Assessing liver toxicity of organic compounds based on their physicochemical properties for the purpose of calculating occupational exposure limits

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Occupational Exposure Limits (OEL's)

The basic model of occupational exposure assumes repeated inhalation exposure during long periods of time, i.e. 8-hours per day for a 40-hour working week on average. Occupational exposure limits (OELs) are developed to prevent and control potential health hazards in workplace.

It is assumed that at the level of OEL for a given chemical, all or almost all of the exposed workers will not experience adverse health effects.

OEL's are established by different organizations. The most popular is the list published every year by American Conference of Governmental Industrial Hygienists.

About 45% of the Threshold Limit Values (TLV) established by this organization for organic compounds are based on the sensory irritation effect. Liver is considered to be a critical organ for 13 % , CNS for 12% of substances. The other effects include inhibition of acetylocholinoesterase activity (8%), methemoglobinemia (6.0 %) and other, mainly cancer and reproductive toxicity (14%).

Together about 70% of TLV's are based on sensory irritation and disturbances in liver or CNS functions.

OEL's are based on the points of departure (NOAEL, LOAEL ,BMDL) deriving from industrial settings as well as experimental human and animal studies.

In view of the scarcity of epidemiological data and the tendency to limit the animal testing procedures , the possibility for calculating occupational exposure limits for organic compounds on the basis of their physicochemical properties is of great importance.

There is a large number of steps on the pathway between administration of an external dose and the final toxic effect. The continuous process between the external dose and the toxic response can be subdivided into steps related to the distribution of the chemical in the body (toxicokinetics) and those related to the actions of the chemicals in the organism (toxicodynamics).

The processes involved in toxicokinetics of xenobiotics are described by PBTK models, however, such models are still scarce and developed for single substances.

Abraham (1993) have developed the general equation that seems satisfactory for explaining the transfer of VOCs from the gaseous phase to a large number of solvents or other condensed phases, including biophases.

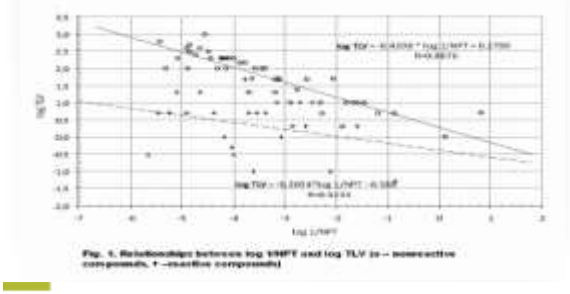
$$SP = c + eE + sS + aA + bB + lL \quad (1)$$

In this equation, the dependent value SP is either a physicochemical property of a given VOC, such as logK, where K is the gas to solvent partition coefficient for a series of VOCs into the given solvent or condensed phase, or a biological property of VOC, such as an odor or nasal pungency threshold (NPT), for a series of VOCs.
In equation (1), E, S, A, B, and L are the properties, or descriptors, of the VOC:
E – excess molar refraction;
S – dipolarity/polarizability;
A and B – overall or effective hydrogen bond acidity and basicity, respectively, of the VOC
L (log L16) is defined through L16, the VOC hexadecane-air partition coefficient at 298 K, and is a measure of the lipophilicity of a VOC.

The Abraham's group have then developed several specific equations making possible evaluation of the transfer of organic compounds to different organs and tissues such as chemestetic receptors, liver, CNS, lung, muscle, fat and blood.

The possibility of prediction of a potential toxic effects on the basis of the efficiency of transfer of given compounds to chemestetic receptors in the case of exposure to sensory irritants and to the liver was of particular interest from the point of view of calculating occupational exposure limits for a new compounds.

The obtained relationship between the rate of transfer of sensory irritants to chemestetic receptors (1/NPT) and TLVs suggested that Abraham's equations may be used for prediction of toxic properties of organic compounds at least as relates to their toxicokinetics (Jakubowski and Czerczak, 2010).



The aim of present study was to investigate to what extent the relationship between the distribution coefficients K_{liver} from air to the liver (Abraham et al., 2007) could be used for calculating LOAEL values for compounds that are responsible for liver toxicity.

Distribution coefficients K_{liver} from the air to the liver were calculated according to the equation published in the Pharma Algorithms database, ADME Boxes, Version 4.0, 2008. (Pharma Algorithms Inc., Toronto, ON, Canada).

