4%	2 – 2.7%	0%
sec-butanol				<2%			1 – 2%
1,3-dioxolane		<3%		<2%			2%

("+" indicates present but weight fraction not specified. From web search for MSDS sheets for currently available formulations; does not reflect compositions of solvents used in past decades)

Table 1.2 Synonyms for Common Solvent Stabilizers

1,4-DIOXANE	*1,3-DIOXOLANE*	*1,2-BUTYLENE OXIDE*	*TETRAHYDRO FURAN*	*EPICHLOROHYDRIN*
DX	1,3-dioxolan	1,2-Epoxybutane	THF	Chloromethyloxirane
1 4-Diethylene-dioxide	Glycolformal	EBU	1,4-epoxybutane	glycidyl chlonde
		Propyl Oxirane	furanidine	chloropropylene oxide
diethylene oxide	1,3-dioxole	Epoxybutane	Cyclotetra-methylene oxide	Glycerol epichlorohydnn
p-dioxane	dioxolane	2-Ethyloxirane	tetramethylene oxide	1,2-epoxy-3-chloropropane
tetrahydro-1,4-dioxan	Glycol methylene ether	**DIMETHYL AMINE**	hydrofuran	3-chloro-1,2-epoxypropane
			oxacyclopentane	
Dioxyethylene-ether	dihydroethylene glycol formal	DMA	Oxolane	(chloromethyl)-ethylene oxide
Glycolethylene ether	formal glycol	N-methyl-methanamine	***NITROMETHANE***	gamma-chloropropylene oxide
			NMT	1-chloro-2,3-epoxypropane
			Nitrocarbol	2,3-epoxypropyl chlonde

Composition of Trichloroethylene

TCE composition also varies with grade, producer, and intended application, but generally stabilizers comprise less than 1% of TCE. Stabilizers in TCE formulations include a long list of specialty compounds, most of which are not reflected on Material Safety Data Sheets due to the small quantities of additives and the proprietary nature of commercial solvent formulations. Table 1.3 presents a compilation of individual stabilizer compounds added to TCE as listed in the cited references.

Table 1.3 Additives to Trichloroethylene at Concentrations Totaling Less than 1%

Epichlorohydrin	1,2-epoxybutene	2,2,4-trimethylpentene-1
[1,4-dioxane]**	Propanol	Thymol
1,3-dioxolane	diethyl amine	amyl alcohol
Triethylamine	Isoeuganol	Diethanolamine
pentanol-2-triethanolamine	n-methylpyrrole	Isocyanates
styrene oxide	cyclohexene oxide	Diisopropylamine
p-tert-butylphenol	n-ethyl pyrrole	ethyl acetate
Diisobutylene	Thiazoles	Alkoxyaldehyde hydrazones
Pyridine	p-tert-amylphenol	5,5-dimethyl-2-hexene
1,2-propylene oxide	tetrahydrofuran	glycidyl acetate
Tetrahydropyran	Trioxane	n-methylmorpholine
2-methoxyphenol	borate esters	pentene oxide
Morpholine	Aniline	3-methoxy-1,2-epoxy propane
Isocyanates	Butadiene oxide	2-methyl-1,2-epoxypropanol
2,3-epoxy 1-propenol	o-cresol	Nitropropanes
Epoxy cyclopentanol	Stearates	(2-pyrryl)-trimethylsilane
methyl ethyl ketone		
n-methylpyrrole		

Sources: Kircher, 1957, Hardie, 1964, Mertens, 1993, Archer, 1996, Vonder Haar et al, 1994, Joshi et al, 1989, US EPA, 1984. **Primary evidence for the presence of 1,4-dioxane in TCE could not be found by the author or Doherty, 2001, although numerous articles list it as an additive to TCE. Officials at DOW Chemical assert that 1,4-dioxane was not a constituent of TCE (Mertens, 2001). Kircher, 1957, lists "normal ethers and inner ethers" as stabilizers of TCE, but does not explicitly list 1,4-dioxane.

Jackson and Dwarakanath (1999) presented many of these compounds classed by chemical type and purpose, as shown in Table 1.4:

Table 1.4 – TCE Additives classed by chemical type and purpose

Chemical Type	Examples	Purpose
Aliphatic amines	Triethylamine, diisopropyl-amine	Free radical scavengers
Heterocyclic nitrogen compounds	Pyridine, pyrrole, alkyl pyrroles	Antioxidants
Substituted phenols	2-methoxyphenol, cresol	Antioxidants
Oxygenated organics	1,4-dioxane, acetone, butylene oxide, propylene oxide, tetrahydrofuran, epichlorohydrin	Acid acceptors**

(after Jackson and Dwarakanath, 1999) **Jackson and Dwarakanath identify 1,4-dioxane as an acid acceptor, while Joshi et al, 1989, identify it as an aluminum stabilizer in TCA which is not needed in TCE.

Stabilizers are continually depleted during normal degreasing operations. Dow Chemical markets Maxistab™ (packaged stabilizer concentrates) for use with TCE and PCE in vapor degreasing applications. These products are said to boost performance and extend the use of the solvent. A vapor degreasing test kit for monitoring the solvent to determine when new stabilizers are required is also available (DOW Chemical 2001).

Presence of stabilizers in TCE cannot be readily discerned from current MSDS sheets, as the quantities added, often in the parts per million range, do not meet the threshold for listing. Table 1.5 summarizes a review of currently available MSDS Sheets for TCE.

Table 1.5 Composition of Trichoroethylene from Material Safety Data Sheets

Compound	ChemCentral/Kansas	Fisher	New Hermes Neu-TRI (DOW)	Baxter
Trichloroethylene	99.4%	100%	>99%	99%
1,2-butylene oxide (epoxybutane)	0.5%		<1%	1%

Methylene Chloride

Methylene chloride (DCM, also called dichloromethane) is preferred for low-temperature applications, to clean electronic parts with temperature sensitive components. It is generally distributed as 99.9% MC, with stabilizer additives commonly in the parts per million range. Cyclohexane, cyclohexene, amylene, and other olefins and hydrocarbons may be included with DCM to inhibit reactions with metals.

Methylene Chloride is a stable compound when pure and free of moisture, and will not corrode common metals such as mild or galvanized steel, copper, tin, nickel or lead. In contact with free phase moisture, however, DCM may slowly hydrolyze to form acidic by-products that will corrode these metals. The rate of the corrosion process is self-accelerating. Pure DCM absorbs atmospheric moisture slowly but will eventually become saturated.

DCM is less reactive to light metals such as aluminum, magnesium, and their alloys, than many other chlorinated solvents. These metals are naturally insulated from corrosion by the presence of an oxide film. Contact with well-stabilized DCM will not normally produce an adverse reaction. However, if the oxide layer is broken, for example by the metal surface becoming scratched, and the fresh, active metal surface comes into contact with DCM which is unstabilized, or has depleted or inadequate stabilization, a Friedal-Craft reaction can be initiated. Once started, the reaction will proceed rapidly, and in some cases explosively, with the evolution of heat and large quantities of hydrochloric acid (Chlor-chem, 2001).

Percholorethylene

Perchloroethylene (PCE, also called tetrachloroethylene) does not require a metal inhibitor, but may require acid acceptors for degreasing applications. In the presence of light and air, PCE slowly autooxidizes to trichloroacetyl chloride. Stabilizers, such as amines or phenols, inhibit the decomposition process to extend solvent life and protect equipment and materials. Cyclohexene oxide and butoxymethyloxirane are also listed as inhibitors in PCE (Joshi et al, 1989). Compared to other chlorinated ethanes and ethenes, PCE is relatively stable, and generally requires only small amounts of stabilizers (Keil, 1978).

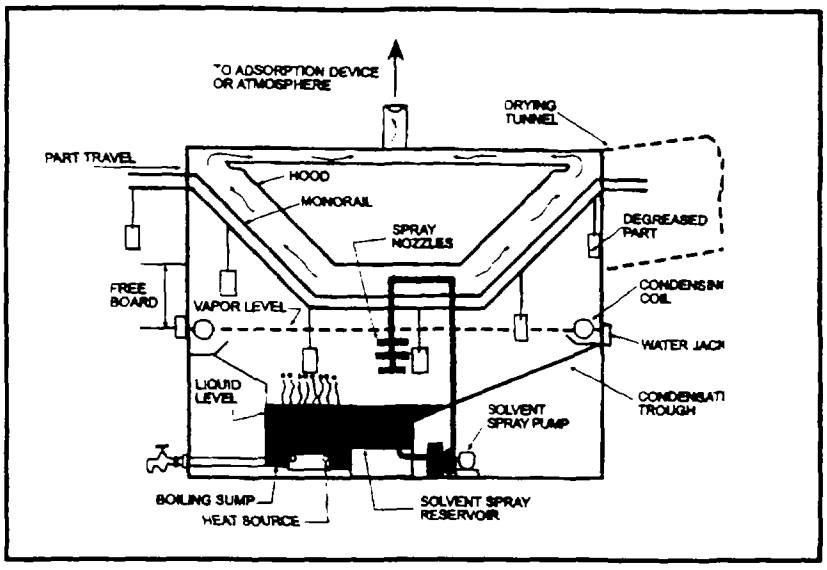
1.3 Relative Proportions of Stabilizers in Vapor Degreasing Waste Residuals

Vapor Degreasing

A vapor degreaser is an enclosed chamber with a solvent reservoir and a heat source to boil the solvent, and a cooling surface to condense the vapor in the upper section. A schematic of a vapor degreasing system is shown in Figure 1.1. Metal objects from which grease will be removed are hung in the air-free zone of solvent vapor. The hot vapor condenses onto the cool parts dissolving oils and greases and providing a continuous rinse in clean solvent (ASTM, 1989; Murphy, 2000).

In vapor degreasing systems, stabilizers partition between the vapor phase and boiling liquid phase according to their boiling points. 1,4-dioxane boils at 101° C while TCA boils at 74°C (see Table 2.1). Systems designed to handle heavy loads of oil and grease are designed to distill the solvent for ongoing purification. In such vapor degreasers, additives such as 1,4-dioxane tend to be concentrated in sludges known as still bottoms. In vapor degreasing systems used by the aerospace industry, still bottoms generated by typical in-process distillation is composed of 70% to 80% solvent and 20 to 30% oil, grease, and solids with traces of water. In electronics industry manufacturing using CFC-113, still bottom compositions of 85 - 95% CFC113 with oil and flux comprising 5 to 15% (Jackson, 1999; Evanoff, 1990). Solvents are also reclaimed using activated carbon; however, this technique selectively sorbs some additives, requiring their reintroduction after reclamation.

Figure 1.1 Typical Vapor Degreaser Configuration



A study on the effects of distillation on solvent stabilizers and inhibitors for different solvents found that distillation significantly concentrates several stabilizers in still bottoms. Tables 1.6a, 1.6b, and 1.6c, below, profile results of this study (Joshi, et al, 1989). For all three solvents studied, stabilizers were retained in still bottoms in excess of 35% of their concentrations in the feed spent solvent. Used TCA showed a 68% increase in the weight fraction of 1,4-dioxane. This study also found that usage in vapor degreasers not equipped with in-process distillation units caused concentrations of several inhibitors and stabilizers to decrease with duration of use.

Table 1.6a ***Stabilizer Concentrations of Reclaimed Trichloroethylene***

(Joshi et al, 1989)	Inhibitor Concentration (weight fraction)			
Sample	**Butylene Oxide** ($x10^3$)	**Epichlorohydrin** ($x10^3$)	**Ethyl Acetate** ($x10^4$)	**Methyl Pyrrole** ($x10^4$)
New TCE	1.64	1.66	3.46	1.59
Spent TCE	0.685	1.69	2.85	2.18
TCE Distillate	0.718	1.61	2.58	1.66
Carbon Adsorbed TCE	0.44	1.31	2.65	0.90

Table 1.6b ***Stabilizer Concentrations of Reclaimed Perchloroethylene***

(Joshi et al, 1989)	Inhibitor Concentration (weight fraction)	
Sample	**Cyclohexene Oxide** ($x10^3$)	**Butoxymethyl Oxirane** ($x10^3$)
New PCE	1.06	4.26
Used PCE	0.988	7.45
PCE Distillate	0.968	5.42
Carbon Adsorbed PCE	0.091	5.40

Table 1.6c *Stabilizer Concentrations of Reclaimed 1,1,1-Trichloroethane*

(Joshi et al, 1989)	Inhibitor Concentration (weight fraction)		
Sample	**n-methoxy-methanamine** ($x10^4$)	**Formaldehyde dimethyl-hydrazone** ($x10^3$)	**1,4-Dioxane** ($x10^3$)
New TCA	8.92	5.78	17.2
Used TCA	4.14	6.16	29.0
TCA Distillate	4.60	7.22	19.6
Carbon Adsorbed TCA	1.30	3.37	23.4

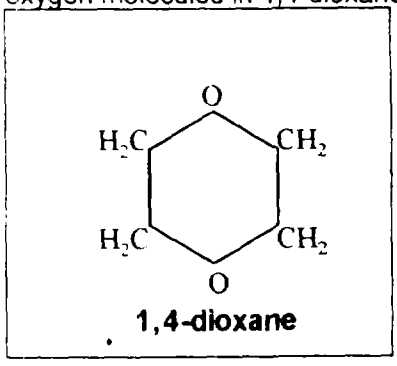
Guidance for operation of vapor degreasers often calls for adding additional solvent to restore solvent performance, thus further concentrating stabilizers in the still bottoms with each addition of new solvent. Waste solvent released to soil and groundwater from improperly disposed still bottoms may therefore have a substantially higher fraction of stabilizers than was originally formulated, particularly in the case of 1,4-dioxane and TCA.

Because vapor-degreasing processes consume solvent stabilizers and inhibitors or concentrate stabilizers in still bottoms, operators may also add stabilizers back into the solvent to ensure the solvent performs as intended. Stabilizer packages such as DOW Chemical's MaxiSTAB are marketed for this purpose. The need to reintroduce stabilizers into spent solvents has bearing for cleanup investigations at solvent recycling facilities, where solvent stabilizer compounds may have been stored in pure form to refortify spent solvents.

