Adjusting TLVs® for Reproductive and Developmental Health

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ABSTRACT

TLVs® are not designed to be used as regulatory standards. They are to be used by professional industrial hygienists while assessing health risks to chemicals. A necessary part of this assessment needs to include reproductive and developmental susceptibility. This includes the health risks of the pregnant worker during fetal development and to workers who are trying to become pregnant.

The industrial hygienist needs some guidelines in their repertoire for adjusting TLVs for the pregnant worker in the workplace. Some TLVs already take into account reproductive effects however many do not. Where the toxic effects of specific chemicals are known, determining the appropriate protective action to be taken is fairly straightforward. Where no reproductive and developmental toxicity data is given, the following provides some information to assist in assessing occupational exposures during pregnancy.

INTRODUCTION

There are many studies assessing the affects of pharmaceuticals on reproductive health and developmental health of the fetus[1]. However there are very few studies assessing the impact of industrial chemicals on the reproductive health of women or the impact on the developmental health of the child. Women make up a large part of the workforce, yet there is a lack of appropriate technical guidance for dealing with occupational exposures for the pregnant worker.

There is an appreciable difference in the responses of different laboratory animals, between animals and humans, and variation between humans[2]. Correlations made between animal test data and human are not definitive[3]. The major gender difference in mammals tends to be related to cytochrome P450 metabolism by the liver. Testosterone can increase the rate of the flavin-containing monooxygenase enzyme metabolism[2,4]. As a result, males are more susceptible when the metabolite is more toxic than the parent chemical. Females would be more susceptible when the parent chemical is more toxic.

Studies have not found any significant gender differences in the response to chemical exposures[5]. However, chemical exposure may have an adverse effect on fertility and pregnancy outcomes, so appropriate protective actions must be taken.

REPRODUCTION

The reproductive age for women is generally from 15 to 45 years. In Canada, the estimated percent of women in the labour force in 2014 and 2022 is given in Table 1. There is a high percent of women in the work force that are of childbearing age and who may become pregnant. While the women cannot be removed from the work force in order to protect their unborn child, the child must still be protected (as far as reasonably practicable) from chemical exposure.

Table 1: Labour force participation rate by women for 2015 and projected for 2022[6].

Age Group	2015	2022
15-19	53	54
20-24	77	77
25-29	82	83
30-34	82	82
35-39	82	83
40-44	83	83
45-49	84	85
50-54	83	85

All workers of reproductive age must be protected this includes male workers. Chemical exposure that occurs prior to conception may affect the pregnancy outcome. Chemicals can have an affect pre- and post-conception. Exposures during these times must be considered when assessing the worker's health and determining their occupational exposure limit.

Preconception Physiology

Exposure to chemicals can affect a number of physiological processes in females and males. When the reproductive system is compromised in either gender, a successful pregnancy outcome will be in doubt. Industrial chemicals can affect hormone production, gamete production and release, and development of the reproductive system. The resulting effects before conception can result in mutations, chromosomal abnormalities, spontaneous abortion, birth defects, and functional impairments[7,8,9].

During Pregnancy

There are a number of maternal changes that occur during the pregnancy. These changes include an increased respiratory rate and kidney function, increased blood volume, which leads to an increase in cardiac output, and increase storage of fat tissue[10,11]. The blood-placenta barrier allows for transfer of pharmaceuticals and likewise industrial chemicals[10].

Chemical exposures can result in spontaneous abortions/fetal death, major structural malformations, decrease in growth rate, and developmental and cognitive impairments[9,12].

Embryonic Period (up to 8th week)

This first trimester is the most sensitive to chemical insult however there is variation depending on when during this developmental stage of growth the fetus was exposed[12]. Chemical effects during the first trimester can result in of structure, growth, and function abnormalities[7]. During this early stage, significant exposures may lead to spontaneous abortions[13].

The third to eighth weeks are very susceptible to chemical exposures. Cells start differentiating into what will eventually become tissues and organ systems, damage at this point will have catastrophic effects[12]. Many birth defects occur during this time, making prevention critical.