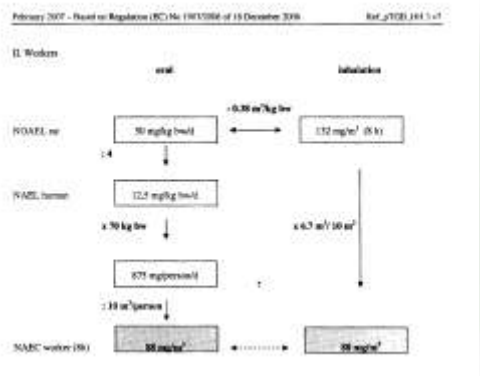
$\log K_{liver} = -1.031 + 0.059E + 0.774S + 0.593A + 1.049B + 0.654L$

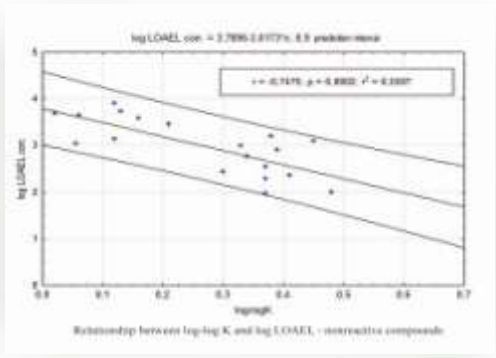
The descriptors E,S,A,B and L were also obtained from the Pharma Algorithms database.

LOAEL values were obtained from the literature data both as a result of inhalation and oral exposure (early effects, mainly subchronic experiments on rats). They have been transformed into concentrations in mg/m^3 and corrected for the kind of animal (scaling) according to the procedure described in REACH document (2011).Compounds have been divided into two groups:

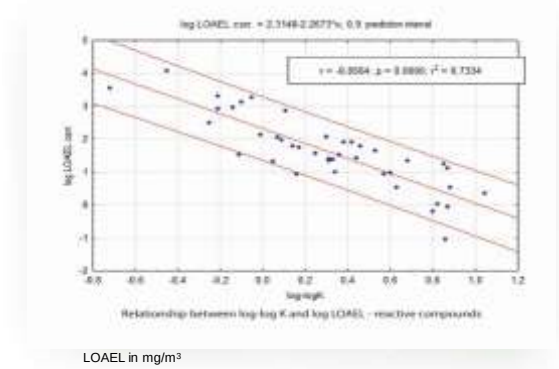
►non-reactive (n=19): alcohols, ketones, esters, ethers, aromatic and aliphatic hydrocarbons, amides

► reactive (41): aldehydes, allyl compounds, aliphatic amines, benzyl halides, halogenated hydrocarbons carboxylic acids, acrylates





LOAEL in mg/m³

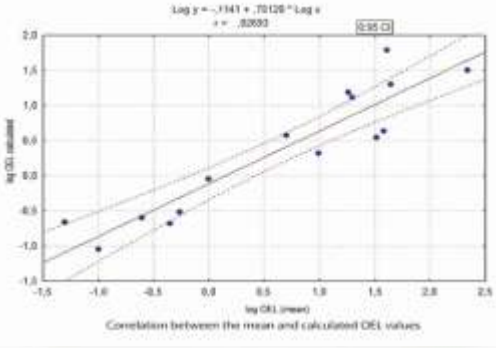


LOAEL in mg/m³

Validation

The mean LOAEL values have been used as the basis for calculating OELs for 16 compounds where liver was considered as critical organ by at least two of three organizations (ACGIH, DFG, Polish MK).
For this purpose the LOAELs obtained on the basis of regression equations for reactive and non-reactive compounds were divided by 10 (assessment factors: 2 for LOAEL/NOAEL extrapolation and 5 for intraspecies differences)

Substances	OEL's mg/m3			Mean mg/m3	Calc. OEL	Calc./Mean
	TLV	MAK	NDS			
Bromoform	5.2	-	5	5.1	3.7	0.72
Carbon tetachloride	31	3.2	20	18.1	15	0.83
Chlorobenzene	46	47	23	38.7	4.3	0.17
Chloroform	49	2.5	8	19.8	12.9	0.65
Dieldrin	0.25	0.25	-	0.25	0.24	0.96
Diethanoloamine	1.00	1.00	-	1.00	0.90	0.90
Endosulfan	0.10	-	0.10	0.10	0.09	0.90
Ethyl bromide	22.0	50	50	40.6	62	1.52
Ethylene dichloride	40	-	50	45.0	20	0.44
Halothane	404	41	-	222	31.6	0.14
Heptachlor	0.05	0.05	-	0.05	0.22	4.40
Hexachloro ethanol	9.7	9.8	10	9.8	2.1	0.21
4,4'-methylene dianiline	0.81	-	0.08	0.45	0.21	0.47
Trichloropropane	60	-	7	33.5	3.5	0.10
Trinitrotoluene	0.1	-	1.0	0.55	0.3	0.54
Vinylidene chloride	20	8	12.5	13.5	15.5	1.15



OEL in mg/m³

Conclusions

The results on the possibility of calculating the OEL's based on sensory irritation effects have been already published (Jakubowski and Czerczak, J.Occup. Environ. Hyg., 2010)

The obtained results suggest that LOAELs and consequently OELs for organic compounds responsible for liver toxicity can be predicted based on the $logK_{liver}$ values calculated according to the Abraham's equation

In view of the scarcity of human data and the tendency to limit animal testing procedures, the method proposed in this paper can improve the practice of setting exposure gidelines for unstudied compounds

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