As the use of TCA has been phased out due to laws and taxes intended to reduce ozone depletion, alternative solvents have become available. Alternative vapor degreasing formulations, for example EnSolv Vapor Degreasing & Cleaning Solvent, use n-propyl bromide as an alternative solvent, but also use 3% 1,3-dioxolane as a stabilizer (Ensolv, 1996).

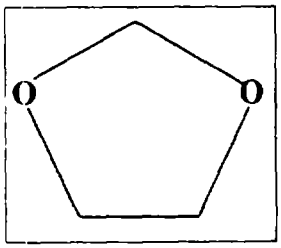
1.4 Chemistry of Solvent Stabilizers

1,4-Dioxane is a cyclic ether, and is also known by the synonyms *p*-dioxane, diethylene ether, diethylene dioxide, and glycol ethylene ether. It is a dimer of ethylene oxide. Dioxane is a Lewis base because the oxygen molecules in 1,4-dioxane have electrons available for sharing (a base is a proton acceptor; a Lewis base is an electron pair donor). The molecular structure of 1,4-dioxane is shown at left. Its two oxygen atoms make it hydrophilic and infinitely soluble in water. Dioxane has no dipole moment owing to the symmetrical position its two oxygen atoms. Dioxane boils at 101 °C (Windholz et al, 1983).



1,4-dioxane

1,4-Dioxane is made from diethylene glycol by heating and distilling glycol with dehydration catalysts such as sulfuric acid. It can also be manufactured by treatment of bis(2-chloroethyl)ether with alkali, or by dimerization of ethylene oxide (IARC, 1972).



1,3-dioxolane is a stable reaction product of ethylene glycol and formaldehyde. It is a volatile liquid, miscible with water in all proportions. 1,3-dioxolane has a melting point of –95°C, and a boiling point of 78°C. 1,3-dioxolane is also known by the synonyms dioxolane; glycol methylene ether; 1,3-dioxacyclopentane; glycolformal; 1,3-dioxoledioxolane; dihydroethylene glycol formal; and formal glycol.

1.5 Other Uses of Solvent Stabilizer Compounds in Manufacturing

Approximately 90% of the 1985 1,4-dioxane production in the United States was used as a stabilizer for chlorinated solvents, particularly, TCA (US EPA 1995). Knowledge of other industries using 1,4-dioxane in pure form, or producing 1,4-dioxane as a by-product of manufacturing, may aide in site investigation and forensic geochemical investigations for source apportionment.

1,4-dioxane is used in numerous industrial processes and is included with a variety of consumer and commercial products. Table 1.7 summarizes common applications of 1,4-dioxane. 1,4-dioxane may also occur as a by-product of some manufacturing processes, and as a contaminant in some products.

Table 1.7 Additional Industrial and Commercial Uses of Dioxane

Solvent in paper manufacturing	as a wetting & dispersing agent in textile process
Paints, lacquer, and varnish remover	In microscopy
Stain and printing compositions	as a purifying agent in pharmaceuticals
In liquid scintillation counters	In resins, oils, waxes, and cements
In deodorants, shampoos & cosmetics	In fumigants
Impregnating cellular acetate	as an additive in aircraft deicing fluid formulations
'inert' ingredients of pesticides	as an additive in antifreeze
As a by-product formed during esterification of polyester	

(Sources: Montgomery, 1996; Beernaert et al, 1987; Mackison et al, 1981; US EPA, 1979; ILO, 1979; NCI/DCE, 1985);

Polyethoxyleated surfactants used in detergents may contain dioxane formed during the polymerization of ethylene oxide. (Black et al, 1983; Abe, 1996, US EPA, 1999b). 1,4-dioxane is a contaminant in some surfactant compounds used in herbicides, such as polyoxyethyleneamine in the isopropylamine salt of glyphosate, an ingredient in the most common herbicides (common trade names Roundup, Pondmaster; Rattler; Rodeo) (Briggs et al, 1992; Brooks, et al, 1973). 1,4-dioxane and epichlorohydrin are listed as contaminants of toxicological concern among inert ingredients of pesticides (US EPA, 1989).

Cosmetics containing ethoxylated surfactants may be contaminated by 1,4 dioxane (Scalia et al, 1992). In shampoo manufacturing, 1,4-dioxane is introduced into the product via the use of ethoxylated fatty alcohol sulfates as cleansing agents. During the process of alcohol ethoxylation, ethylene oxide can dimerize to form 1,4-dioxane, which is subsequently carried through the shampoo manufacturing process[1]. A variety of commercially available cosmetics, including shampoos, liquid soaps, sun creams, moisturizing lotions, after-shave balms, baby lotions, day creams, and hair lotions, were analyzed for 1,4-dioxane; 56% of the total products investigated contained 1,4-dioxane with levels ranging from 3.4 to 108.4 mg/kg (Italia and Nunes, 1991). 1,4-dioxane is commonly found in treated wastewater effluent and landfill leachate (see Section 2.6, below). Many producers have begun vacuum stripping procedures in their manufacture of the fatty alcohol sulfates to limit contamination of their products by 1,4-dioxane.

1,4-dioxane is a by-product in the production of polyethylene teraphthalate (PET) plastic, and substantial soil and groundwater contamination has occurred at some PET manufacturing facilities and waste sites in North Carolina (Zenker, 2001). 1,4-dioxane is used to impregnate cellular acetate membranes in the

[1] For those curious to know whether their sundries may contain 1,4-dioxane, the following is a list of some of the commonly used ethoxylated ingredients in shampoos and other cosmetic products: Sodium laureth sulfate; Ammonium laureth sulfate; Triethanolamine laureth sulfate; Cocamide; Cocamide DEA; ingredients with TEA, MEA, DEA, MIPA, PEG; Polysorbates, Triethanolamine; Sodium C14-16 Olefin Sulfate (Sulphonate); Disodium Oleomido Sulfosuccinate; Cocamidopropyl Betaine; Ammonium Cocoyl Isethionate; Ammonium Lauryl Sulphate; Sodium C12-15 Pareth Sulfonate; Disodium Cocoamphodiacetate. Presence of these ingredients does not equate to presence of 1,4-dioxane, it only establishes an increased likelihood of its presence if vacuum removal of 1,4-dioxane is not employed during manufacturing. Direct testing is the only valid means of verification, and probably is not warranted. 1,4-dioxane has a comparatively low dermal toxicity to laboratory animals (see Section 4.3).

production of filters used in reverse osmosis and in laboratory and groundwater sampling filters. The Gelman Sciences facility in Scio, Michigan, which manufactures groundwater sampling filters familiar to groundwater professionals, is the site of one of the nation's largest releases of 1,4-dioxane in groundwater, where the municipal water supply has been impacted (Michigan Department of Environmental Quality, 2001).

1,3-dioxolane

1,3-dioxolane is primarily used for the production of polyacetals and other polymers (rigid plastics). Only 5% is used for other purposes, including stabilizers for halogenated organic solvents (Dioxolane Manufacturers Consortium, 2000).

1.6 History of Solvent and Solvent Stabilizer Production and Use

The following discussion highlights which solvents were preferred for common industrial applications in the past four decades, and accordingly, which stabilizers may have been released from past mishandling of solvent wastes.

TCE was the preferred solvent used in many industrial applications throughout the fifties and sixties. In the late 1960s, TCE came under increasing scrutiny for occupational exposure because it was identified as an animal carcinogen. As a result, many firms switched to TCA. During the late 1980s and early 1990s, many firms using Freon-113 as a solvent converted to TCA as it is a less potent ozone depleter. Because of the current production ban on TCA, some firms are now converting back to TCE.

1,4-dioxane has been produced in commercial quantities by relatively few American manufacturers (Table 1.8). In 1990, between 10.5 and 18.3 million pounds of dioxane were produced in the United States. Approximately 90% of the 1985 1,4-dioxane production was used as a stabilizer for chlorinated solvents, particularly TCA.

Table 1.8 Major American Producers of 1,4-dioxane

Manufacturer	Headquarters Location	Production Location
Ferro Corporation	Cleveland, Ohio	Baton Rouge, Louisiana
CPS Chemical Company Inc.	Old Bridge, New Jersey	New Jersey
Dow Chemical USA	Midland, Michigan	Freeport, Texas

(Source: Stanford Research Institute, 1989)

Table 1.9 Production Data for 1,4-dioxane, Pounds per Year

1973	1974	1975	1976	1977	1982
1,620,485	1,762,775	1,258,150	1,485,683	1,222,467	6,750,000

(Source, United States International Trade Commission, 1994)

The date that a manufacturer began synthesizing a chlorinated solvent is frequently used as evidence regarding when it was available at a facility. This approach assumes that potential suppliers and/or products containing chlorinated solvents are known. Table 1.10 identifies manufacturers of four chlorinated solvents in the United States from 1908 to 2000 (Morrison, 2001, after Doherty, 2000).

Table 1.10 Period of Solvent Production by Manufacturer

MANUFACTURER	TCE	TCA	MANUFACTURER	TCE	TCA
Carbide & Carbon Chemicals	1922-1935	-	Pittsburgh Plate Glass/ PPG Industries	1956-2000	-
Diamond Alkali/ Diamond Shamrock	-	-	PPG Industries	-	1962-2000
Dow Chemical	1921-2000	1936-1994	R&H Industries	1925-1972	-
DuPont Company	-	-	Vulcan materials	-	1970-2000
Ethyl Corporation	1967-1982	1964-1976	Westvaco Chlorine	1933-1949	-
Hooker Chemical/ Occidental Chemical	1956-1980	-	Diamond Shamrock	1969-1977	-
Hooker-Detrex/Detrex Chemical	1947-1972	-	Niagara Alkali	1949-1955	-

(adapted from Morrison, 2001. First compiled by Richard Doherty, and presented on the Internet by Robert Morrison)

1.7 History of Solvent Waste Disposal Practices

Historical handling, storage, and disposal practices for chlorinated solvents and their wastes have resulted in widespread soil and groundwater contamination by solvents. In the Silicon Valley, where accelerated demand for semiconductors and printed circuit boards lead to rapid expansion of the electronics industry in the 1970s, the large quantities of solvents needed for wafer fabrication and parts cleaning. Public safety agencies required that these solvents and solvent wastes be stored in underground tanks. Many of these tanks and associated piping leaked, resulting in numerous instances of soil and groundwater contamination.

Among the oldest citations of solvent contamination of groundwater, the following text is an excerpt from a description of TCE contamination of groundwater in England published in the Analyst, in March of 1949 by F. Kyne and T. McLachlan (cited in Morrison, 2001).

> *Cases of contamination of wells by trichloroethylene have come to our notice. In the first, the well was situated beside a factory that used large quantities of trichloroethylene as a solvent. During a fire at the factory a tank of the liquid burst and the ground was saturated with the solvent. After more than four years the water in the well still had an odour of trichloroethylene and the well had to be abandoned. The well was sunk in gravel only about 20 feet from a river and one might have expected that the movement of water through the gravel would have removed the contaminant.*
>
> *In the other case, the well was situated 150 to 200 yards from a pit in an open field where waste trichloroethylene had been dumped. It was in valley gravel and in the direct line of flow towards the river. The water in it had a slight odour of trichloroethylene and was said to cause stomach disorders, giddiness, etc. The amount of trichloroethylene in the water was found to be 18 parts per million when estimated by . a modification of the Fujiwara pyridine-sodium hydroxide reaction. From these two cases it is evident that contamination by compounds of this nature is likely to be very persistent and there is some evidence of toxicity at very low concentrations.*

Users of chlorinated solvents were routinely advised to dispose of waste solvents,by pouring onto the ground or into trenches for evaporation or burning. As we now know, these practices resulted in significant soil and groundwater contamination by still bottoms. The following industry guidance, cited in Pankow and Cherry, 1996, is notable:

Routine disposal practices Vapor Degreasing Sludge that Contains Chlorinated Solvents (1964):

> *Any procedure for disposal depends on local, state and federal regulations. In the absence of any clearly defined ordinances, the sludge is usually poured on dry ground well away from buildings, and the solvents are allowed to evaporate. If the sludge is free flowing, it is placed in shallow open containers and allowed to evaporate before the*

solids are dumped on the ground. [American Society of Metals, Metals Handbook: Heat Treating, 8th Edition, Volume 2. Metals Park, Ohio]

Chlorinated Solvent Disposal (1972):

> *Waste mixtures should not be discharged into drains or sewers where there is a danger that the vapor may be ignited. In cases such as these, the waste should be removed to a safe location (away from inhabited areas, highways, buildings, or combustible structures) and poured onto dry sand, earth, or ashes, then cautiously ignited. Burning of chlorinated hydrocarbon wastes should be done only when permitted by controlling authorities and then under constant supervision. In other instances, the chlorinated hydrocarbon waste may be placed in an isolated area as before and simply allow the liquid to evaporate. [Chemical Hazards Bulletin, American Insurance Association, C-86, March 1972. New York, NY. Pg. 42]*

At electronics manufacturing, metals fabrication, and other industrial solvent release sites in the 1960's, 1970's and 1980's, improper disposal of still bottoms was often the cause of solvent contamination. Given the evidence for elevated concentrations of solvent stabilizers in still bottoms, stabilizers are likely to be present at these sites at elevated concentrations.

2.0 Environmental Occurrence and Subsurface Behavior of Solvent Stabilizer Compounds

Like many commonly used industrial chemicals, 1,4-dioxane is widespread in the atmosphere and hydrosphere. This section examines the properties of 1,4-dioxane and other solvent stabilizers that dictate its behavior in the atmosphere, surface water, and groundwater, presents calculations of expected migration rates of 1,4-dioxane in groundwater, and cites laboratory and field studies of 1,4-dioxane's propensity to move relatively unimpeded through the subsurface.

2.1 Physico-Chemical Properties of Solvent Stabilizers

Ethers, which include 1,4-dioxane and 1,3-dioxolane, have been classified as generally resistant to hydrolysis (Lyman et al, 1982). 1,4-Dioxane has a moderate vapor pressure at 25 °C (37 mm Hg). Volatilization from dry soil may be significant. The linear partitioning coefficient between soil organic matter, or humic substances, and dissolved phase 1,4-dioxane (K_{OC}) is 1.23. As this value is low compared to most compounds, 1,4-dioxane is not expected to significantly sorb to suspended sediments or soil organic matter (Lyman, et al, 1982, Kenaga, 1980). 1,4-dioxane exhibited a negligible biochemical oxygen demand in two activated sludge experiments and the compound has been classified as relatively non-degradable. It is expected, therefore, that 1,4-dioxane will not biodegrade extensively in the aquatic environment (Lyman, et al, 1982).