Fetal Period (8th week to term)

During this fetal development period tissues and organ systems mature further. There is a decrease in significant observable defects, however as the brain matures during this time, chemical exposure may lead to developmental and cognitive impairments. There is an increased demand in gas exchange and nutrient uptake, which is provided by an increase in supply of maternal blood to the fetus[12].

TLVs AND REPRODUCTIVE EFFECTS

Many of the TLVs address reproductive effects. A number of TLVs are based on or takes into account the reproductive effect of the chemical (Table 2). A number of other TLVs are based on non-reproductive adverse effects but are set low enough that the reproductive effects are protected (Table 3). The exposure limit for these chemicals does not have to be adjusted for reproductive effects.

There are still a large number of chemicals in the TLVs and BEIs that do not have clear guidance. The TLV Documentation for these chemicals may not contain an overt statement as to reproductive safety however; there may be useful information in the Reproductive/Developmental section of the Documentation. For example, in the summary for chlorobenzene, it states that the TLV is based on slight liver changes, including increased weight and congestion, reported for rats exposed by inhalation to 50 or 75 ppm. In the Reproductive/Developmental section it states that rats exposed by inhalation at 0, 50, 150, or 450 ppm for two generations showed no adverse reproductive effects. This would suggest that reproductive effects occur at concentrations above the TLV and that adjustments are not required.

Table 2: Examples of chemicals with TLVs that are based on reproductive and/or developmental effects as listed in column 6 of the 2014 TLV booklet[14].

Acetophenone	Diglycidyl Ether	Methyl n-Butyl Ketone
tert-Amyl Methyl Ether	N,N-Dimethyl Acetamide	Methyl Chloride
Atrazine	Dinitrotoluene	Methyl Isopropyl Ketone
Benomyl	Epichlorhydrin	α-Methyl Styrene
1-Bromopropane	2-Ethoxyethanol	Nitrous Oxide
n-Butyl Glycidyl Ether	2-Ethoxyethyl Acetate	p,p'-Oxybis(Benzenesulfonyl Hydarzide)
Carbaryl	2-Ethylhexanoic Acid	Phenyl Glycidyl Ether
Chloroform	Hexafluoroacetone	Phenylphosphine
2-Chloropropionic Acid	Lead Chromate	Toluene
Dibutyl Phthalate	Methomyl	1,3,5-Triglycidy-s-triazinetrione
Dichloroacetic Acid	2-Methoxyethanol	4-Vinyl Cyclohexene
Dieldrin	2-Methoxyethyl Acetate	Vinyl Cyclohexene Dioxide

Table 3: Examples of chemicals with TLVs based non-reproductive effects, but are believed to be low enough to take into account possible reproductive and/or developmental effects[15].

Acrylic Acid	Dibutyl Phosphate	Mercury (Alkyl Compounds)
Acrylonitrile	1,4 Dichloro-2-butene	Mercury (Inorganic)
Adiponitrile	Diethanolamine	Methanol
Alachlor	Endosulfan	1-Methoxy-2-propanol
Amitrole	Ethyl Benzene	Methylacrylonitrile
Benomyl	Ethyl Chloride	Methyl Parathion
Borate	Ethylene Dibromide	Nitromethane
Butenes	Ethylene Glycol	Parathion
Captan	Ethylene Oxide	o-Phthalodinirile
Carbofuran	Ferbam	m-Phthalodinirile
Carbon Disulfide	Halothane	Piperazine
Carbon Monoxide	Hexachlorobenzene	Sodium Fluoroacetate
Chlorobenzene	Hydrogen Sulfide	Sulprofos
β-Chloroprene	Hydroquinone	Tributyl Phosphate
Citral	Iodine and Iodides	Trichloroethylene
Coumaphos	Lead	Trimellitic Anhydride
Cumene	Lithium Hydride	Warfarin
Cyclohexanone	Maleic Anhydride	Xylene
Cyclonite	Manganese	

GENERAL TLV ADJUSTMENTS FOR REPRODUCTIVE EFFECTS

When the TLV Documentation is unclear whether a pregnant worker would be adequately protected, a rough guideline would be to reduce the TLV by 30% to take into account the increase respiratory volume expected during pregnancy[16].

