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Your chemical may be listed in the attached tables.

A Screening Method for Occupational Reproductive Health Risk

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Most currently recognized occupational exposure limits do not consider reproductive toxicological end points consistently when establishing recommended exposure limits. In many cases the information is not available, but perhaps as often, existing data is not employed. Further, many manufacturer's material safety data sheets omit reproductive hazard information. A method for identifying potential reproductive toxins and screening levels for associated health risks useful for hazard communication and exposure control is presented. To date, the Registry of Toxic Effects of Chemical Substances lists between 5000 and 6000 chemicals, drugs, and natural substances that show a positive outcome in at least 1 reproductive effects study. This reproductive health risk assessment began with these substances. Using elements of the Environmental Protection Agency's health risk assessment process, the list was reduced to 213 chemicals during the hazard identification step. Occupational reproductive guidelines (ORGs) were developed in the dose-response evaluation step. At the time of this writing, 85% of the chemicals identified in the hazard identification step have had a screening level dose-response assessment completed. Of these, 13% are greater than or equal to a threshold limit value (TLV®). The remaining 87% do not have a TLV or ORGs below the TLV. The reproductive toxins list, along with the corresponding dose-response-derived ORGs that have been completed, appears at the end of the text.

Keywords: exposure limits, hazard communication, material safety data sheets, reproductive hazards, reproductive toxins

APPLIED STUDIES

A method for identifying potential reproductive toxins is presented in Figure 1. This method is useful for hazard communication and in establishing guidelines for exposure control. The objectives are to provide information on potential reproductive hazards that safety and health professionals can use to establish a healthful workplace for all employees, regardless of gender, and to protect all workers regardless of reproductive status. By treating reproductive toxicity as any other toxicological end point, establishing/adjusting occupational exposure guidelines, and controlling exposures below these levels, the need for a special reproductive health program is eliminated.

Based on the current state of health protection legislation and scientific knowledge, such a method is timely and justifiable. The Occupational Safety and Health Administration (OSHA) requirements for employee hazard communication include reproductive toxins in the definition of "health hazard,"[2] yet according to a 1991 Government Accounting Office report,[3] workers, as well as the general public, remain inadequately protected from reproductive hazards under federal regulations. Although material safety data sheets are required for employee health protection in the workplace, these sheets generally do not provide reproductive hazard information.[4] Established occupational exposure limits

Note: The term "reproductive" includes developmental effects. A reproductive toxicant is one that "interferes with reproductive or sexual functioning of the male or female from puberty through adulthood. A developmental toxicant produces an effect in the offspring from conception to puberty. The four principal manifestations of developmental toxicity are (1) death of the conceptus, (2) structural abnormality, (3) altered growth, and (4) functional deficiency."[1]