Table 2.1 summarizes key physico-chemical properties governing fate and transport processes for common solvent stabilizer compounds and the solvents to which they're added.

Table 2.1 Properties of Common Solvent Stabilizers and Host Solvents

Property	1,4-dioxane	1,3-dioxolane	1,1,1-trichloro-ethane	Tetrahydro Furan	1,2-butylene oxide	Trichloro-ethylene
CAS RN (a)	123-91-1	646-06-0	71-55-6	109-99-9	106-88-7	79-01-6
Molecular weight	88.10 [4]	74.09	133.4	72.11	72.12	131 39
Molecular Form	$C_4H_8O_2$	$C_3H_6O_2$	$C_2H_3Cl_3$	C_4H_8O	C_4H_8O	C_2HCl_3
H_2O Solubility mg/L @ 20°C	Miscible	Miscible	1,360	Miscible	82,400	1,100
Boiling Pt. °C at 760 mm Hg	101.1 °C	78°C	74.1	66°C	63°C	87°C
Vapor Pressure Mm Hg @ 20° C	37 mm Hg @ 25° C	70 mm Hg @ 20°C	96 mm Hg @20 °C	114 mm Hg @ 15°C	140 mm Hg @20°C	55 mm Hg @ 20°C
Vapor Density	3.03 [6]	2.6	5.45	2.5	2.2	5.37
Henry's Const. atm-m3/mol	3×10^{-6}	2.4×10^{-5}	1.5×10^{-2}	7.06×10^{-5}	$\sim 1.6 \times 10^{-4}$	9.9×10^{-3}
Log K_{ow}	0.43	- 0.37	2.49	0.46	0.26	2.6
Log K_{oc}	0.54	1.18	2.85	1.37		2.6
Specific Gravity	1.03 @ 20°C	1.06 @ 20°C	1.34 @ 20°C	0.8892	0.84@17°C	1.46 @ 20°C

Sources: Montgomery, 1996; Mackay et al, 1996; Verschueren, 1983; Lyman, et al, 1982; Hansch et al, 1995; Sax, 1984.

The hydrophilic nature of 1,4-dioxane, 1,3-dioxolane, tetahydrofuran, and 1,2-butylene oxide makes these compounds miscible or highly soluble, in either case significantly more soluble than TCA and TCE. The mobility of a compound in the subsurface is directly proportional to its solubility. Hydrophilic compounds are only weakly retarded by sorption during transport. Retardation of chlorinated organics is expected to be directly proportional to the octanol-water partition coefficient (K_{OW}), such that these stabilizers will migrate much more quickly than their host solvents (Jackson and Dwarakanath, 1999).

2.2 Susceptibility to Microbial Degradation

1,4-dioxane is not typically degraded by indigenous soil microorganisms under ambient conditions (Fincher et al, 1962; Howard, 1990). Under enhanced conditions, or where selected strains of bacteria capable of degrading 1,4-dioxane are cultured, microbial degradation has been documented to be viable in engineered bioreactors (see Section 5.3 for discussion). Like MtBE, which was at first thought to be highly resistant to microbial degradation, there is promise for the use of microbial degradation in the cleanup of 1,4-dioxane from extracted groundwater.

2.3 Simulated Migration of Solvent Stabilizers Using BIOCHLOR

To determine expected relative rates of migration of 1,4-dioxane, 1,3-dioxolane, and TCA in groundwater, transport and biotransformation of TCA, and transport of 1,4-dioxane and 1.3-dioxolane without biodegradation were modeled. The objective of the modeling was to anticipate relative rates of migration at release sites, and the relative distances within which regulatory thresholds would be exceeded for the stabilizers, TCA, and the biotransformation products of TCA, 1,1-dichloroethane and chloroethane. At actual solvent release sites, 1,4-dioxane has been found to migrate considerably farther in groundwater than TCA or its breakdown products (see Section 2.5). The model selected to estimate relative rates of migration was US EPA's BIOCHLOR.

BIOCHLOR is a spreadsheet template developed for the USEPA that executes an analytical solute transport model for a saturated, anaerobic, porous medium that may include any or all of the following processes: one-dimensional advection, dispersion in up to three dimensions, instantaneous sorption, and biotransformation (Aziz et al, 2000). The model is used as a tool to predict the spatial distribution of the concentration of chlorinated ethenes or ethanes in porous media. The advection-dispersion equation contains terms that account for various transport processes and can be adjusted or eliminated individually. A source of contamination is defined by width and thickness measured as the distance from the top of the water table downward. The duration of the source is defined (denoted as the simulation time). The source may be of constant concentration or undergo first order decay.

The results of this modeling exercise do not necessarily represent true behavior of a mixture of these compounds as would be expected in the field. Among other basic limitations, running BIOCHLOR separately for the chlorinated ethanes, 1,4-dioxane, and 1,3-dioxolane ignores any competitive sorption that may occur, thereby possibly underestimating the spatial extent of an actual plume. Competitive sorption is likely to occur between DCA, chloroethane, dioxane, and dioxolane, since they have similar linear organic carbon partitioning coefficients (K_{OC}). TCA, however, has an order of magnitude larger K_{OC} and therefore would experience relatively less competition. The model does not account for aquifer heterogeneities such as channels or other preferential pathways. Use of BIOCHLOR in this application is not intended to simulate dioxane migration absolutely. It is used to simulate relative mobility and persistence of 1,4-dioxane and 1,3-dioxolane in contrast to the host solvent TCA.

Hydraulic and soil properties of an aquifer studied at the Cape Canaveral Air Station, Florida, included as a preloaded case study in BIOCHLOR, were used to model transport of TCA, 1,4-dioxane, and 1,3-dioxolane (Table 2.2). With the exception of redefining source dimensions (50 feet wide by 5 feet in thickness), dispersivities, simulation time, and domain length, all other parameters were left as the defaults of the Cape Canaveral case study for TCA simulations. Table 2.3 summarizes the transport parameters for each compound. The model imposes first order decay of TCA and its two degradation products, DCA and chloroethane, terminating in sequential fashion with ethane. Sorption is modeled according to K_{OC} values. In cases of multiple contaminants, the median K_{OC} was arbitrarily used. No biotransformation was assumed for 1,4-dioxane and 1.3-dioxolane.

Table 2.2 Hydraulic parameters for modeled domain.

Seepage velocity	111.7 ft/y	α_x	26.9
Conductivity	0.018 cm/s	α_y	2.69
$\alpha_x, \alpha_y, \alpha_z$ = dispersivities (ft)		α_z	0

Table 2.3–Regulatory levels and transport properties of modeled compounds.

	TCA	DCA	Chloroethane	1,4-dioxane	1,3-dioxolane
Regulatory level ug/L	200	5	16	3	-
K_{OC}(L/kg)	426	130	125	-	15.1
R	7.13	2.87	2.8	1.1	1.22
Degradation, λ (yr^{-1})	2.0	1.0	0.7	0	0

R -value used in model for all chlorinated ethanes.

Dispersion is a term inclusive of physical processes that cause a plume to shear. Fixed values for dispersivities in the mean flow and horizontally orthogonal directions were used in all model runs. The BIOCHLOR model was run several times using different source durations with an initial aqueous concentration of 100 mg/L TCA (zero initial concentrations of degradation products). Separate trials were performed each for 1,4-dioxane at initial concentrations of 3 and 15 mg/L and 1,3-dioxolane at 3 mg/L.

The 3 mg/L scenario represents virgin TCA released to groundwater, while the 15 mg/L scenario is intended to represent the release of still bottoms enriched with respect to 1,4-dioxane due to partitioning in the vapor degreasing process. Modeling 1,3-dioxolane at 3 mg/L was done to estimate behavior of currently available formulations of TCA in the subsurface; the two stabilizers are not expected to both be present in high proportions in TCA. 1,3-dioxolane was not modeled higher than 3 mg/L because enrichment of still bottoms with 1,3-dioxolane is not expected to any significant degree due to its boiling point being within a few degrees of the boiling point for TCA.

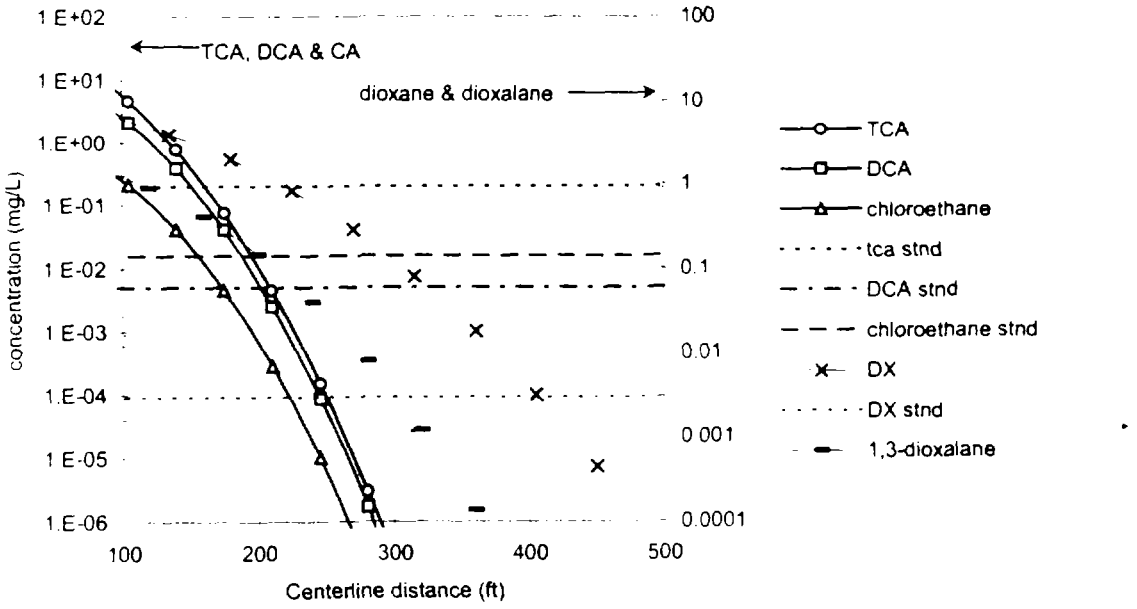


Figure 2.1 ***BIOCHLOR*-modeled transport of chlorinated ethanes, 1,4-dioxane (DX), and 1,3-dioxolane; 1-year continuous source release; source concentrations: 100 mg/L TCA, 15 mg/L 1,4-dioxane, and 3 mg/L 1,3-dioxolane. ("stnd" = regulatory threshold)**

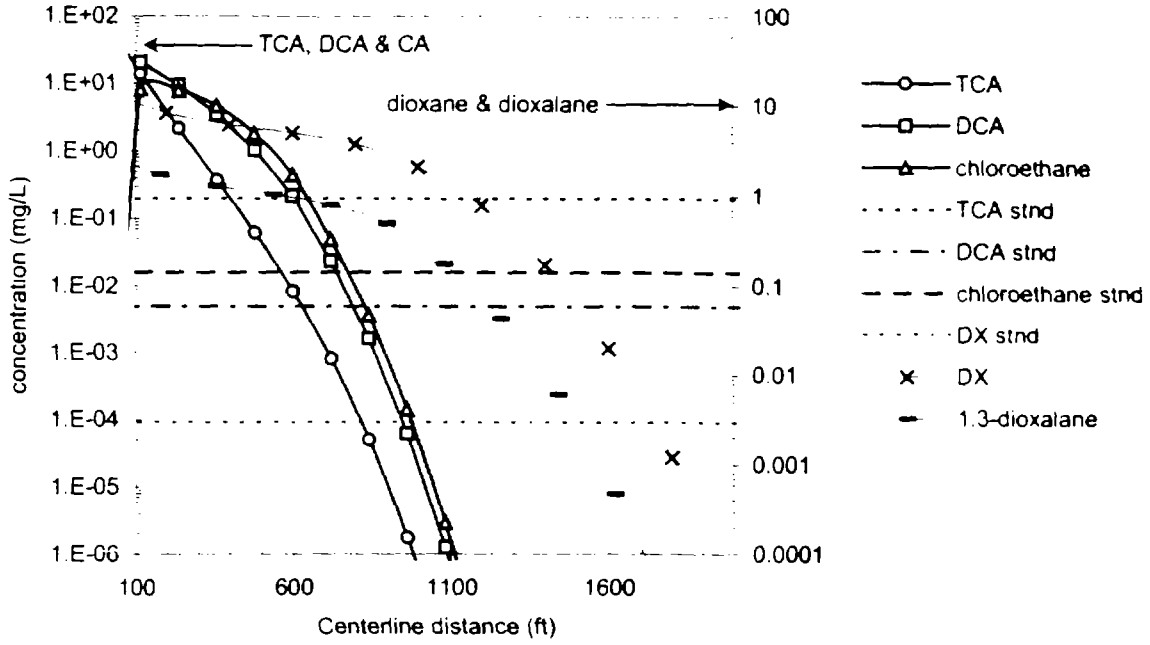


Figure 2.2–*BIOCHLOR*-modeled transport of chlorinated ethanes, 1,4-dixoane (DX), and 1,3-dioxolane; 10-year continuous source release; source concentrations: 100 mg/L TCA, 15 mg/L 1,4-dioxane, and 3 mg/L 1,3- dioxolane.