During pregnancy, there is an increase in kidney function by 30 – 50% [17,18]. Kidney function increases due to the increased blood volume. This increase in kidney filtration rate would decrease the biological half-life of a chemical proportionally. However, considering that not all chemicals are eliminated through the kidneys, any TLV correction for increased renal elimination must be chemical specific.

Complications using the biological half-life arise if the mother works an unusual work schedule. For example, if the biological half-life is 20 hours or greater, the lowering the half-life could result in an increased effective maternal exposure with respect to longer work shifts such as 4 10-hour days.

GUIDANCE FROM OTHER SOURCES

There are a number of other sources that can be used to gather information about the reproductive and developmental effects of industrial chemicals. The information from these sources can be used as guidance in determining occupational exposure limits.

There are a number of databases that contain information regarding reproductive and developmental toxicity. These databases include: Registry of Toxic Effects of Chemical Substances (RTECS)[19], Integrated Risk Information System (IRIS)[20], Toxicology Data Network (TOXNET)[21], NIOSHTIC-2 Publications Search[22], and REPROTOX[23]. These databases include data such as mutagenic effects, reproductive effects, tumorigenic effects, acute toxicity, and other multiple dose toxicity.

There are several publications that have compiled lists of chemicals that have identified reproductive and developmental effects. The United States Navy Environmental Health Center has published a technical manual titled: Reproductive and Developmental Hazards: A Guide for Occupational Health Professionals, which has extensive lists of workplace chemicals and drugs that have reproductive effects[16].

Environmental exposure data can also be used in determining a chemical's health effects. The Minnesota Department of Health has published Health Risk Values for a number of chemicals[24]. This list of environmental exposure levels includes chemicals with reproductive effects. As environmental limits, they are not to be used for workplace exposure limits. However, the acute concentration level that are believed safe for 1 hour a day, seven days a week. This concentration could be considered a lower limit, with the TLV as the upper limit.

Brown et al. wrote a paper titled A Methodology for Assessing Developmental and Reproductive Hazards of Chemicals. They have published a list of 110 chemicals and the corresponding reproductive and developmental toxicity[25].

Rudolph and Forest list a number of chemicals that have an adverse effect on reproductive and developmental health (Table 4).

Table 4: Chemicals With Animal Evidence for Adverse Effects on Reproductive Outcome[9].

Effect	Chemical Cause
Altered Pituitary-Hypothalamic-Ovarian Function	Benzene, carbon tetrachloride, kepone, mercury, PCBs
Decreased Fertility	Chloroprene, DBCP, DDT, epichlorhydrin, ethylene dibromide, lead, manganese
Impaired Implantation	Cadmium, lead, PCBs
Fetotoxicity or Embryolethality	Anesthetic gasses, arsenic, benzene, chloroform, 2,4-D, DDT, dichloromethane, ethylene dibromide, ethylene oxide, lead, mercury, nitrogen dioxide, polybrominated biphenyls, PCBs, selenium, tetrachloroethylene, thallium, vinyl chloride, vinylidene chloride, xylene
Teratogenicity	Acrylonitrile, arsenic, bayleton, benlate, benzene, benzo(a)pyrene, cadmium, carbaryl, chlorodifluoromethane, chloroprene, chromium, diethylstilbestol, endrin, glycol ethers, mercury, methaacrylates (some), methyl ethyl ketone, methyl formamide, phthalates (some butyl), tellurium, thiram, TOK (2,4-dichlorophenyl-p-nitrophenyl ether), vinyl chloride
Transplacental Carcingens	Arsenic, benzo(a)pyrene, DES, vinyl chloride
Reduced Reproductive Capacity (in offspring)	DES, kepone, PAHs

McGuigan has published a list of materials including industrial chemicals that have an adverse effect of the female reproductive system (Table 5) and the male reproductive system (Table 6)[7].