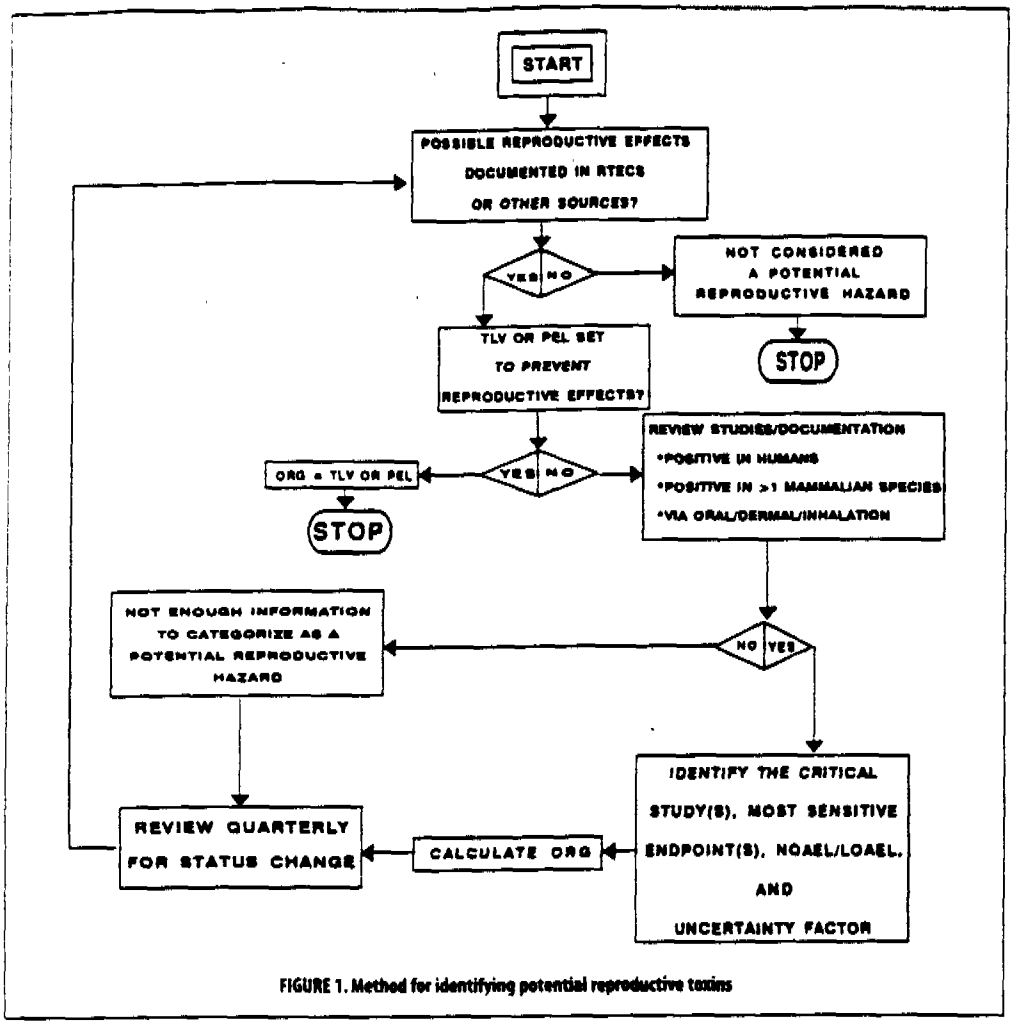

FIGURE 1. Method for identifying potential reproductive toxins

frequently do not take into consideration reproductive end points that are clearly below the thresholds established for other toxic effects.[3]

There is a growing legal imperative for nondiscriminatory gender-neutral occupational health policy[5] that is contrary to traditional reproductive health policy, which relies solely on pregnancy reporting and job reassignment as a means of fetal protection. Such limited policy falls short of preventing harmful parental exposures that may adversely impact the health of the unborn child or the reproductive capacity of adults. For all of these reasons, this effort is considered necessary.

METHODS

Creation of the reproductive toxins database required identification of potential reproductive toxicants, searching the literature for reproductive no-observed-adverse-effect levels (NOAEL) and lowest-observed-adverse-effect levels (LOAEL) for the reproductive toxicants, and determining corresponding occupational reproductive guidelines (ORG). Aspects of the Environmental Protection Agency's (EPA's) procedure for risk assessment were used for hazard identification and dose-response assessment as applied in the National Institute for Occupational Safety and Health (NIOSH) glycol ether criteria document.[6] ORGs were calculated using the uncertainty factor method.[7]

The hazard identification process included the development of the reproductive toxins list that was derived from the Registry of Toxic Effects of Chemical Substances (RTECS) database. RTECS, developed by NIOSH, has toxicity information on approximately 250,000 chemical substances. A search of the database for any substance with a positive outcome in at least one reproductive effects study yielded more than 5500 substances. The list was narrowed by a search for substances with positive outcomes in humans or more than one mammalian species via dermal exposure, ingestion, or inhalation. The query refined the list to approximately 1000 drugs, chemicals, and natural substances. This list was further reduced to only those substances believed to be important in an occupational setting, omitting substances used exclusively as drugs or hormones. The final reproductive toxins list consists of 213 potential toxins. These were entered into a FoxPro® database (Table I).

Dose-response assessment involved several assumptions. First was the assumption that reproductive effects have thresholds.[7] The assumption of a threshold underestimates the risk for a toxin that does not have a threshold. An adjustment for this concern was made in the case of transplacental carcinogens by the use of an additional uncertainty factor of 10.

The second assumption was that animal data is a reasonable human predictor. This is based on the evidence from known human developmental toxicity, which in most cases demonstrates that animal data are predictive of human developmental effects.[7] An uncertainty factor of 10 was used for animal-to-human extrapolation. Using a single positive animal study for initial inclusion in the database is designed to minimize the possibility of missing a true human reproductive toxin, i.e., a false negative. Requiring positive effects in two or more species is an attempt to limit the number of potential false positives.

The third major assumption was that absorption of dose is complete regardless of the route of entry, and that the toxicity is unaltered.[8] This assumption frequently leads to an overestimation of the risk at a particular exposure level, and no uncertainty factor is applied for route-to-route extrapolation. Taken in total it is likely that these assumptions provide a reasonable margin of safety.