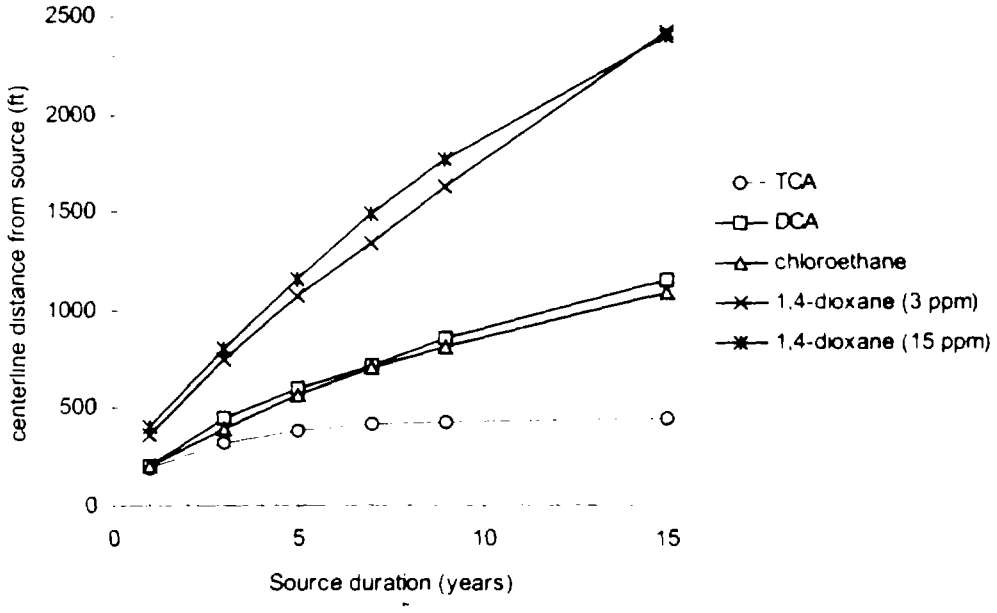


Figure 2.3–*BIOCHLOR*-modeled distance along plume centerline at which contaminant concentration exceeds regulatory levels (source TCA concentration 100 mg/L).

BIOCHLOR does not account for movement of solvents in the subsurface as dense non-aqueous phase liquids; only dissolved phase movement is considered. The initial concentration modeled, 100 mg/L, is less than 10% of the overall solubility of TCA.

Figure 2.1 illustrates the distribution of the various compounds along the centerline of the plume. 1,4-dioxane and 1,3-dioxolane persist over larger distances from the source than the chlorinated ethanes due to lower sorption, incorporated in a lower retardation factor (R), and lack of biochemical degradation. Figure 2.2 illustrates similar results for a 10-year source duration. Differing by only a lower estimate of R (1.1 compared to 1.22), an initial concentration of 3 mg/L 1,4-dioxane would appear parallel and slightly higher than the curves for 1,3-dioxolane (Figures 2.1 and 2.2). Figure 2.3 illustrates the distance from the source at which the contaminant concentration reaches the regulatory level (see Table 2.3) as a function of the source lifetime.

2.4 Migration Experiments and Studies

Three studies have been conducted on the migration of 1,4-dioxane in soil and groundwater, by laboratory column studies and analysis of field observed plume behaviors. 1,4-dioxane passes through saturated and unsaturated soils relatively quickly due to its high solubility and low affinity for sorption to soil organic matter.

An adsorption coefficient (K_D) for 1,4-dioxane was estimated based on laboratory diffusion tests in a saturated and undisturbed clayey soil (Barone, et al, 1992). A K_D value of 0.17 mL/g was estimated for 1,4-dioxane, based on a measured diffusion coefficient of 4 $x10^{-6}$ cm^2/s in a clayey soil with grain sizes of clay (45%), silt (43%), sand (10%), and gravel (2%), and mineralogy of the sub-gravel grains as calcite/dolomite (34%), quartz and feldspars (15%), illite (25%), chlorite (24%), and smectite, (2%). Soil organic carbon content was 0.58%, and the cation exchange capacity of this soil was 10 milliequivalents per 100 grams dry weight. In contrast, the same study produced an estimated adsorption coefficient for toluene of 26 mL/g (Barone et al, 1992). Estimated breakthrough times for vertical transport in a clay soil were also given, with 1,4-dioxane advancing more than five meters in 100 years, while toluene advanced less than one meter in the same time frame. The inference made in this study is that given a leachate containing 1,4-dioxane in sufficient amounts, enough 1,4-dioxane could pass through a one-meter thick clay landfill liner in five years to contaminate underlying groundwater to concentrations in excess of drinking water action levels.

Another laboratory column experiment using cores of sandy aquifer material contrasted measured retardation factors of several volatile organic compounds to field derived retardation factors estimated from plume lengths at the Gloucester Landfill site in Ontario, Canada. Retardation factors were measured at different groundwater velocities and over different test durations. The measured retardation factors, listed in Table 2.4, compared well with field derived estimates based on plume lengths and purge tests. Dioxane and tetrahydrofuran were found to have the lowest retardation factors (Priddle and Jackson, 1991).

While the different methods for deriving retardation factors in Priddle and Jackson's study yield somewhat different results, strong evidence is provided for the propensity of dioxane and tetrahydrofuran to migrate much further than chlorinated solvents with which they are commonly released to aquifers. The failure of the Schwartzenbach and Westall equation[2] to accurately predict retardation factors is attributed to it being derived from empirical relationships of compounds with much higher octanol-water coefficients (K_{OW}).

At the Seymour Superfund site in Indiana, field sampled distribution of 1,4-dioxane, tetrahydrofuran, benzene, and chloroethane were compared to model-predicted transport distances. The model, a combination of USGS MODFLOW and the SWIFT code, accounted only for retardation and dispersion.

[2] see notes, Table 2.4

Table 2.4 Comparison of Retardation Factors in Column Tests and Field Derived Estimates for 1,4-dioxane, Tetrahydrofuran and other VOCs (Priddle and Jackson, 1991)

Compound	1) Plume Length	2) Purge Well	3) Correlation Equation	4) S & W equation	5) Column Center of Mass	6) Column C_{max}
1,4-dioxane	1.6	1.4	1.6	1.0	1.1	1.2
Tetrahydrofuran	2.2	2.2	2.5	1.0	-	-
Diethyl ether	3.3	3.0	3.4	1.1	1.7	1.6
1,2-DCA	7.6	nm	5.7	1.2	7.2	4 – 5
Trichloromethane	nm	nm	9.3	1.3	7.5	4 – 5
Benzene	8.8	nm	10.0	1.4	14.3	6 – 8
1,1-DCE	nm	nm	11.0	1.5	10.7	6 – 7

Notes: Retardation Factor = $R_f = 1 + \rho_b K_D / n = V_W/V_C$ where ρ_b is bulk density [M/L^3], K_D is contaminant distribution coefficient [L^3/M], n is the dimensionless porosity of the aquifer material, V_W is velocity of water, and V_C is velocity of contaminant. 1) R_f interpreted from length of organic compound plume vs. length of chloride plume. nm = not mapped or measured. 2) Purge well evaluation test, cited in Whiffin and Bahr, 1985. 3) Correlation equation log(Rf –1) = 0.5 log KOW - 0.065, from field data (Patterson et al, 1985). 4) Schwarzenbach and Westall equation: Rf = 1 + ρ_b KD/n where KD = 3.2 f_{OC} K_{OW} 0.72 (Schwartzenbach and Westall, 1981) 5) Column Tests comparing center of mass of organic compound to center of mass of iodide. 6) Column test comparing C/CMAX = 0.5 organic vs. C/CMAX = 0.5 of iodide.

Travel distance for 1,4-dioxane was accurately predicted, but failure to account for biochemical reactions resulted in an overestimated travel distance for the other compounds. 1,4-Dioxane was found to travel 2.5 times further than tetrahydrofuran. These two compounds have nearly identical retardation factors and solubilities, but tetrahydrofuran is slightly biodegradable whereas 1,4-dioxane is not amenable to biodegradation (Nyer et al, 1991).

Calculated and laboratory measured migration rates for 1,4-dioxane in the subsurface suggest this compound should move rapidly in groundwater, well ahead of a plume of chlorinated solvents. The following sections profile examples of measured 1,4-dioxane plumes.

2.5 Occurrence and Distribution of 1,4-dioxane at Solvent Release Sites

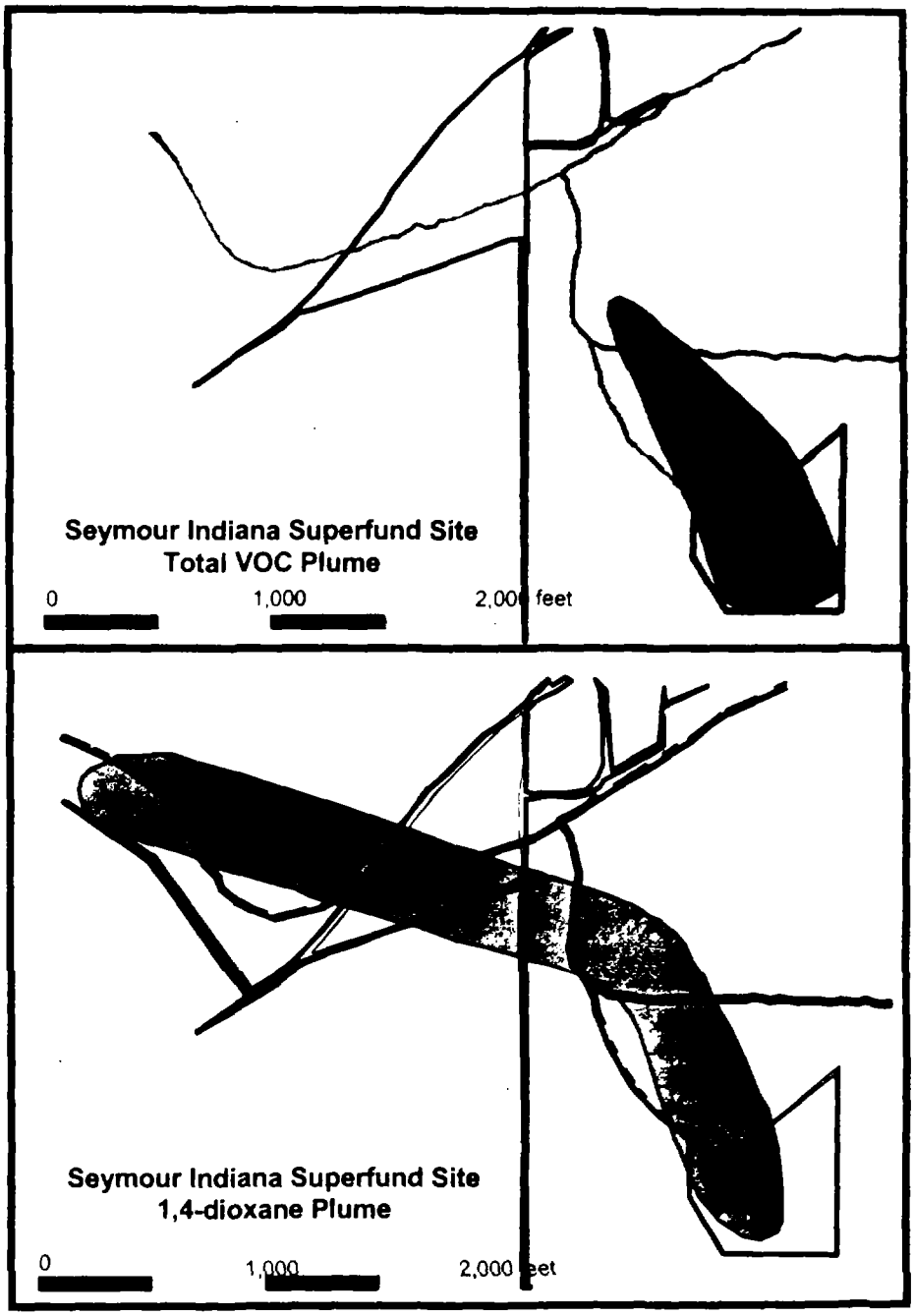
Data from contaminant release sites at which the occurrence and distribution of 1,4-dioxane has been characterized were collected with the goal of compiling a reference set for 1,4-dioxane plume behavior. Because there have been relatively few published studies, sources are primarily regulatory compliance reports obtained from those firms and agencies willing or able to share their work. While the resulting compilation is ad hoc in nature, useful attributes of 1,4-dioxane behavior in the subsurface can nonetheless be discerned.

Seymour, Indiana Superfund Site

A solvent recovery and recycling plant in Seymour Indiana went bankrupt after nine years of operation, abandoning 50,000 drums and 98 large tanks, all filled with organic chemicals, many of which were found to be leaking. This case is documented in detail in Fetter, 1994 (see page 494). Shallow groundwater flow was estimated to be 400 feet per year. In the space of six years, between 1984 and 1990, the plume of dioxane contaminated groundwater advanced approximately 2,000 feet, for a total length of approximately 3,500 feet. Data from July of 1999 provided by the remedial project manager for this site indicate that remedial efforts have been successful in capturing the plume of 1,4-dioxane at the Seymour Site (Feldman, 2000). Figure 2.4 presents the migration distances from sources at the Seymour site for total volatile organic compounds reported on a routine scan for halogenated VOCs, for tetrahydrofuran, and for 1,4-dioxane.

Fetter notes: "as it turned out, one of the tentatively identified compounds was more mobile and less subject to natural biodegradation than any of the compounds on the target organic list. The reported extent of this compound, 1,4-dioxane, a cyclical ether . . . and another mobile compound, tetrahydrofuran, had spread much farther than expected." Roy and Griffin, 1985, list 1,4-dioxane first, and tetrahydrofuran fourth, in a comprehensive list ranking the mobility of more than 100 organic compounds.