Table 5: Agents reported to affect human female reproductive capacity[7].

Chemical group	Examples of chemicals
Steroids	Androgens (natural and synthetic), estrogens, progestins
Antineoplastic agents	Alkylating agents, antimetabolites
CNS Drugs	Anesthetic gases/vapors (halothane, enflurane, methoxyflurane, chloroform)
Metals and trace elements	Arsenic, beryllium, cadmium, lead (organic and inorganic), lithium, mercury (organic and inorganic), molybdenum, nickel, selenium, thallium
Insecticides	Benzene hexachlorides (lindane), carbamates (carbaryl), chlorobenzene derivatives (DDT, methoxychlor), indane derivatives (aldrin, chlordane, dieldrin), phosphate esters (parathion), miscellaneous (chlordecone, ethylene oxide, hexachlorobenzene, mirex)
Herbicides	Chlorinated phenoxyacetic acids (2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid)
Food additives and contaminants	Cyclohexamine, diethylstilbestrol, dimethylnitrosamine, monosodium glutamate, nitrofuran derivatives, nitrosamines, sodium nitrate
Industrial chemicals and processes	Aniline, carbon monoxide, chlorinated hydrocarbons (PCBs, PBBs, trichloroethylene, tetrachloroethylene), epchlorohydrin, ethylene dibromide, ethylene dichloride, ethylene oxide, ethylene thiourea, formaldehyde, methylene chloride, nitrogen dioxide, phthalic acid esters, plastic monomers (caprolactam, styrene, vinyl chloride, vinylidene chloride, chloroprene), polycyclic aromatic hydrocarbons (benzo(a)pyrene), solvents (benzene, carbon disulfide, ethanol, glycol ethers, hexane, toluene, xylene), miscellaneous (canoketone, hydrazines)
Consumer products	Ethano l, tobacco smoke, flame retardants [tris-(2,3-dibromopropyl)phosphate]

Table 6: Agents reported to affect human male reproductive capacity[7].

Chemical group	Examples of chemicals
Steroids	Androgens (natural and synthetic), estrogens, progestins
Antineoplastic agents	Alkylating agents, alkaloids, antimetabolites, antitumor antibiotics
CNS Drugs	Alcohols, anesthetic gases/vapors
Metals and trace elements	Aluminum, arsenic, boron, boranes, cadmium, cobalt, lead (organic and inorganic), Manganese, Mercury (organic and inorganic), molybdenum, nickel, silver, uranium, zinc
Insecticides	Benzene hexachlorides (lindane), carbamates (carbaryl), chlorobenzene derivatives (DDT, methoxychlor), indane derivatives (aldrin, chlordane, dieldrin), phosphate esters (dichlorvos, hexamethylphosphamide), miscellaneous (chlordecone)
Herbicides	Chlorinated phenoxyacetic acids (2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, yalane), quaternary ammonium compounds (diquat, paraquat)
Rodenticides	Metabolic inhibitors (fluoroactate)
Fungicides, fumigants, and sterilizers	Apholate, captan, carbon disulfide, dibromochloropropane, ethylene dibromide, ethylene oxide, thiocarbamates, triphenyltin
Food additives and contaminants	Aflotoxins, cyclamate, diethylstilbestrol, dimethylnitrosamine, gossypol, metanil, monosodium glutamate, nitrofuran derivatives
Industrial chemicals and processes	Chlorinated hydrocarbons (hexafluoroactone, PCBs, PBBs, TCDD), hydrazines (dithiocarbamoylhydrazine), plastic monomers (vinyl chloride, chloroprene), polycyclic aromatic hydrocarbons (benzanthracine, benzo(a)pyrene), solvents (benzene, carbon disulfide, glycol ethers, epichlorhydrin, hexane, thiophene, toluene diisocyanate)
Consumer products	Ethanol, plasticizers (phthalate esters), flame retardants [tris-(2,3-dibromopropyl)phosphate]
Miscellaneous	Physical factors (heat, light), radiation, hypoxia