The dose-response evaluation began with an examination of current occupational exposure guides for established limits reported as protective of reproductive health. If an exposure limit inclusive of reproductive health was found, it was adopted as the ORG for that substance and entered into the database. The references for occupational limits included the American Conference of Governmental

TABLE I. Reproductive Toxin Guidelines[A]

Chemical Name	Cas No.	ORG[B]	UF	Endpoint[C]	CR
2,4'-DDD	53-19-0	incomplete			
2,4,5-T	93-76-5	0.18 mg/m^3	100	R	NA
2,4,5-T, N-butyl ester	93-79-8	0.18 mg/m^3	100	R	NA
2,4-D	94-75-7	1.50 mg/m^3	100	R	NA
2,4-D butyl ester	94-80-4	6.0 mg/m^3	100	D	NA
2,4-D, isooctyl ester-	25168-26-7	incomplete			
2-MePA	70657-70-4	7.06 mg/m^3	100	D	NA
Acetaldehyde	75-07-0	14.4 mg/m^3	100	D	NA
Acetic acid, indolyl-	87-51-4	6 mg/m^3	100	D	NA
Acetonitrile	75-05-8	22.7 mg/m^3	100	D	NA
Acrolein	107-02-8	0.12 mg/m^3	100	D	NA
Acrylamide☺	79-06-1	0.03 mg/m^3	NA	NA	220
Aflatoxin-B	1162-65-8	incomplete			
Alcohol, 2-ethylhexyl	104-76-7	97.7 mg/m^3	100	D	NA
Alcohol, ethyl-☺	64-17-5	1880 mg/m^3	NA	NA	NA
Alcohol, methyl☺	67-56-1	262 mg/m^3	NA	NA	NA
Aldrin	309-00-2	0.012 mg/m^3	1000	D	3.4
Allyl chloride☺	107-05-1	3 mg/m^3	NA	NA	NA
Aluminum-chloride-	7446-70-0	0.36 mg/m^3	100	R	NA
Aminonicotinamide	329-89-5	0.02 mg/m^3	1000	D	NA
Aminopteridine	54-62-6	1.2 µg/m^3	100	D	NA
Amitrole☺	61-82-5	0.2 mg/m^3	NA	NA	NA
Amudane	126-07-8	0.75 mg/m^3	1000	D	NA
Aroclor 1016	12674-11-2	1.4 µg/m^3	30	D	3.3
Aroclor 1254	11097-69-1	1.4 µg/m^3	30	D	3.3
Aroclor 1260	11096-82-5	1.4 µg/m^3	30	D	3.3
Arsenic (elmtl/organic)	7440-38-2	0.5 µg/m^3	1000	D	4.7
Atrazine	1912-24-9	2.1 mg/m^3	100	R	NA
BAPN	151-18-8	0.68 mg/m^3	1000	D	NA
BAPN Fumarate	2079-89-2	0.68 mg/m^3	1000	D	NA
Baygon☺	114-26-1	0.5 mg/m^3	NA	NA	NA
Benomyl	17804-35-2	0.30 µg/m^3	1000	R	NA
Benzene	71-43-2	0.05 mg/m^3	1000	D	1.4
Benzene, (epoxy ethyl)-	96-09-3	0.78 mg/m^3	100	D	NA
Benzimidazolecarbamic	10605-21-7	incomplete			
Benzo(A)pyrene	50-32-8	0.175 µg/m^3	NA	TC	1
Bisphenol A	80-05-7	0.3 mg/m^3	1000	D	NA
Boric acid	10043-35-3	1.5 mg/m^3	100	R	NA
Butadiene, 1, 3-	106-99-0	0.26 mg/m^3	1000	D	400
Butyl alcohol, tert-	75-65-0	106 mg/m^3	100	D	NA
Butyronitrile,	10232-92-5	incomplete			
Cacodylic acid	75-60-5	0.18 mg/m^3	1000	D	NA
Cadmium☺	7440-43-9	2 µg/m^3	NA	NA	8
Cadmium chloride	10108-64-2	2 µg/m^3	NA	NA	NA
Captan	133-06-2	0.75 mg/m^3	100	D	NA
Carbaryl☺	63-25-2	5 mg/m^3	NA	NA	NA
Carbofuran	1563-66-2	0.03 mg/m^3	100	R	NA
Carbon dioxide	124-38-9	1800 mg/m^3	10	D/R	NA
Carbon disulfide	75-15-0	8.4 mg/m^3	100	D	NA
Carbon monoxide	630-08-0	14 mg/m^3	NA	D/R	NA
Cartap	15263-52-2	incomplete			
Chlorhydrin	96-24-2	incomplete			
Chlorine dioxide☺	10049-04-4	0.28 mg/m^3	NA	D	NA
Chloroamphenicol	56-75-7	12 mg/m^3	100	D	NA
Chlorobenzene☺	108-90-7	46 mg/m^3	NA	NA	NA
Chloroform	67-66-3	2.6 mg/m^3	100	D	200
Chloromethyl mercury	115-09-3	LOD	NA	NA	NA

continued

TABLE 1. Reproductive Toxin Guidelines[A] (continued)