Figure 2.4



San Gabriel Basin, California Superfund Sites- Baldwin Park Operable Unit

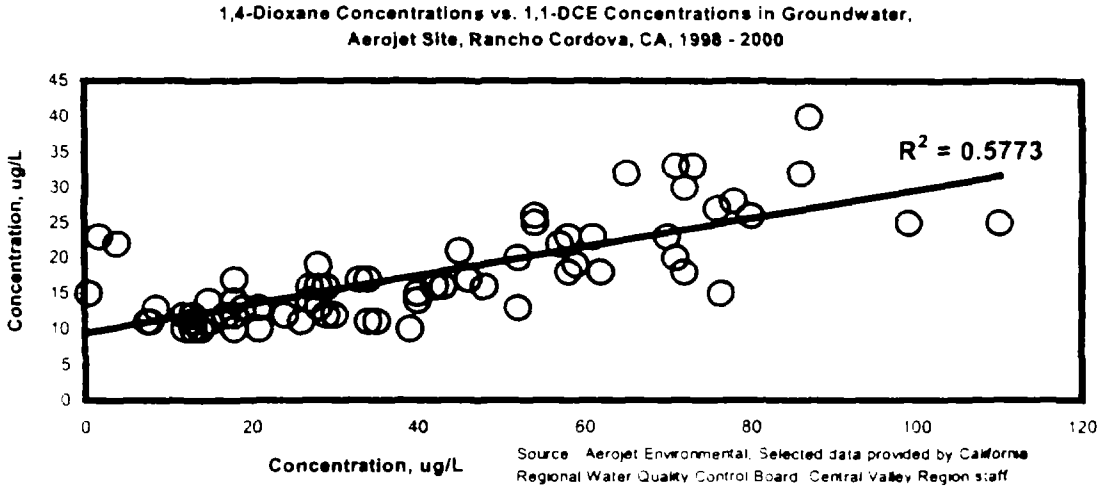
Several dozen sources have combined to form a plume extending eight miles in the San Gabriel Basin. 1,4-dioxane has been found to occur at many locations within the plume, but has not been found to extend significantly beyond the plume. One of the sources in this set of commingled plumes was a solvent recycler. Contamination by 1,4-dioxane has impacted some supply wells, requiring well-head treatment. In El Monte, California, the average ratio of 1,4-dioxane to the sum of TCA, and its daughter products DCA and DCE is 76% (Bowman, et al, 2001).

The City of Industry installed a high-volume air stripper to treat a suite of volatile organic compounds including TCE, TCA and PCE. After discovery of 1,4-dioxane and other contaminants at nearby contamination sites, influent flow was tested for 1,4-dioxane. Influent 1,4-dioxane concentrations measured at this air stripper were 610 ug/L, while effluent concentrations were 430 ug/L. The ratio of dioxane to the sum of TCA and DCA was 50% (Bowman, et al, 2001).

Rancho Cordova, California: Liquid Rocket Fuel Production Facility

1,4-dioxane has been detected during investigations for rocket fuel components at the Aerojet facility in Rancho Cordova, northern California, where it is believed to be associated with chlorinated solvents. A cursory review of available data for 74 analyses in which 1,4-dioxane was detected showed a moderate degree of correlation between 1,4-dioxane and 1,1-dichloroethylene (DCE), as shown in Figure 2.5. DCE is the abiotic transformation product of TCA. This should not be considered a rigorous analysis of data available from this site as non-detects were not included in the evaluation, and samples from the same wells on different dates were not weighted differently. No TCA detections are reported at this site; the solvent present in groundwater at highest concentrations is TCE.

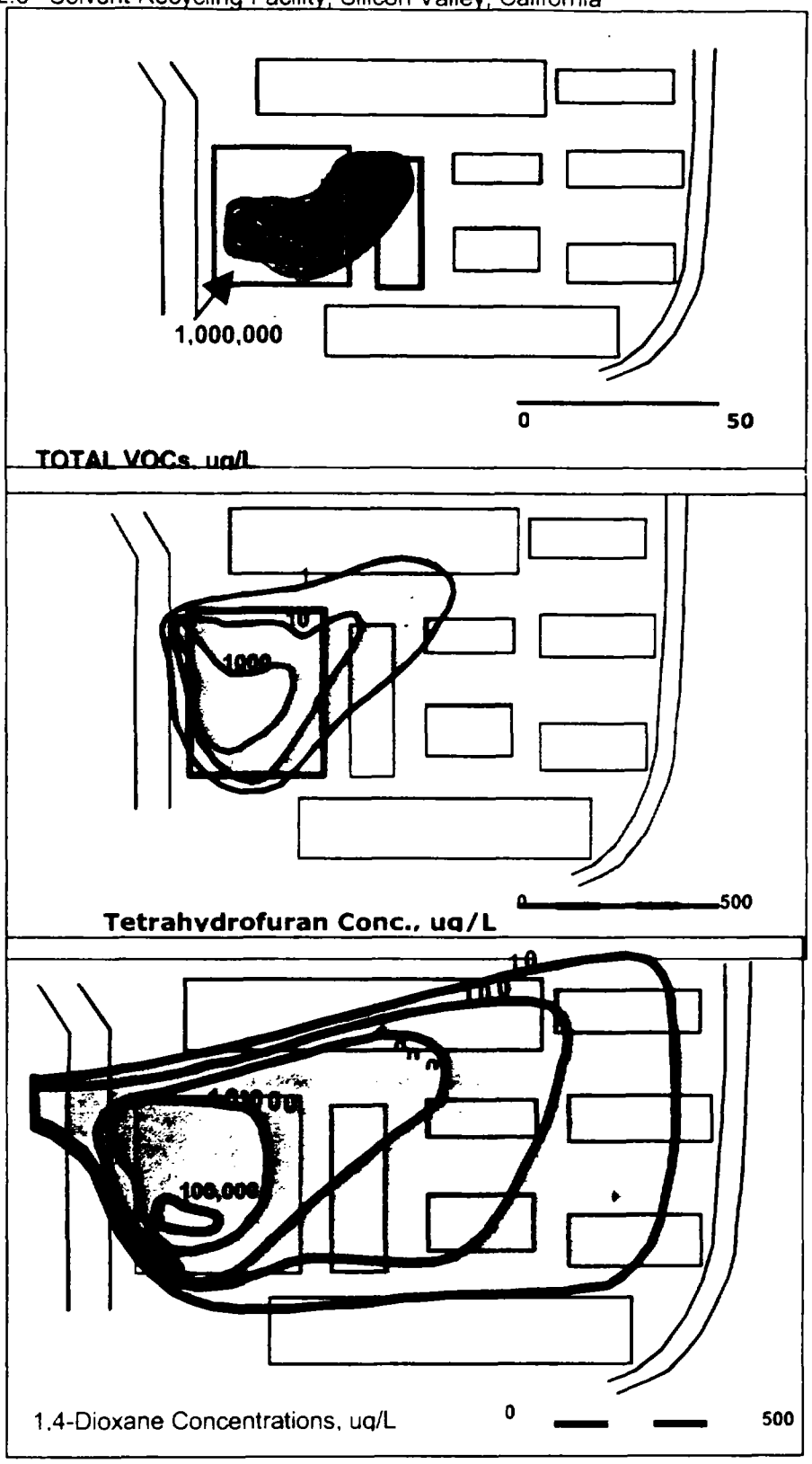
Figure 2.5 Correlation of 1,4-dioxane to 1,1,Dichloroethylene at Rancho Cordova Aerojet Site



Solvent Recycling Facility, Silicon Valley, California

A solvent recycling facility in Silicon Valley, California, had completed design and installation of plume capture and treatment systems to remove chlorinated solvents from a high concentration release when 1,4-dioxane and tetrahydrofuran were reported in 1998. Because concentrations reached a maximum of 340,000 ug/L, additional investigation was performed, and tetrahydrofuran and 1,4-dioxane were determined to have migrated considerably further than the VOCs. Figure 2.6 shows the relative migration of VOCs, tetrahydrofuran, and 1,4-dioxane (Safety Kleen, 2000).

Figures 2.6 Solvent Recycling Facility, Silicon Valley, California



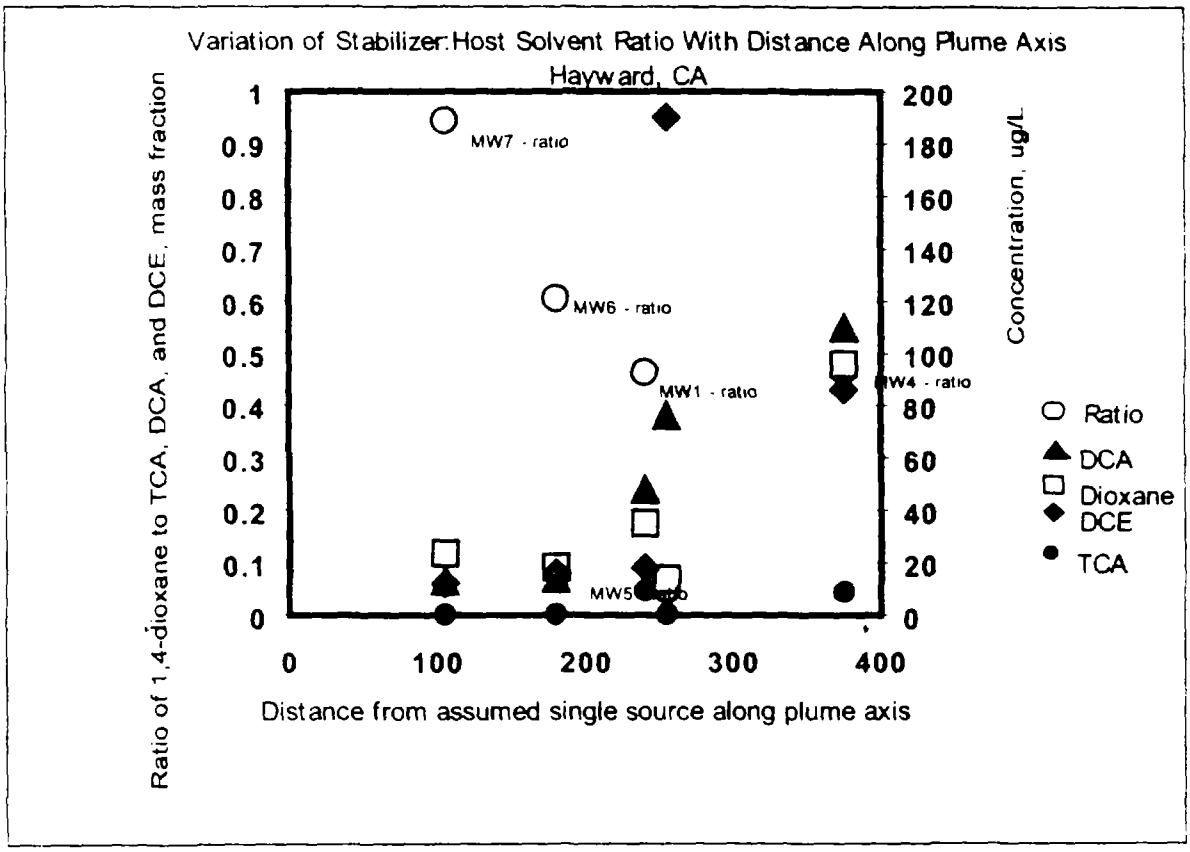
Hayward California, Aluminum Extrusion Facility

An aluminum products facility in Hayward, California at which TCA was used in a jet stream to wash aluminum product, released solvents and fuels to groundwater. Past practices allowed TCA to be released to the subsurface, forming a plume in which peak TCA concentrations were 16,000 ug/L. In 2000, 1,4-dioxane was analyzed in groundwater samples at the request of the Alameda County Water District hydrogeologist, and found to be present in an area of distribution greater than the host solvent, with peak concentrations at 94 ug/L (Trenholme, 2001).

Ratios of 1,4-dioxane to the sum of 1,1-dichloroethane, 1,1-dichloroethene, and TCA on five wells at this site ranged from 5% to 94%. Ratios decreased with distance from the source, counter to the expected trend. With increasing distance, biotransformation is expected to decrease TCA concentrations, resulting in a higher 1,4-dioxane to TCA ratio. Fuel constituents released near the source of the solvents may have resulted in cometabolism of solvents, or multiple sources may result in a more complicated pattern.

Figure 2.7 shows the relative distribution of solvent and stabilizers at this site. Figure 2.8 presents a bar chart contrasting 1,4-dioxane to host solvent concentrations. Solvent concentration is taken as the sum of TCA, the microbially mediated degradation product 1,1-dichloroethane, and the abiotic degradation product 1,1-dichloroethene. This example shows that 1,4-dioxane may occur in all ratios with respect to TCA and its degradation products.

Figure 2.7 Occurrence of 1,4-dioxane at TCA Release Site, Hayward, CA



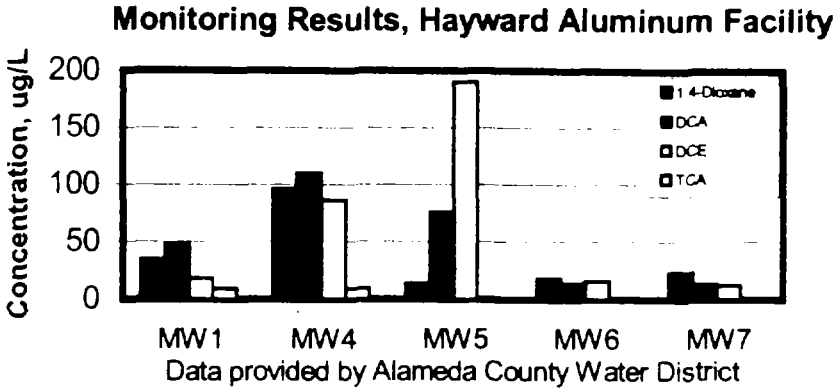


Figure 2.8 Sampling Results from TCA Release Site

Fullerton, California - Defense Industry Site

At the Hughes/Raytheon site in Fullerton, California, shallow groundwater sampled from a well completed in a perched aquifer downgradient of the stills that caused the solvents release was found to contain 1,4-dioxane at up to 133 ug/L, which is about 11% of the total chlorinated solvents detected in this well, and about 12% of the sum of TCA and daughter product concentrations. 1,4-dioxane has not been found in nine other wells sampled, and the extent of 1,4-dioxane in groundwater at this site has not yet been delineated (DTSC, 2001).

Stockton, California Metal Fabricator

At the Kearney-KPF site in Stockton, California, where TCA was used in manufacture of flagpoles and other metal products, 1,4-dioxane has been detected at up to 220 ug/L. At this site, air stripper effluent is reinjected into the aquifer. Because air stripping is ineffective at removing 1,4-dioxane, a nearby water supply well has been impacted, with 1,4-dioxane detected at 2 ug/L (Mello, 2001).

Orange County Groundwater Monitoring for 1,4-Dioxane

Efforts by the Orange County Water District to contain the threat of groundwater contaminated with chlorinated solvents in their forebay region were frustrated by the discovery of 1,4-dioxane in groundwater at concentrations up to 17 ug/L. A feasibility study for the removal of VOCs using air stripping and liquid phase granular activated carbon had already been completed in 2000 when the dioxane was discovered, but these methods are known to be ineffective in removing 1,4-dioxane. They are now completing a second feasibility study to consider advanced oxidation techniques (Orange County Water District, 2001).