The Asia Monitor Resource Center has produced a book detailing the health hazards in the electronics industry[26]. It contains a list of 42 chemicals that have toxic reproduction and developmental effects. This list (Table 7) has been modified to include the roll of the kidneys in

elimination, taken from the TLV Documentation[14]. This illustrates why it is essential to determine the route of elimination for each chemical before adjusting exposure limits due to the effect of increased renal elimination. The chemicals that have a TLV set to protect against reproductive effects are in bold[15].

Table 7: Chemicals with reproductive effects, and the role of the kidney during elimination[26].

Chemical	Roll of kidney in the route of elimination	Teratogen	Reduced fertility or sterility	Miscarriage or fetal death	Birth defect, mutation, fetal damage	Cancer of reproductive organ	Menstrual problems
Acrylonitrile	80%	A				?	
Antimony			A	HA	H	?	H
Arsenic	60%		H s	H	A	H	
Benzene	30%	A	H si		A	?	H
Cadmium	Dominant		H A si	H	H	H	
Carbon dioxide		HA			H/A		
Carbon disulfide	70-90%		H A si	H/A	H A		
Carbon monoxide	nil		H si		A		
Carbon tetrachloride			A			?	
Cellosolve chlorinated hydrocarbons (several kinds)					H/A	?	
Chlorobenzene	Dominant	A	A				?
Chloroform				A			?
Diglycidyl ether			A				?
Dimethyl formamide		A					
Epichlorohydrin	50%		H A s				?
Ethylene diamine tetraacetic acid		A					
Ethylene dibromide			H A s	H/A	H/A	?	

Chemical	Roll of kidney in the route of elimination	Teratogen	Reduced fertility or sterility	Miscarriage or fetal death	Birth defect, mutation, fetal damage	Cancer of reproductive organ	Menstrual problems
Ethylene dichloride		H		H	H	?	
Ethylene oxide	Dominant		A		A	?	
Ethylidene chloride		A					
Freon 31		A					
Lead (absorbed)	Dominant		H A si	H	H	?	H
Lithium		A					
Manganese	Minor		H si			?	
Mercury	variable		H A si	H/A	H/A		
Methyl ethyl ketone	Dominant				H		
Methyl methacrylate	7-14%	A					
Methylene chloride	Minor				H		
Nickel	Dominant		A			?	
Nitrous oxides				H/A	H/A		
Perchloroethylene	nil				A	?	
Phosphorus	Dominant		H s				
Polychlorinated biphenyls			A	H	H	?	
Selenium	Dominant	A					
Tellurium	Dominant	A					
Toluene	80%	A			A		H
1,1,1-trichloroethane	Very Low	A			A		
Trichloroethylene	Dominant		H si	H	H A	?	
Vinyl chloride	Dominant for low	H	H	H	H/A	?	

Chemical	Roll of kidney in the route of elimination	Teratogen	Reduced fertility or sterility	Miscarriage or fetal death	Birth defect, mutation, fetal damage	Cancer of reproductive organ	Menstrual problems
	exposures						
Xylene	Dominant	A			A		H
Zinc chloride		A				?	

H = human evidence, A = animal evidence, H/A = humans and animal evidence, s = causes sterility in men, i = associated with male impotence, ? = known to cause cancer in other parts of the body

Often these other sources do not include exposure guidelines; they bring attention to the need for special consideration when determining occupational exposures for reproductive and developmental effects.

FROM TOXICOLOGY DATA TO WORKPLACE OEL

When reproductive or developmental health data is not available from other sources, as mentioned above, a literature search for toxicology data can be done. Toxicology data can be manipulated to create human health-based exposure limit for the workplace. Unfortunately, there is a great variability in the response of organisms when exposed to a chemical insult. When determining these exposure limits, from animal or human toxicology data, uncertainty factors are used to account for the variations and uncertainties between and within the populations tested and the population to be exposed.