Chemical Name	Cas No.	ORG[B]	UF	Endpoint[C]	CR
Coal-derived complex	None	3 mg/m³	1000	D	6300
Cyclohexanone☺	108-94-1	100 mg/m³	NA	NA	NA
Cyclohexylamine	108-91-8	4.3 mg/m³	25	R	NA
Cyclophosphamide	50-18-0	6 µg/m³	1000	D/R	NA
Cyclophosphoramide	51-18-0	incomplete			
DDT	50-29-3	0.01 mg/m³	1000	R	3
Diaminotoluene, 2, 4-	95-80-7	0.11 mg/m³	1000	R	300
Diazinon	333-41-5	1.08 µg/m³	1000	D	NA
Dibenzofuran,	57117-31-4	incomplete			
Dibromochloropropane	96-12-8	4 µg/m³	1000	R	7.4
Dichlorobenzene, p-☺	106-46-7	60 mg/m³	NA	NA	NA
Dichlorvos	62-73-7	0.03 mg/m³	1000	D	NA
Dicumarol	66-76-2	0.01 mg/m³	10	D	NA
Dieldrin	60-57-1	0.012 mg/m³	1000	R	3.4
Diethylene glycol	111-96-6	0.75 mg/m³	1000	D	NA
Diethylstilbesterol	56-53-1	2 ng/m³	NA	TC	NA
Difolatan	2425-06-1	incomplete			
Dimethoate	60-51-5	0.36 mg/m³	100	D	NA
Dimethyl-2-thiourea,	534-13-4	incomplete			
Dimethylbenzanthracene	57-97-6	0.1 mg/m³	10000	R	NA
Dimethylformamide	68-12-2	1.35 mg/m³	100	D	NA
Dimethylurea, 1,3-	96-31-1	120 mg/m³	100	D	NA
Dinocap	39300-45-3	0.03 mg/m³	1000	D	NA
Dinoseb	88-85-7	0.01 mg/m³	1000	D	NA
Dioctylphthalate	117-81-7	3 mg/m³	100	R	NA
DPPD	74-31-7	0.08 mg/m³	1000	D	NA
Disulfiram	97-77-8	0.06 mg/m³	100	D	NA
EGDME	110-71-4	0.18 mg/m³	1000	D	NA
EGEE	110-80-5	1.8 mg/m³	100	D	NA
EGMBE	111-76-2	3.6 mg/m³	100	D	NA
EGME	109-86-4	0.3 mg/m³	100	D	NA
EGME, di-	111-77-3	9 mg/m³	100	D	NA
EGMEA	110-49-6	0.5 mg/m³	NA	D	NA
EGMEEA	111-15-9	2.7 mg/m³	100	D	NA
EGPE	2807-30-9	25.6 mg/m³	100	D	NA
Endrin	72-20-8	0.012 mg/m³	1000	R	NA
Enflurane	13838-16-9	incomplete			
Epichlorhydrin☺	106-89-8	0.38 mg/m³	NA	NA	1.5
Ergocalciferol	50-14-6	1 µg/m³	NA	D/R	NA
Ethyl methane sulfonate	62-50-0	0.03 mg/m³	10000	R	NA
Ethylene dibromide	106-93-4	8 µg/m³	100	R	5.6
Ethylene glycol	107-21-1	26 mg/m³	100	R	NA
Ethylene glycol diethyl	629-14-1	incomplete			
Ethylene oxide☺	75-21-8	1.8 mg/m³	NA	D	600
Ethylene thiourea	96-45-7	0.30 mg/m³	100	D	10
Ferbam	14484-64-1	6.84 mg/m³	100	D	NA
Firemaster BP-6	59536-65-1	1.4 µg/m³	30	D	NA
Folpet	133-07-3	6 mg/m³	10	D	NA
Formamide	75-12-7	5.22 mg/m³	100	R	NA
Fungaflor	35554-44-0	0.60 mg/m³	100	D	NA
Furlfuramide	3688-53-7	1.8 mg/m³	10000	R	NA
Gallium-arsenide	1303-00-0	incomplete			
Glycidol	556-52-5	0.09 mg/m³	1000	R	NA
Glycol ether	111-46-6	75 mg/m³	10	D	NA
Gossypol	303-45-7	0.02 mg/m³	100	R	NA
Halothane	151-67-7	0.16 mg/m³	1000	D	NA
Hexachlorobenzene☺	118-74-1	0.025 mg/m³	NA	NA	40

continued

TABLE I. Reproductive Toxin Guidelines[A] (continued)