Gloucester Landfill, Ontario, Canada

This landfill received and incinerated solvents in trenches from a nearby government laboratory for an 11-year period. Average linear groundwater flow velocity is estimated at 60 feet per year in a semi-confined glacial outwash aquifer consisting of feldspar (50%), quartz (20%), minor fractions of mica, calcite, dolomite, and hornblende, and an organic carbon content averaging 0.06%. The zone of highest concentration of 1,4-dioxane was observed to move 80 feet in six years and remained essentially unchanged. The plume of 1,4-dioxane identified at this facility, while not definitively associated with TCA as a source at this site, leads the plume of TCA by nearly 500 feet (Jackson and Dwarakanath, 1999).

1,4-dioxane migrated about 660 feet overall within 8 years of the cessation of solvent incineration at this landfill, or within 20 years of the introduction of laboratory solvents to the subsurface at this site. 1,4-dioxane migration at this location was therefore a minimum of 35 feet per year. Concentrations ranged from 250 ug/L to 2000 ug/L (Lesage et al, 1990; Jackson and Dwarakanath, 1999).

Duke University Landfill, Durham, North Carolina

At the Duke Forrest Landfill at Duke University in Durham, North Carolina, 1,4-dioxane concentrations have been routinely measured in the 1,000 ug/L range, with peak concentrations before source removal at 2,800 ug/L. Researchers at Duke University determined that a mean retardation factor of 1.2 was suitable for estimating 1,4-dioxane migration following a series of soil column tests using site soils (Liu, et al, 2000).

Other Landfills – Occurrence in Leachate

1,4-dioxane was found in Operating Industries Landfill leachate (Monterey Park, Los Angeles area) at concentrations up to 19 mg/L. (US EPA, 1998b). In leachate samples from three hazardous waste landfills in Japan, 1,4-dioxane concentrations ranged from 20.7 to 1,370 mg/mL (Yasuhara, 1995). 1,4-dioxane is described as occurring in low abundance in leachate from an Oklahoma municipal landfill taking only residential waste and no industrial wastes (Eganhouse et al, 2001).

Printed Circuit Board Manufacturing Facility, Tampa Florida

A printed circuit board plant in Tampa, Florida, used degreaser tanks for preparing printed circuit boards. Leaks from the tanks steadily released solvent and still bottoms including TCE and TCA. Remedial investigations and treatment system design by previous investigators did not initially target or account for 1,4-dioxane, nor did regulatory orders require it. Initial 1,4-dioxane concentrations in extracted groundwater are less than 20 ug/L, however treated effluent in Florida may not exceed 5 ug/L, the Florida drinking water standard. Because discharge from the treatment system is to the sanitary sewer, water agency officials have expressed concern over the discharge of 1,4-dioxane, which could end up in reclaimed water used to recharge groundwater (Alonso, 2001).

2.6 Impacted Supply Wells

Domestic and municipal water supply wells have been impacted by 1,4-dioxane in numerous instances from solvent releases and other sources, including the following examples:

- In the San Gabriel Basin, California, the La Puente Valley Water District's water supply wells were shut down in 1998 due to perchlorate, NDMA, and 1,4-dioxane contamination migrating from the Baldwin Park Operable Unit Superfund Site (CRWQCB-LAR, 1998).
- A Massachusetts drinking water well contained 1,4-dioxane at 2100 ppb (Burmaster, 1982).
- 1,4-Dioxane was detected in 37% of the samples of well water collected near a solid waste landfill located 60 miles southwest of Wilmington, Delaware (Dewalle, et al, 1981).
- In Ann Arbor, Michigan, use of two municipal supply wells was halted in April 2001 pending further investigation when 1,4-dioxane was detected at 1 and 2 ug/L (Ann Arbor, 2001). The contamination is believed to originate from the Gelman Sciences site, which has also impacted domestic supply wells, initially discovered in 1989 (Michigan DEQ, 2000). Many households have been connected to the municipal water supply because 1,4-dioxane in their domestic wells exceeded the State of Michigan's generic residential limit (first 3 ug/L, then 77 ug/L, and revised again to 85 ug/L). Fifty supply wells in Washtenaw County are monitored quarterly for 1,4-dioxane, with 13 of these wells showing presence of 1,4-dioxane from 1 to 24 ug/L.
- In Stockton, CA, 1,4-dioxane was detected in a water supply well at 2 ug/L downgradient of a solvent release site at a metal fabricating facility. To treat solvent contaminated groundwater, extraction wells were installed and discharge was treated using packed tower air strippers, with effluent

reinjected into the ground. Because 1,4-dioxane is not effectively removed by conventional air-stripping, water bearing at least 20 ug/L 1,4-dioxane was reinjected (Mello, 2001).

- The California Department of Health Services tested 116 drinking water sources statewide for 1,4-dioxane between 1984 and November of 2000, and found no detectable concentrations of 1,4-dioxane (DHS, 2001). However, laboratory techniques have only recently allowed detection limits to approach the California DHS drinking water action level. Orange County Water District is in the process of installing and testing monitoring wells near solvent plumes for 1,4-dioxane (Herndon, 2001).

2.7 Distribution and Fate of 1,4-dioxane in Water and Air

1,4-dioxane is short-lived in the atmosphere, but persists in surface and groundwater, and is relatively immune to biodegradation. It is not significantly bioconcentrated in the food chain.

As discussed in Section 5.1 and 5.7, the hydrophilic nature of 1,4-dioxane and 1,3-dioxolane, coupled with their very low Henry's Law constants and octanol-water partition coefficients, cause these compounds to pass through groundwater and municipal wastewater treatment facilities without significant concentration reduction. The following sections examine the fate of these two compounds when released to surface water and the atmosphere.

A 1999 study by Dr. Akemi Abe at the Kanagawa Environmental Research Center in Japan profiled the distribution of 1,4-dioxane in relation to sources in the water environment in Kanagawa Prefecture, Japan (Abe, 1999). The study found that 1,4-dioxane was widely distributed in both surface and groundwater, with detections in nearly all samples with the exception of a few spring water samples. Presence of 1,4-dioxane was closely correlated to the presence of TCA, with a correlation coefficient of 0.872 for 27 samples, and ratios ranging from 0.08 to 5.89% by volume.

2.7.1 Aquatic Fate

1,4-dioxane

1,4-dioxane is not expected to hydrolyze significantly (Lyman, et al, 1982). Volatilization data for 1,4-dioxane were not found in a literature search; since 1,4-dioxane is infinitely soluble in water, a volatilization half-life cannot be estimated. 1,4-dioxane has a moderate vapor pressure at 25 °C (37 mm Hg); therefore, volatilization is possible (Lange, 1967; Lyman et al, 1982). The low estimated Henry's Law Constant (3×10^{-6} atm-m^3/mol) suggests transfer of dioxane from water to air is negligible (Montgomery, 1996). 1,4-Dioxane is photo-oxidized by aqueous hydroxyl radicals with a half-life of 336 days at *p*H 7 (Anbar et al, 1967).

With an estimated K_{OC} of 1.23, 1,4-dioxane is not expected to significantly adsorb on suspended sediments. 1,4-Dioxane exhibited a negligible biological oxygen demand in two activated sludge experiments and the compound has been classified as relatively non-biodegradable (Lyman et al, 1982; Mills and Stack, 1954; Alexander, 1973; Heukelekian and Rand, 1955; Fincher and Payne, 1962; Lyman et al, 1982).

1,4-dioxane should volatilize from dry soil based on its moderate vapor pressure (37 mm Hg at 25° C, Verschueren, 1983). No bioconcentration data for 1,4-dioxane were available. The log octanol/water partition coefficient (K_{OW}) of 1,4-dioxane is -0.27. This very low K_{OW} suggests that 1,4-dioxane will not bioconcentrate significantly in aquatic organisms (Hansch and Leo, 1985).

1,3-dioxolane
Based on an experimental octanol-water partition coefficient (log K_{OW}) of -0.37 and a linear regression relating K_{OC} to K_{OW}, the K_{OC} for 1,3-dioxolane can be estimated to be 15, indicating high mobility in soil. Leaching to groundwater can be expected (Hansch et al, 1985; Lyman et al, 1982; Swann et al 1983). An experimental vapor pressure of 79 mm Hg at 20 °C suggests that volatilization from dry soil surfaces may be important (Riddick, et al, 1986).

Based on an experimental Henry's Law constant for 1,3-dioxolane of 2.4 x 10^{-5} atm-m^3/mole at 25° C (Hine and Mookerjee, 1975), volatilization from water and soil is classified as not rapid but possibly significant (Lyman et al, 1982).

If released to water, hydrolysis, aquatic oxidation with photochemically produced hydroxyl radicals, sorption to sediment and bioconcentration in aquatic organisms are not expected to be environmentally important removal processes of 1,3-dioxolane (US EPA, 1987). The bioconcentration factor for 1,3-dioxolane is estimated to be 0.3 (US EPA, 1987). 1,3-dioxolane has been tested for water stability at pH 4, 7 and 9, and is estimated to be stable in the aquatic environment under typical environmental conditions for over one year, neglecting volatilization (Dioxolane Manufacturers Consortium, 2000).

Volatilization half-lives of 34 hrs and 15 days have been estimated for a model river (one meter deep) and a model environmental pond, respectively (Lyman et al, 1982; US EPA, 1987).

Its complete water solubility suggests that 1,3-dioxolane may be susceptible to significant transport in aquatic environments. Aquatic oxidation with photochemically produced hydroxyl radicals is not likely to be an important fate process based on a half-life of 200 days for 1,3-dioxolane in water under continuous sunlight, with the aquatic oxidation rate experimentally determined to be 4.0X10^9 L/mol-s (pH not stated) (Buxton, et al, 1988).

2.7.2 Atmospheric Fate

1,4-dioxane
The half-life of the reaction of 1,4-dioxane with photochemically produced hydroxyl radicals in the atmosphere was estimated to be 6.69 to 9.6 hr (Brown et al, 1975; US EPA, 1986). Experimental results of sunlight-irradiated mixtures of 1,4-dioxane/NO suggest similar half-lives (Dilling, et al, 1976). The products of the reaction of ethers with hydroxyl radicals are likely to be aldehydes and ketones (Graedel, et al, 1986).

Air samples at three urban sites in New Jersey were collected from July 6-August 16, 1981. The geometric mean 1,4-dioxane concentrations ranged from 0.01-0.02 ppb. Fifty-one percent of the samples were positive for 1,4-dioxane (Harkov, et al, 1984). Dioxane is also found in indoor air samples. 1,4-Dioxane is among the organic compounds emitted from building materials (California Department of Health Services, 1996).

1,3-dioxolane
Based on a measured vapor pressure of 79 mm Hg at 20° C (Riddick et al, 1986), 1,3-dioxolane is expected to exist almost entirely in the vapor phase in the ambient atmosphere (Eisenreich et al, 1981). Vapor-phase 1,3-dioxolane is expected to degrade by reaction with photochemically produced hydroxyl radicals. The rate constant for the vapor-phase reaction of 1,3-dioxolane with photochemically produced hydroxyl radicals can be estimated to be 14.6 x 10^{-12} cm^3/molecule-sec at 25° C, which corresponds to an atmospheric half-life of about 1.1 days at an atmospheric concentration of 5 x 10^5 hydroxyl radicals per cm^3 (Atkinson 1988). Based on its complete water solubility, removal of 1,3-dioxolane from air via wet deposition may occur (Riddick, et al, 1986).

3.0 LABORATORY ANALYSIS OF SOLVENT STABILIZER COMPOUNDS

Commercial laboratories commonly analyze for 1,4-dioxane in water by three methods: EPA 524.2 for drinking water, and EPA 8260 and 8270 for groundwater and hazardous waste (Mackenzie, 2001). Use of EPA 8260 without modifications typically leads to detection limits in the range of 100 to 150 ug/L due to the water solubility of dioxane, i.e., purging efficiency is poor.

A modification to EPA 8260 has allowed lower detection limits. A salt, sodium sulfate, is added to samples to enhance the purge efficiency of 1,4-dioxane. A heated sparge is also used to further improve the sensitivity of the method. Combined with optimized scan parameters on the GCMS system, sensitivity was greatly improved, allowing detection limits of 2.0 ug/L. However, these low detection limits are not consistently achievable, leaving doubt as to the reliability of this approach (West Coast Analytical Services, 2001).

Determination of 1,4-dioxane in water at low detection levels is most often accomplished using modified EPA 8270 with liquid-liquid extraction and isotope dilution by capillary column gas chromatography-mass spectrometry (GC-MS). This GC-MS method is optimized for a single analyte, 1,4-dioxane, and is not appropriate as a multi-residue procedure due to the scan range, chromatographic conditions, and tuning requirements specified. The method is described as follows:

> A one-liter sample is dechlorinated by addition of sodium sulfite. An internal standard, 1,4-dioxane-d_8, is added and the sample is transferred to a continuous liquid-liquid extractor. The sample is extracted with methylene chloride for several hours, often overnight, and the extract is concentrated under a stream of nitrogen to a one-mL final volume. 1,4-dioxane and the deuterated internal standard are separated, identified, and determined by GC-MS, using a system equipped with a fused silica capillary column. Compounds are identified by retention time and selected ions relative to authentic standards and a user generated mass spectrum library. Reference spectra, retention times, and response factors are determined under conditions used in the analysis of sample extracts. The concentration of 1,4-dioxane is measured by relating the MS response of its quantitation ion to the response of the deuterated internal standard quantitation ion. Deuterated dioxane and pure dioxane standards are available from Aldrich Chemical in St. Louis, Missouri (Draper et al, 2000).

The California Department of Health Services' Sanitation and Radiation Laboratory Branch in Berkeley conducted an evaluation of available analytical techniques for reliable determination of 1,4-dioxane in drinking water. This investigation determined that conventional purge and trap is strictly limited by 1,4-dioxane's poor purge efficiency with detection limits about 100 times higher than for more efficiently purged volatile organic compounds. Liquid-liquid extraction techniques can achieve reliable reporting limits of 0.2 ug/L. Methane chemical ionization MS-MS offers detection limits three orders of magnitude lower than for electron ionization MS ion trap methods, making it possible to analyze for dioxane in the part per trillion range. Analytical precision is improved by the use of isotope-labeled standards (1,4-dioxane-d_8), which also results in significantly improved accuracy, approaching 100%. Isotope dilution is also possible using non-selective gas chromatographic detectors because of the high resolving power of capillary GC columns that separate deuterium labeled compounds from their native analogues (Draper, 2000).