The process starts with the preferred no-observable-adverse-effect level NOAEL, which can be obtained from the literature or one of the databases, mentioned above. This concentration is then divided by the uncertainty factor (Table 8). When more than one factor is selected, they are multiplied together before being applied to the NOAEL. If the resulting product is greater than 3000, or more than 4 uncertainty factors are used, the NOAEL should not be used as the data is insufficient to derive an exposure limit[27].

Table 8: Uncertainty factors for different experimental data[27,28,29].

Data to which Uncertainty Factor is Applied	Uncertainty Factor	When to Use the Uncertainty Factor
Transplacental Carcinogen	10	When the toxin does not have a threshold
Animal-to-human Extrapolation	10	When data is from animal studies
Variation Between Humans	10	This takes into account the most sensitive persons
Extrapolating from a LOAEL	10	If only a LOAEL is available, this factor is used
Sub-chronic to Chronic	10	When the study duration was less than a lifetime exposure
Poor Study Design	10	When the study is lacking in some aspect
High Animal Dose	0.1	When the animal dose was >1000 mg/kg/day
Maternally Toxic in Animal Study	0.1	When the effects were only noted at maternally toxic levels

Use the following calculations in order to transform animal reproductive toxicology data into the human equivalent of a reproductive exposure guideline[29,30].

If the NOAEL is from animal data expressed as mg/m^3, convert it to mg/kg/day using the data from Table 9.

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

Convert to equivalent exposure for a female (for male use 70 kg), breathing 10 m^3 for an 8-hour workday.

$$Human\ Exposure = \frac{NOAEL_{\text{adj}}\ \text{x}\ 60\ kg}{10\ m^3/day}$$

Calculate the reproductive exposure guideline (REG).

$$Reproductive\ Exposure\ Guideline = \frac{Human\ Exposure}{uncertainty\ factor}$$

Table 9: Reference values for laboratory animals[30].

Species	Body Weight (kg)	Inhalation rate (m^3/day)
Mouse	0.03	0.039
Rat	0.35	0.223
Hamster	0.14	0.13
Guinea pig	0.84	0.40
Rabbit	3.8	2.0
Dog	12.7	4.3
Rhesus monkey	8.0	5.4
Human	70	20
Female	60	20

The following Table 10 contains selected examples of occupational reproductive exposure guidelines (REG) along with the uncertainty factor used in their calculation[29]. The 2014 TLVs are shown for comparison. The chemicals that have a TLV set to protect against reproductive effects are in bold. In some cases the REG is less than the TLV when the TLV is based on reproductive effects (Toluene), and in other cases the REG is higher than the TLV when it's based on other effects (carbon disulfide).

Table 10: Samples of calculated occupational reproductive exposure guidelines. When the TLV was based on reproductive effects, the material is in bold.

Chemical name	Uncertainty Factor	REG (mg/m^3)	TLV (mg/m^3)
Acetaldehyde	100	14.4	25 (C)
Benzene	1000	0.05	1.6
Carbon disulfide	100	8.4	3.13
Epichlorhydrin	NA	0.38	1.9
Glycidol	1000	0.09	6.1
Lead	1000	0.01	0.05
Mercury (Inorganic)	NA	0.01	0.025
Nitrogen dioxide	10	0.18	0.38
Toluene	10	9.6	75

CONCLUSION

At present there is little guidance for the industrial hygienist to use in order to modify the TLV guidelines to meet the needs of a worker who is or wants to become pregnant. This paper gives some recommendations to assist with this necessity. There is evidence to suggest that the failure to take the reproductive and developmental health effects into account may have a detrimental effect. It is important for the industrial hygienist to recognize these possibilities,

and to work with other professionals such as physicians, to meet the needs of these workers. As advised by the TLV Committee, the TLVs should not be used as standards as indicators of safe/not safe concentrations, but to be used as guidelines or recommendations to be used by occupational hygienists in their practice.

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