Chemical Name	Cas No.	ORG[B]	UF	Endpoint[C]	CR
Hexachlorphene	70-30-4	0.6 mg/m^3	100	D	NA
Hexane☺	110-54-3	176 mg/m^3	NA	NA	NA
Hexanedione, 2,5-	110-13-4	incomplete			
Hydrazine	302-01-2	0.006 mg/m^3	1000	D	NA
Hydroxymethyl mercury	1184-57-2	LOD	NA	NA	NA
Iodine	7553-56-2	incomplete			
Isocyanate, Methyl-	624-83-9	0.002 mg/m^3	1000	D	NA
Kanechlor 500	61788-33-8	1.4 µg/m^3	30	D	NA
Kepone	143-50-0	incomplete			
Lead	7439-92-1	0.01 mg/m^3	1000	D	NA
Lead acetate	301-04-2	0.01 mg/m^3	1000	D	NA
Lead, tetraethyl	78-00-2	0.01 mg/m^3	1000	D	NA
Lewisite	541-25-3	0.5 µg/m^3	1000	D	NA
Lindane	58-89-9	0.003 mg/m^3	1000	R	NA
Maneb	12427-38-2	3 mg/m^3	NA	D	NA
Melamine, hexamethyl-	645-05-6	incomplete			
Mercury (II) chloride	7487-94-7	0.01 mg/m^3	NA	NA	NA
Mercury (II) oxide	21908-53-2	0.01 mg/m^3	NA	NA	NA
Mercury and compounds	7439-97-6	0.01 mg/m^3	NA	NA	NA
Methanesulfonic acid,	66-27-3	incomplete			
Methotrexate	59-05-2	0.15 mg/m^3	100	D	NA
Methoxychlor	72-43-5	3.01 mg/m^3	10	R	NA
Methoxyflurane	76-38-0	8.1 mg/m^3	100	D	NA
Methyl benzimidazole	1065-21-7	incomplete			
Methyl chloride	74-87-3	4.65 mg/m^3	100	R	NA
Methyl ethyl ketone☺	78-93-3	590 mg/m^3	NA	NA	NA
Methyl mercury	22967-92-6	LOD	NA	NA	NA
Methyl metiram	8064-35-5	incomplete			
Methylene chloride	75-09-2	2.4 mg/m^3	100	R	14
Methylformamide, N-	123-39-7	5.4 mg/m^3	10	D	NA
Methylpyrrolidone, N-	872-50-4	0.91 mg/m^3	1000	D	NA
MIBK☺	108-10-2	205 mg/m^3	NA	NA	NA
Mintezol	148-79-8	0.6 mg/m^3	100	D	NA
Mirex	2385-85-5	incomplete			
Molybdenum	7439-98-7	incomplete			
Morpholine	24602-86-6	incomplete			
Mustard gas	505-60-2	0.003 mg/m^3	1000	R	NA
Nickel (II) chloride	7718-54-9	0.01 mg/m^3	100	R	NA
Nickel and compunds	7440-02-0	0.01 mg/m^3	100	R	8
Nickel carbonyl	13463-39-3	0.01 mg/m^3	100	R	NA
Nicotine	54-11-5	0.01 µg/m^3	100	D	NA
Nitrofen	1836-75-5	10 µg/m^3	100	D	NA
Nitrofurazone	59-87-0	0.09 mg/m^3	1000	R	NA
Nitrogen dioxide	10102-44-0	0.18 mg/m^3	10	R	NA
Nitrosamine, diethyl-	55-18-5	7 ng/m^3	NA	TC	1
Nitrosamine, dimethyl-	62-75-9	0.02 µg/m^3	NA	TC	1
Nitrosomethylurea	684-93-5	0.4 µg/m^3	10000	TC	NA
Nitrotoluene, o-	88-72-2	incomplete			
Nitrous oxide☺	10024-97-2	90 mg/m^3	NA	NA	NA
Oxygen	7782-44-7	ppO_2 148 mm Hg	NA	D	NA
Perchloroethylene	127-18-4	11.87 mg/m^3	100	R	20
Petroleum naphtha	64742-95-6	12 mg/m^3	100	D	NA
Phenol	108-95-2	3.6 mg/m^3	100	D	NA
Phenylalanine nitrogen	148-82-3	incomplete			
Phenylmercuric acetate	62-38-4	LOD	NA	NA	NA
Phosmet	732-11-6	0.01 mg/m^3	1000	D	NA
Phosphate, trimethyl-	512-56-1	0.60 mg/m^3	1000	R	NA

continued

TABLE I. Reproductive Toxin Guidelines[A] (continued)