West Coast Analytical Services reports that replicate analysis of samples spiked with 3 ug/L analyzed by the Modified EPA 8270 Isotope Dilution, Extraction and GCMS yielded a Relative Standard Difference of only 5%, i.e. a three standard deviation detection limit of 0.5 ug/L (West Coast Analytical Services, 2001).

Matrix Environmental Group of Ann Arbor, Michigan, has contributed to the development of a GC/MS technique, Method 1624 (Holodnick, 2001). This method is applicable to the analysis of 1,4-dioxane in water in the range of 1-200ug/L. The practical quantitation limit is 1 ppb (ug/L). Reproducibility as Relative Percent Difference is typically less than 10%.

Analysis by Method 1624 is performed by heated purge and trap technology preparing the sample in the presence of a salt and a deuterated form of 1,4-dioxane. Detection is achieved via an Ion Trap Detector. Qualitative identification is made by comparing resultant mass spectra and GC retention time against the same for the standard reference material. Quantitation is achieved by relating the MS response for the selected ion produced by 1,4-Dioxane with the MS response for the selected ion of the internal standard (Holodnick, 2001).

An ad hoc survey of a few analytical laboratories for the methods, detection limits, reporting limits, and sample requirements is summarized in Table 3.1 below.

Table 3.1 Comparison of Commercial Laboratory Services for Analysis of 1,4-dioxane

Laboratory	Method	MDL	PQL	Sample Volume	Pres.
E.S. Babcock & Sons (1)	EPA 524.2	20 ug/L	30 ug/L	2 x 40 mL	HCl
E.S. Babcock & Sons	EPA 8260	20 ug/L	30 ug/L	2 x 40 mL	HCl
E.S. Babcock & Sons	EPA 8270	0.06 ug/L	0.2 ug/L	1 Liter	None
Matrix Environmental Group, Inc. (2)	EPA 1624	-	1 ug/L RPD<10%	2 x 40 mL	HCl
WCAS (3)	EPA 8270	0.23 ug/L	0.5 ug/L	1 Liter	None

1) Riverside, CA 909-653-3351; 2) Ann Arbor, Michigan, 734-665-4610; 3) West Coast Analytical Services, Santa Fe Springs, CA, 562-948-2225

Current prices for analysis of 1,4-dioxane range from $90 - $120 for EPA 8260, $180 to $275 for modified EPA 8270, and $120 - $150 for EPA 1624 (surveyed Spring 2001, including additional commercial laboratories not listed here).

To verify the accuracy of the laboratory performing the analysis, third-party whole-volume standards are available to submit double-blind samples of 1,4-dioxane. This may be important for new projects as most labs do not routinely analyze for 1,4-dioxane, and accuracy and precision should be verified. Environmental Resources Associates of Colorado, among others, provides whole volume custom standards (3-40 mL VOAs for EPA 8260 and 2-1 L bottles for EPA 8270); both for less than $300 plus express shipping (ERA, 2001).

dioxane Search Clear Limits

For chemicals, add synonyms and CAS numbers to search: Yes No

Item 111 of 1038

Chemicals with carcinogenic activity in the rodent liver; mechanistic evaluation of human risk.

Authors:

WILLIAMS GM

Author Address: American Health Foundation, One Dana Road, Valhalla, NY 10595, USA.

Source: CANCER LETTERS; 117 (2). 1997. 175-188.

Abstract:

BIOSIS COPYRIGHT: BIOL ABS. A wide variety of chemicals, both naturally occurring and synthetic, have exhibited carcinogenic activity in rodent liver. Some are clearly DNA reactive whereas others produce only epigenetic effects. Hepatocarcinogens are categorized according to these properties and the characteristics of examples of both types are reviewed. DNA-reactive rodent hepatocarcinogens represent human cancer risks even at non-toxic exposures, whereas epigenetic agents pose either no risk because their effects are specific to rodents, or a risk only at high exposures at which they produce the same cellular effects in humans that are the basis for their carcinogenic activity in rodents.

Medical Subject Headings (MeSH):

BIOCHEMISTRY
DIGESTIVE SYSTEM DISEASES/PATHOLOGY
DIGESTIVE SYSTEM/PATHOLOGY
POISONING
ANIMALS, LABORATORY
CARCINOGENS
RODENTIA

Keywords:

Biochemical Studies-General
Digestive System-Pathology
Toxicology-General
Neoplasms and Neoplastic Agents-Carcinogens and Carcinogenesis
Rodentia-Unspecified

CAS Registry Numbers:

dioxane Search Clear Limits

For chemicals, add synonyms and CAS numbers to search: Yes No

Item 91 of 1038

Health Hazard Evaluation Report HETA-95-0296-2547, Automotive Controls Corporation, Independence, Kansas.

Authors:

Krake AM
Herrera-Moreno V

Author Address: National Inst. for Occupational Safety and Health, Cincinnati, OH. Hazard Evaluations and Technical Assistance Branch.

Source: Govt Reports Announcements & Index (GRA&I), Issue 24, 1996

Abstract:

TD3: In response to a confidential employee request, an investigation was begun into possible exposures to solvents at Automotive Controls Corporation (SIC-3694), Independence, Kansas. Workers were concerned about exposure to solvents, including dioxane (123911) and 1,1,1-trichloroethane (71556) (TCE) used to wash parts in the Hybrid Department. Problems included weakness, shakiness, blurred vision and eye irritation, inability to think or talk, depression, and respiratory and thyroid problems. The Hybrid Department produced ignitions, regulators, and distributorless ignition systems, and had 60 workers on two shifts. Full shift personal breathing zone (PBZ) exposure for TCE ranged from 69 to 198 parts per million (ppm), all below the OSHA exposure limit of 350ppm. PBZ exposure for dioxane ranged from 1.5 to 13.3ppm; all 21 samples taken exceeding the NIOSH recommended ceiling of 1ppm. Short term PBZ exposures were 422ppm for TCE and 11.8ppm for dioxane. Full shift area concentrations ranged from 92

Keywords:

Occupational safety and health
Health hazards
Automotive industry

Order Number: NTIS/PB96-209614, 19p

Price: NTIS Prices: PC A03/MF A01

Entry Month: December, 1996

Year of Publication: 1996

1: Mutat Res 1997 Oct 31;380(1-2):3-11

An update of the National Toxicology Program database on nasal carcinogens.

Haseman JK, Hailey JR.

Statistics and Biomathematics Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA. haseman@fred.niehs.nih.goo

Nearly 500 long-term rodent carcinogenicity studies carried out by the National Cancer Institute and the National Toxicology Program were examined, and 12 chemicals were identified that produced nasal tumors: allyl glycidol ether, p-cresidine, 1,2-dibromo-3-chloropropane, 1,2-dibromoethane, 2,3-dibromo-1-propanol, dimethylvinyl chloride, 1,4-dioxane, 1,2-epoxybutane, iodinated glycerol, procarbazine, propylene oxide, and 2,6-xylidine. All 12 of these chemicals produced nasal tumors in rats, and 5 also produced nasal tumors in mice. Most of the nasal carcinogens (1) produced tumor increases in both sexes, (2) produced tumors at other sites as well, (3) had significantly reduced survival at doses that were carcinogenic, and (4) were genotoxic. Only 5 of the 12 nasal carcinogens were administered by inhalation. A variety of different types of nasal cavity tumors were produced, and specific tumor rates are given for those chemicals causing multiple tumor types. Increased incidences of nasal neoplasms were often accompanied by suppurative/acute inflammation, epithelial/focal hyperplasia and squamous metaplasia. However, high incidences of these nonneoplastic nasal lesions were also frequently seen in inhalation studies showing no evidence of nasal carcinogenicity, suggesting that in general nasal carcinogenesis is not associated with the magnitude of chronic toxicity observed at this site.

PMID: 9385384 [PubMed - indexed for MEDLINE]

1: Am Ind Hyg Assoc J 1997 Jun;58(6):425-31

Lactational transfer of volatile chemicals in breast milk.

Fisher J, Mahle D, Bankston L, Greene R, Gearhart J.

Armstrong Laboratory, Toxicology Division, Wright-Patterson AFB, Ohio 45433, USA.

Lactational transfer of chemicals to nursing infants is a concern for occupational physicians when women who are breast-feeding return to the workplace. Some work environments, such as paint shops, have atmospheric contamination from volatile organic chemicals (VOCs). Very little is known about the extent of exposure a nursing infant may receive from the mother's occupational exposure. A physiologically based pharmacokinetic model was developed for a lactating woman to estimate the amount of chemical that a nursing infant ingests for a given nursing schedule and maternal occupational exposure. Human blood/air and milk/air partition coefficients (PCs) were determined for 19 VOCs. Milk/blood PC values were above 3 for carbon tetrachloride, methylchloroform, perchloroethylene, and 1,4-dioxane, while the remaining 16 chemicals had milk/blood PC values of less than 3. Other model parameters, such as solid tissue PC values, metabolic rate constants, blood flow rates, and tissue volumes were taken from the literature and incorporated into the lactation model. In a simulated exposure of a lactating woman to a threshold limit value concentration of an individual chemical, only perchloroethylene, bromochloroethane, and 1,4-dioxane exceeded the U.S. Environmental Protection Agency non-cancer drinking water ingestion rates for children. Very little data exists on the pharmacokinetics of lactational transfer of volatile organics. More data are needed before the significance of the nursing exposure pathway can be adequately ascertained. Physiologically based pharmacokinetic models can play an important role in assessing lactational transfer of chemicals.

PMID: 9183837 [PubMed - indexed for MEDLINE]

1: Bull Exp Biol Med 2001 Sep;132(3):832-6 Related Articles, Links

Effect of chronic inhalation of toluene and dioxane on activity of free radical processes in rat ovaries and brain.

Burmistrov SO, Arutyunyan AV, Stepanov MG, Oparina TI, Prokopenko VM.

Laboratory of Perinatal Biochemistry, D. O. Ott Institute of Obstetrics and Gynecology, Russian Academy of Medical Sciences, St. Petersburg.

The effects of toluene and dioxane inhalations on the intensity of free radical oxidation in rat ovaries and brain cortex were studied. Both toxins in a dose 10-fold surpassing the maximum permissible concentration increased activity of glutathione peroxidase in brain tissue; moreover, toluene increased chemiluminescence intensity, which attested to activation of free radical processes. In ovarian tissue toluene increased activities of glutathione peroxidase and catalase and the intensity of lipid peroxidation. These changes were associated with the appearance of normally absent circadian rhythm.

PMID: 11740571 [PubMed - indexed for MEDLINE]

AR100149

1: J AOAC Int 2001 May-Jun;84(3):666-70 Related Articles, Links

Occurrence of 1,4-dioxane in cosmetic raw materials and finished cosmetic products.

Black RE, Hurley FJ, Havery DC.

US Food and Drug Administration, Washington, DC 20204, USA.

Surveys of cosmetic raw materials and finished products for the presence of the carcinogen 1,4-dioxane have been conducted by the U.S. Food and Drug Administration since 1979. Analytical methods are described for the determination of 1,4-dioxane in ethoxylated cosmetic raw materials and cosmetic finished products. 1,4-Dioxane was isolated by azeotropic atmospheric distillation and determined by gas chromatography using n-butanol as an internal standard. A solid-phase extraction procedure based on a previously published method for the determination of 1,4-dioxane in cosmetic finished products was also used. 1,4-Dioxane was found in ethoxylated raw materials at levels up to 1410 ppm, and at levels up to 279 ppm in cosmetic finished products. Levels of 1,4-dioxane in excess of 85 ppm in children's shampoos indicate that continued monitoring of raw materials and finished products is warranted.

PMID: 11417628 [PubMed - indexed for MEDLINE]

AR100150

1: Med Lav 1999 Sep-Oct;90(5):650-70 Related Articles, Links

[Occupational agents and endocrine function: an update of the experimental and human evidence]

[Article in Italian]

Baccarelli A.

Scuola di Specializzazione in Endocrinologia e Malattie del Ricambio, Universita di Milano, Ospedale Maggiore IRCCS.

Many environmental and occupational agents have been shown to cause detrimental effects on endocrine function and growing scientific evidence supports the hypothesis that such alterations may produce serious consequences for health. Although those chemicals mimicking (or contrasting) estrogenic or androgenic actions have raised great concern, the relevance of disruption of other hormonal pathways is not negligible. This article reviews the effects of chemical and physical agents on the hypothalamus-pituitary unit, pineal gland, thyroid, parathyroid and calcium metabolism, adrenal glands, and glucose metabolism. Metals (Pb, Mn, Cd, organotin compounds), solvents (benzene, dioxane, styrene, tetrachloroethylene, toluene), organochlorines (PCBs, TCDD), and physical agents have been shown in human, animal or in vitro studies to cause alterations of the blood levels, and of the activity or circadian rhythm of pituitary hormones. Melatonin has been proposed as the link between environmental/occupational factors and the immunologic and neoplastic diseases, which in addition to disturbances of the circadian timing system, feature pineal hormone reduction. Thyroid gland diseases (goiter, autoimmune thyroiditis, carcinoma) are associated with exposure to many chemical or physical agents. Disruptions of calcium control secondary to metal exposures, as well as the effect of radiation on parathyroid, are addressed. Adrenal cortex and medulla function alterations by several chemical agents are considered. Finally, diabetes mellitus as an outcome of occupational or environmental exposures and as susceptibility to occupational and environmental factors is discussed.