Chemical Name	Cas No.	ORG[B]	UF	Endpoint[C]	CR
Phthalate, dibutyl-	84-74-2	0.72 mg/m^3	1000	D	NA
Piperonyl butoxide	51-03-6	0.90 mg/m^3	1000	R	NA
Polybrominated biphenyl	67774-32-7	1.4 µg/m^3	30	D	NA
Polychlorinated biphenyl	1336-36-3	1.4 µg/m^3	30	D	3.3
Potassium iodide☺	7681-11-0	1.0 mg/m^3	NA	NA	NA
Propionic acid,	120-36-5	incomplete			
Resorcinol methyl ether	150-19-6	incomplete			
Ronnel	299-84-3	0.08 mg/m^3	1000	D	NA
Sodium arsenite☺	7784-46-5	0.01 mg/m^3	NA	NA	100
Sodium chlorite	7758-19-2	6.84 mg/m^3	1000	D	NA
Sodium fluoride☺	7681-49-4	2.5 mg/m^3	NA	NA	NA
Sodium iodide☺	7681-82-5	1 mg/m^3	NA	NA	NA
Sodium nitrite	7632-00-0	incomplete			
Sodium selenate	13410-01-0	incomplete			
Sodium selenite	10102-18-8	incomplete			
Styrene	100-42-5	85 mg/m^3	NA	D	0.3
Sulfur dioxide	7446-09-5	2.3 mg/m^3	100	D	NA
TCDD	1746-01-6	incomplete			
TEG	112-27-6	338 mg/m^3	100	D	NA
TEGDiME	112-49-2	75 mg/m^3	10	D	NA
Tetraglyme	143-24-8	3.6 mg/m^3	NA	NA	NA
Tetrahydrofuran☺	109-99-9	590 mg/m^3	NA	D	NA
Thiadiazole,	26907-37-9	4 µg/m^3	100	D	NA
Thiourea	62-56-6	6 mg/m^3	1000	D	NA
Thiram	137-26-8	0.16 mg/m^3	1000	D	NA
Toluene	108-88-3	9.6 mg/m^3	10	D	NA
Toluenediamine, o-	95-80-7	1.8 mg/m^3	100	D	NA
Toluenesulfonamide, o-	88-19-7	2.4 mg/m^3	100	D	NA
Toxaphene	8001-35-2	0.02 mg/m^3	1000	D	20
Tributyl tin oxide	56-35-9	incomplete			
Trichlorfon	52-68-6	0.48 mg/m^3	100	D	NA
Trichloroethylene	79-01-6	5.5 mg/m^3	100	D	NA
Tridiphane	58138-08-2	0.02 mg/m^3	500	R	NA
Triethylenemelamine	51-18-3	60 ng/m^3	10000	R	NA
Triethylenetetramine	112-24-3	2.9 mg/m^3	10	D	NA
Trifluralin	1582-09-8	3 mg/m^3	1000	D	NA
Urethane	51-79-6	6 mg/m^3	1000	D	NA
Vinyl chloride	75-01-4	4 µg/m^3	NA	TC	1
Vinylidene chloride	75-35-4	14 mg/m^3	10	D	NA
Warfarin	81-81-2	10 µg/m^3	10	D	NA
Xylene, o-, m-, p-	1330-20-7	1.5 mg/m^3	10	D	NA
Zinc sulfate	7733-02-0	2 mg/m^3	1000	D	NA

[A] These exposure guidelines have been derived from a screening level of risk assessment and should not be construed as unequivocally safe exposure limits.
[B] ORGs represent 8 hour time-weighted averages unless otherwise noted.
[C] D = Developmental; R = reproductive; TC = transplacental carcinogen; CR = cancer risk/10,000; UF = uncertainty factor; ☺ = TLV believed to be adequate to protect reproductive health; LOD = limit of detection

Industrial Hygienists' *Documentation of Threshold Limit Values*, OSHA substance-specific standards permissible exposure limits, (PELs), the German Maximum Concentrations in the Workplace[9] (MAKs), and NIOSH recommended exposure limits (RELs).

If an exposure limit was not found, the literature was searched for a NOAEL or LOAEL with a reproductive end point. The search for information on the NOAEL/LOAEL consisted of studies from peer-reviewed literature found in the following databases: Hazardous Substances Database,[9] TOXLINE,[10] NIOSHTIC,[11] REPROTOX,[12] and IRIS.[13] Human data were preferred for the NOAEL/LOAEL, but in the majority of cases quantitative human exposure data were not available. If human data were not found, NOAELs/LOAELs obtained from animal studies were used, typically employing the most sensitive end point from the most sensitive mammalian species. If inhalation data were unavailable, ingestion studies or dermal studies were used.

The NOAEL or LOAEL was converted to a value for humans using the calculations employed by NIOSH[6] and IRIS, i.e., scaling the NOAEL or LOAEL to a human equivalent

dose and dividing by a combined uncertainty factor, including a 10 for variability in human susceptibility. For inhalation data the absorbed animal dose was determined using the average animal body weights and inhalation rates described in EPA's *Toxicology Handbook*.[14]

Absorbed animal dose (inhalation) for reproductive end points:

$$(\text{mg/kg/day}) = \text{NOAEL}\ (\text{mg/m}^3) \times \frac{\text{inhalation rate}\ (\text{m}^3/\text{day})}{\text{animal body weight}\ (\text{kg})} \times \frac{\text{exposed hours}}{24\ \text{hours}}$$

The absorbed animal dose was converted to an equivalent human concentration by assuming a 60-kg body weight (average female weight[15]) and a 10-m^3 inhalation rate for an 8-hour workday.[13] The average female body weight was used, as it results in a more conservative ORG.

Equivalent exposure for humans:

$$(\text{mg/m}^3) = \frac{\text{absorbed dose for animals}\ (\text{mg/kg/day}) \times 60\ \text{kg}}{10\ \text{m}^3/\text{day}}$$

When oral or dermal animal data was used, it was converted to an equivalent human airborne concentration by assuming a 60-kg body weight and a 10-m^3 inhalation rate.

Equivalent exposure for humans (oral and dermal):

$$(\text{mg/m}^3) = \text{mg/kg/day} \times \frac{60\ \text{kg}}{10\ \text{m}^3/\text{day}}$$

The equivalent exposure for humans was then divided by an uncertainty factor to obtain the ORG:

$$\text{ORG} = \frac{\text{equivalent exposure for humans}}{\text{uncertainty factor}}$$

The multiplicative uncertainty factors[16] included 10 for most sensitive human, 10 for animal to human extrapolation, 10 for use of a LOAEL, 10 for inadequate study design and a possible modifying factor of 0.1 for a high animal dose (>1000 mg/kg/day),[17] and 0.1 for an animal study with effects seen only at maternally toxic doses. The modifying factor for studies reporting developmental effects only at maternally toxic doses was included since "adverse effects on development that occur only with maternal toxicity may not indicate a specific hazard to the conceptus" and thus are not as great a concern.[18] The uncertainty factors (UF) applied in each ORG determination are included in the list at the end of this article.

For carcinogens with slope factors published by EPA,[19] an upper bound estimate of the cancer risk expected over a lifetime of occupational exposure at the ORG was determined using the following calculations.

$$\text{Unit risk per } \mu\text{g/m}^3 = \frac{\text{slope factor per mg/kg/day} \times \text{inhalation rate}\ (10\ \text{m}^3/\text{day})}{\text{body weight}\ (60\ \text{kg}) \times 1000\ \mu\text{g/mg}}$$

$$\text{Lifetime cancer risk} = \frac{\text{exposure at ORG}\ (\mu\text{g/m}^3) \times 40\ \text{yrs} \times \text{unit risk per } \mu\text{g/m}^3}{70\ \text{yrs}}$$

The lifetime cancer risk was included to provide a comparison between the reproductive guideline and the cancer risk at that level.

For substances listed by the World Health Organization[20] as transplacental carcinogens in animals, the ORG was established based on the exposure corresponding to an occupational lifetime risk of 1 in 10,000 when an EPA slope factor was available. This risk was chosen to represent a level equated with the risk of mortality from work in the retail clothing sector.[15] If a slope factor was unavailable, the ORG was calculated using the uncertainty factor method with an added uncertainty factor of 10 for the nonthreshold possibility extant with transplacental carcinogenesis.

$$\text{Unit risk per } \mu\text{g/m}^3 = \frac{\text{slope factor per mg/kg/day} \times 10\ \text{m}^3/\text{day}}{\text{body weight}\ (60\ \text{kg}) \times 1000\ \mu\text{g/mg}}$$

$$\mu\text{g/m}^3 = \frac{(10^{-4}) \times (70\ \text{yrs.})}{(40\ \text{yrs}) \times \text{unit risk per } \mu\text{g/m}^3}$$

An example of a reproductive toxins database record is depicted in Figure 2. Fields includes chemical name, CAS number, update code, class of chemical compound, animal species with positive reproductive studies, ORG, UF, end point, and the cancer risk associated with the ORG (if an EPA unit risk was available). A memo field containing descriptive information on human and animal reproductive/developmental data along with the information used for establishing the ORG (including the uncertainty factors) was also included. Substances may be added, selected for a screening assessment, or deleted from the database on the basis of new information.

A copy of the database including the ORG list and the descriptive memo field is available by sending two floppy disks and a self-addressed envelope to the authors.

DISCUSSION

The purpose of this study was to provide a frame of reference for reproductive health protection in the workplace regardless of gender or reproductive status. The safety of the workplace depends on hazard identification followed by exposure control below an established limit, and these limits should protect workers from all adverse effects, including reproductive effects. While ORGs do not represent consensus standards or limits, they are based on reproductive end points. ORGs can be used to flag potential reproductive toxicity concerns for workers at the levels listed. As stated earlier, where a TLV is believed to be protective of reproductive effects, it is used as the ORG. The assumption that other nonreproductive effects are automatically safeguarded at a particular ORG or TLV is not justified. As a case in point, consider carcinogens. Of 28 substances for which cancer risk could be estimated, 84% (26/31) of the corresponding ORGs equated to a cancer risk in excess of 1 in 10,000; some consider risk above this level unacceptable.