Publication Types:
- Review

dioxane Search Clear Limits

For chemicals, add synonyms and CAS numbers to search: Yes No

Item 77 of 1038

1,4-Dioxane

Authors:

Anonymous

Source: TA:ACGIH. Documentation of the threshold limit values and biological exposure indices PG:5 p YR:2001 IP: VI:7 th Ed

Abstract:

A TLV-TWA of 20 ppm (72 mg/m3) is recommended for occupational exposure to 1,4-dioxane to minimize the potential for liver and kidney toxicity and at high concentrations, eye and respiratory tract irritation. The rapid absorption of dioxane following application to the skin of rabbits and guinea pigs led to signs of incoordination and narcosis, which, together with the systemic toxicity seen in workers following dermal exposure, warrants a Skin notation. Liver, lung, and nasal tumors in rats and mice fed dioxane in the diet or administered in drinking water are the basis for an A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, notation. Sufficient data were not available to recommend a SEN notation or a TLV-STEL.

Keywords:

< ANIMAL >
acute toxicity
subacute toxicity
irritancy
carcinogenicity
carcinogens
genetic toxicity
reproductive and developmental tests
embryo-fetal toxicity
toxicokinetics
nervous system
liver
respiratory system
urinary tract
dose response
< HUMAN >
epidemiological study
case report
human exposure
acute effect
chronic effect

dioxane Search Clear Limits

For chemicals, add synonyms and CAS numbers to search: Yes No

Item 6 of 1038

1,4-Dioxane

Authors:

Anonymous

Source: TA.IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans PG:589-602 YR:1999 IP:2 VI:71

Abstract:

Exposure data. Exposure to 1,4-**dioxane** may occur during its manufacture and its use as a solvent in a wide range of organic products. It has been detected in ambient air. Human carcinogenicity data. Deaths from cancer were not elevated in a single, small prospective study of workers exposed to low concentrations of **dioxane**. Animal carcinogenicity data. 1,4-Dioxane was tested for carcinogenicity by oral administration in mice, rats and guinea-pigs. It produced an increased incidence of hepatocellular adenomas and carcinomas in mice, tumours of the nasal cavity, liver subcutaneous tissues, mammary gland and peritoneal mesotheliomas in rats and tumours of the liver and gall-bladder in guinea-pigs. No increase in tumours was seen in rats following inhalation exposure. In the mouse-lung adenoma assay, intraperitoneal injection of 1,4-**dioxane** increased the incidence of lung tumours in males; no such effect was seen following oral administration. In a two-stage liver foci assay in rats, 1,4-**dioxane** showed promoting activity. Other relevant data. 1,4-**Dioxane** is rapidly absorbed upon inhalation or after oral administration, but its penetration of skin is poor. The major metabolite is beta-hydroxyethoxyacetic acid, which is rapidly excreted. In rats, the elimination of 1,4-dioxane and its metabolites is progressively delayed as doses are increased, indicating saturation of metabolism. No clinical signs or changes in mortality were found in a cohort of exposed workers. In rats, 1,4-**dioxane** produces degenerative and necrotic changes in liver and renal tubules. High doses can significantly increase the total hepatic cytochrome P450 content. No reproductive effects of 1,4-**dioxane** exposure of rats have been reported. Most of the broad of tests for genotoxic activity have produced negative results, but positive results were obtained in a cell transformation assay and conflicting results were obtained in mouse bone-marrow cell tests for micromicleus induction. Evaluation. There is inadequate evidence in humans for the carcinogenicity of 1,4-**dioxane**. There is sufficient evidence in experimental animals for the carcinogenicity of 1,4-**dioxane**. Overall evaluation. 1,4-Dioxane is possibly carcinogenic to humans (Group 2B).

Keywords:

< ANIMAL >
carcinogenicity
carcinogens
genetic toxicity
reproductive and developmental tests

1: Environ Mol Mutagen 1998;32(3):269-80

1,4-Dioxane is not mutagenic in five in vitro assays and mouse peripheral blood micronucleus assay, but is in mouse liver micronucleus assay.

Morita T, Hayashi M.

Tsukuba Research Laboratories, Nippon Glaxo Ltd., Ibaraki, Japan. tm28417@glaxowellcome.co.uk

1,4-Dioxane, an animal carcinogen, was not previously genotoxic in in vitro assays. We reevaluated the compound's genotoxic potential in five in vitro genotoxicity tests in the presence and absence of S9 mix using recommended new protocols. We used the bacterial reverse mutation assay with Salmonella TA and E. coli WP2 strains, including the plate and preincubation methods, the CHO chromosomal aberration assay, including examination of polyploid induction and extended sampling time, the CHO sister-chromatid exchange assay with short and long treatment time, the mouse lymphoma tk assay (microtiter method), including longer treatment time (24 hr), and the CHO micronucleus assay with short and long treatment times. The highest concentration we used was five mg/ml or plate. We also evaluated the genotoxic effect of 1,4-dioxane in vivo by conducting peripheral blood and liver micronucleus assays in the same mice after single oral administration of up to 3,000 mg/kg. All in vitro assays and the peripheral blood micronucleus assay were negative. The mouse liver micronucleus assay, on the other hand, was positive, indicating that 1,4-dioxane might be genotoxic. It is also conceivable that the positive result in mouse liver micronucleus assay was due to a nongenotoxic mechanism, i.e., errors in genetic repair following enhancement of hepatocyte proliferation.

PMID: 9814442 [PubMed - indexed for MEDLINE]

Display Abstract Show 20 Sort Send to Text

1: J Epidemiol Community Health 1996 Feb;50(1):18-23

An epidemiological study after a water contamination incident near Worcester, England in April 1994.

Fowle SE, Constantine CE, Fone D, McCloskey B.

Department of Public Health, Worcester and District Health Authority.

STUDY OBJECTIVES: To investigate whether exposure to tap water contaminated in a major river pollution incident with 2 ethyl 5,5 dimethyl 1,3 dioxane (EDD) and 2 ethyl 4 methyl 1,3 dioxolane (EMD) was associated with an increase of self reported symptoms. To assess the extent of association between noticing the water had an unusual taste or odour and self reported symptoms. DESIGN: Retrospective cohort study. SETTING: A city and two nearby towns in a semi-rural area of England, UK. PARTICIPANTS: A total of 3861 people who replied to a postal questionnaire asking about symptoms and water consumption sent to a sample of 1000 households in each of three areas--one area supplied with contaminated water (study group) and two control areas that were unaffected (control groups). MAIN RESULTS: The household response rates were 65% for the study group and 56% and 57% for the two control groups. Self reporting of 10 individual symptoms was significantly increased in the study group compared with controls. Within the study group, reporting of one or more symptoms was significantly higher in subjects who consumed contaminated water but not among subjects who used it to wash or cook. Subjects who drank contaminated water showed a dose-response relationship for self reporting of one or more symptoms and for seven individual symptoms. Within the study group, however, only 62% (867 of 1398 subjects) noticed that the water had an unusual taste or odour. Among subjects who did not notice that the water had an unusual taste or odour, no association was found between drinking contaminated water and reporting one or more symptoms, or between drinking contaminated water and reporting of individual symptoms, although a dose-response relationship was shown between the amount of water consumed and self reporting of nausea. Among subjects who noticed the water had an unusual taste or odour, both an association and a dose-response relationship were found between consumption of contaminated water and the self reporting of six symptoms--diarrhoea, nausea, headache, stomach pains, skin irritation, and itchy eyes. CONCLUSIONS: Higher rates of symptom reporting were

associated with the water contamination incident. Reported symptoms seemed, however, to be associated with the ability to detect an unusual taste or odour in the water. Because concentrations of the contaminants would be expected to be evenly distributed in the tap water in the affected area, irrespective of taste or odour, and because of the known toxicity of the parent compounds of EMD and EDD, it is concluded that the increase in self reported symptoms in the study group respondents was associated with noticing the unpleasant taste or odour of the tap water and not with the chemical contamination. It is concluded that the observed increase in reporting of nausea with increasing water consumption was due to public anxiety caused by the incident but did not pose a serious risk to the public's health. The increase in self reported symptoms in the area affected by the contamination was an important reminder of the wider health implications of "health scares".

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dioxane Search Clear Limits

For chemicals, add synonyms and CAS numbers to search: Yes No

Item 1 of 1038

1,4-Dioxane

Authors:

Anonymous

Source: TA:NICNAS: Priority existing chemical assessment report PG:112 p YR:1998 IP: VI:7

Abstract:

Assessment findings. 1,4-Dioxane (CAS No. 123-91-1) was declared a Priority Existing Chemical on 3rd May 1994 due to concerns over possible human carcinogenicity, its potential for widespread occupational and public exposure and high degree of partitioning to, and persistence in, the aquatic environment. In Australia, 1,4-dioxane is used as a solvent in chemical synthesis, research and analysis (mainly laboratory applications) and in adhesive products used in celluloid film processing. During the period this assessment was underway, 1,4-dioxane was also used in optical lens manufacture as a surface coating agent. Until 1st January 1996, 1,4-dioxane was used in large quantities as a stabiliser in 1,1,1-trichloroethane. 1,4-Dioxane is also produced in trace amounts as an unwanted by-product in the manufacture of ethoxylated chemicals, in particular, surfactants. Occupational and environmental exposure may occur from any of the above sources, as well as during formulation and use of ethoxylated chemicals. Exposure to the general public may occur from use of consumer products containing ethoxylated chemicals (e.g., detergents, cosmetics/toiletries, pharmaceuticals and food products) containing 1,4-dioxane as an impurity, in addition to its reported natural occurrence in certain foods. 1,4-Dioxane is absorbed by inhalation, dermal and oral routes. Metabolism in rats and humans appears to be similar, with the vast majority of the dose being rapidly excreted in urine as phydroxyethoxyacetic acid (HEAA) and small amounts of unchanged 1,4-dioxane being eliminated in urine and expired air. Evidence from animal studies indicates that metabolism may involve cytochrome P-450 and that saturation occurs at high doses, as indicated by an increase in unmetabolised 1,4-dioxane and a change in elimination kinetics. There is also some evidence to suggest that metabolic saturation is associated with toxicity, particularly hepatotoxicity. In animals, 1,4-dioxane is distributed to liver, kidney, spleen, lung, colon and skeletal muscle, with evidence of selective uptake by liver and kidney. 1,4-Dioxane exhibits low acute toxicity, but has been shown to cause irritation of eyes and respiratory tract in humans and animals. Short-term exposure to high levels of 1,4-dioxane is associated with severe kidney and liver damage in animals and humans. A number of human fatalities have been reported in the literature from occupational exposure (combined inhalation and skin contact) to high levels of 1,4-dioxane. The cause of death in all cases was reported as kidney failure (haemorrhagic nephritis). Liver necrosis and CNS nerve fibre damage were also reported at autopsy. Chronic effects seen in animals include lesions (neoplastic and non-neoplastic) in kidney, liver, nose, testes, lung and spleen. The critical organ for adverse effects in chronic animal studies is the liver, where effects include hepatocyte degeneration, hyperplasia, adenoma, carcinoma and cholangioma (bile duct tumour). The chronic no observed adverse effect levels (NOAELs) in rats are 111 ppm (105 mg/kg/d) for inhalation and 10-40 mg/kg/d for oral exposure to 1,4-dioxane. A reliable NOAEL for chronic

dermal effects has not been determined. Effects from long term exposure to 1,4-dioxane in humans are not well characterised. Several epidemiological studies have been carried out in workers potentially exposed to 1,4-dioxane, with one study (comparative mortality study) indicating a significant increase in liver cancer, although potential exposure to other hepatotoxic chemicals, including alcohol, were confounding factors. Based on the assessment of health effects, 1,4-dioxane should be classified in accordance with the NOHSC Approved Criteria for Classifying Workplace Hazardous Substances (NOHSC, 1994a), as 'Irritating to eyes and respiratory system' (risk phrase 36/37) and 'Carcinogen Category 3' (risk phrase R40), which is in accord with the NOHSC List of Designated Hazardous Substances (NOHSC, 1994b). In accordance with the Australian Code for the Transport of Dangerous Good by Road and Rail (FORS, 1998), 1,4-dioxane meets the criteria for assignment to 'Class 3 (Flammable Liquid) - packaging group II'. The occupational risk assessment concluded that, for known Australian work situations, potential atmospheric concentrations of 1,4-dioxane are unlikely to reach levels likely to cause acute effects, including eye or respiratory irritation. In addition, it is unlikely that workers in these occupations will be at risk from chronic adverse health effects related to 1,4-dioxane exposure, as margins of safety/exposure are generally high for inhalation and/or dermal exposure. In the absence of any monitoring data for workers involved in optical lens manufacture and the potential for inhalation exposure during the coating process, estimates for 1,4-dioxane exposure were obtained using the UK EASE model. Results from this modelling indicate a potential risk for exposed workers. The public health risk assessment concluded that the main potential source of exposure to the general public is from exposure to consumer products containing 1,4-dioxane as an impurity. No analytical data were available on levels of 1,4-dioxane in consumer products in Australia, however levels were estimated from data on surfactant composition submitted by applicants and notifiers. A so-called 'worst case scenario' for daily intake (inhalation and dermal exposure) for 1,4-dioxane from consumer products (not including pharmaceuticals or food products) was calculated at around 71lg/kg based on an assumed level of 30 ppm 1,4-dioxane in end-use products. This represents a margin of safety of >1000 (with respect to the chronic animal (oral) NOAEL) and therefore 1,4- dioxane was not considered to pose a significant health risk to the general public. The environmental risk assessment indicates that the majority of 1,4-dioxane used, and produced as by-product in Australia, will be released to sewer. 1,4-Dioxane released to soil is likely to leach to groundwater. Fugacity modelling (US EPA 1996a) predicts a partitioning of 91% to water and 9% to air. Rapid degradation (half-life < 7 hours) of 1,4-dioxane is expected in the atmosphere, whereas biodegradation and photooxidation half-lives in surface and ground waters were estimated at between 1 month and several years. 1,4-Dioxane was classified as practically non-toxic to aquatic organisms and on account of its high hydrophilicity and partition coefficient (log Pow), the potential for bioaccumulation was considered negligible. Worst case scenarios for PEC/PNEC ratios for local and continental compartments suggest that 1,4-dioxane does not present a significant risk of adverse effects to the Australian aquatic environment. Similarly, 1,4-dioxane is considered unlikely to contribute to global warming or ozone depletion.

Keywords:

< ANIMAL >
acute toxicity
subacute toxicity
subchronic toxicity
chronic toxicity
irritancy
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genetic toxicity
reproductive and developmental tests
reproductive effect
metabolism
eye
respiratory system
liver
urinary tract
reproductive system