The study has generated a database consisting of 213 potential reproductive toxins. The majority of the substances have associated ORGs based on animal reproductive NOAELs or LOAELs. As expected, there are differences between the ORGs and existing TLVs. At this time 85% (180/213) of the dose/response determinations have been completed; of these, 47% (85/180) do not have established TLVs. For substances with TLVs, 25% (24/95) have established limits equal to or lower

CAS NO: 67-56-1
Ud: 9509
Chem type: A C D M S T
Species: Rat Mus
ORG: 262 mg/m^3
UF: NA—TLV believed to be protective
CA-RISK/1E4: NA
ENDPOINT: D

PROFILE: METHYL ALCOHOL

PHYSICAL DATA: MW: 32.04; Physical state: liquid; VP: 96 mm Hg at 20°C.

OCCUPATIONAL STANDARDS: ACGIH 262 mg/m^3; NIOSH 260 mg/m^3; MAK 260 mg/m^3. Group D, "Classification in a pregnancy group is not yet possible."

PPE: Material is toxic via skin absorption. Therefore, skin *contact must be prohibited* or else the ORG is invalidated. Butyl Rubber and Saranex are best PPE materials. Natural Rubber, Nitrile Rubber, PVAL, and PVC are not recommended.

ANIMAL DATA: Rogers, et al., reported two studies in mice with inhalation doses of MeOH at 5000 and 10,000 ppm (study 1) and 2000 and 5000 ppm (study 2) for 7 hours a day on days 6 through 16 of gestation. In both studies the 5000 ppm exposure produced exencephaly in one-third of the fetuses. At 2000 ppm, 1 of 220 fetuses had exencephaly. Controls had no incidence of exencephaly in the offspring. (Rogers, Toxicologist, 11(1):344, 1991). In a more recent study, Rogers exposed mice to 1000, 2000, 5000, 7500, 10,000, or 15,000 ppm methanol for 7 hrs/day on days 6–15 of gestation. The NOAEL for developmental toxicity was reported at 1000 ppm (1310 mg/m^3). A dose-related increase in cervical ribs was significant at the 2000 ppm level. Increased exencephaly and cleft palate were reported at 5000 ppm, and increased embryo/fetal death at 7500 ppm (Rogers, et al., Teratology, Mar; 47(3), pp:175–88, 1993). Rats have been found to be less sensitive than mice to the developmental effects of methanol, with effects seen only at 10,000 ppm and above (Rogers, Toxicologist, Mar; 13(1), pp:13, 1993).

ORG RECOMMENDATION: Using the NOAEL of 1000 ppm (1310 mg/m^3), the ORG is 458.5 mg/m when an uncertainty factor of 10 is applied (10 for most sensitive human, 10 for animal extrapolation, and 0.1 as a modifying factor for the high dose). Since the calculated ORG is above the TLV, the TLV of 262 mg/m^3 is accepted as the ORG as protective of reproductive effects.

FIGURE 2. Example of a database record

than the calculated ORG and were assumed adequate for protection of reproductive effects, leaving 75% that have established limits greater than the ORG. Overall, 87% (156/180) of the substances identified by the dose/response portion of this assessment method have inadequate reproductive exposure limits. As expected, animal data make up the majority of the available toxicological information, although 9% (17/180) of the ORGs are based on human data. Several limitations to this method must be recognized. The two major categories of limitations are lack of information on specific chemicals and inadequate mechanistic models useful in extrapolating from animals to humans. The identification process of potential reproductive toxins is limited by the amount of currently available toxicological data on reproductive effects. If, during the literature search, insufficient data is found on the reproductive effects of a substance, this is reported in the memo field. RTECS is used as a primary data source due to its comprehensive inclusion of positive data. However, RTECS does not report negative studies, which limits the documentation available for a weight of evidence approach to substance selection or elimination. Another problem frequently encountered is the difficulty in finding certain citations, especially foreign citations. Less frequently encountered, but just as limiting, a citation is located that does not include a dose level from which to calculate an ORG. The ORGs presented are based on the most sensitive (lowest) reproductive NOAEL/LOAEL discovered using the sources referenced earlier. A reasonable effort was made to locate the best available information. Beyond this no claim of veracity is made. The majority of the available reproductive data used in establishing human inhalation ORGs is from oral studies in animals. The difficulties with extrapolation between species and routes of exposure are frequently discussed in the literature. In the absence of human data or mechanistic models the usual alternative is to apply uncertainty factors for the various assumptions inherent in the assessment.

CONCLUSION

This study presents information on reproductive exposure guides on which to base hazard assessment and make informed decisions on the need for exposure control. In most cases, the ORGs have been derived from a screening level of risk assessment and should not be construed as unequivocally safe exposure limits. It is hoped that they will serve as a catalyst and forum for further debate resulting in refinements that will enhance occupational health without being unnecessarily burdensome.

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