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A PROPOSAL FOR CALCULATING THE NO-OBSERVED-ADVERSE-EFFECT LEVEL (NOAEL) FOR ORGANIC COMPOUNDS RESPONSIBLE FOR LIVER TOXICITY BASED ON THEIR PHYSICOCHEMICAL PROPERTIES

MAREK JAKUBOWSKI and SŁAWOMIR CZERCZAK

Nofer Institute of Occupational Medicine, Łódź, Poland
Department of Chemical Safety

Abstract

Objectives: Both environmental and occupational exposure limits are based on the no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL) or benchmark dose (BMD) deriving from epidemiological and experimental studies. The aim of this study is to investigate to what extent the NOAEL values for organic compounds responsible for liver toxicity calculated based on their physicochemical properties could be used for calculating occupational exposure limits. **Material and Methods:** The distribution coefficients from air to the liver (log K_{liver}) were calculated according to the Abraham solvation equation. NOAEL and LOAEL values for early effects in the liver were obtained from the literature data. The descriptors for Abraham's equation were found for 59 compounds, which were divided into 2 groups: "non-reactive" (alcohols, ketones, esters, ethers, aromatic and aliphatic hydrocarbons, amides) and "possibly reactive" (aldehydes, allyl compounds, amines, benzyl halides, halogenated hydrocarbons, acrylates). **Results:** The correlation coefficients between log-log K and log NOAEL for non-reactive and reactive compounds amounted to r = –0.8123 and r = –0.8045, respectively, and were statistically significant. It appears that the Abraham equation could be used to predict the NOAEL values for compounds lacking information concerning their liver toxicity. **Conclusions:** In view of the tendency to limit animal testing procedures, the method proposed in this paper can improve the practice of setting exposure guidelines for the unstudied compounds.

Key words:
Liver, NOAEL, LOAEL, Organic compounds, Physicochemical properties, Abraham's Eq

INTRODUCTION

Both, environmental and occupational exposure limits for chemical substances are developed to prevent and control potential health hazards.

Generally, for all the effects with the exception of those induced by direct interaction of the compound or its metabolites with genetic material, it is assumed that there is a threshold exposure, below which the probability of harm is negligible. Occupational Exposure Limits (OELs), Reference Doses (RfD) or Concentrations (RfC) are based on the points of departure such as the no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level

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Corresponding author: S. Czerczak, Department of Chemical Safety, Nofer Institute of Occupational Medicine, św. Teresy 8, 91-348 Łódź, Poland (e-mail: sak@imp.lodz.pl).

(LOAEL) deriving from industrial settings as well as experimental studies. In view of the scarcity of epidemiological data and the tendency to limit animal testing procedures or human volunteer studies, the possibility of calculating the above-mentioned points of departure 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 the external dose administration 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 chemical in the organism (toxicodynamics). Transfer of organic compounds from the air to the target tissues is of crucial significance in understanding their potential toxic effects. The processes involved in the absorption and distribution of xenobiotics are similar. They are presently described by physiologically based toxicokinetic (PBTK) models. However, such models are still scarce, complicated and developed only for single substances.

Abraham [1] constructed a general equation that seems satisfactory in terms of explaining the transfer of VOCs from the gaseous phase to a large number of condensed phases, including biophases (e.g. mucosa, serum for different organs).

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

In this equation, the dependent value SP is some free energy related property, such as an adsorption or absorption constant, 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 odour or nasal pungency threshold (NPT), for a series of VOCs.

The independent variables in Equation 1 – E, S, A, B, and L – are the properties, or descriptors, of the VOC's, i.e., E – excess molar refraction, S – dipolarity/polarisability, A and B – overall or effective hydrogen bond activity and basicity, respectively, L – (log L^{16}) is defined through L^{16}, the VOC hexadecane-air partition coefficient at 298 K, and is a measure of VOC lipophilicity.

The coefficients c, e, s, a, b and l are found by multiple linear regression analysis. They reflect the complementary properties of the receptor phase. The e coefficient gives the tendency of the phase to interact with a compound through polarisability-type interactions, mostly via electron pairs. The *s* coefficient is a measure of the phase dipolarity/polarisability. The a coefficient represents the complementary property to the compound hydrogen-bond acidity, and so, is a measure of the phase hydrogen-bond basicity. Likewise, the b coefficient is a measure of the phase hydrogen-bond acidity. Finally, the l coefficient is a measure of the hydrophobicity of the phase.

In order to apply Equation 1 to any given process, a correlation between a reasonable number of data concerning the property is needed as the dependent variable. Simple multiple linear regression against the known compound descriptors leads to the coefficients. Once the latter have been calculated, then for any other compound for which the descriptors are available, the property can be calculated [2]. The descriptors for about 5000 compounds are available in the Pharma Algorithms database, ADME Boxes, Version 4.0, 2008. (Pharma Algorithms Inc., Toronto, ON, Canada). Additional descriptors, if required, can be predicted from the structure [3].

The Abraham's group have developed several equations enabling evaluation of the transfer of organic compounds to different organs and tissues such as liver [4], brain [5] or lungs [6].

Possible applications of the equations developed by Abraham et al. for prediction of retention of volatile organic compounds in the respiratory tract and for calculating occupational exposure limits for volatile organic compounds acting as sensory irritants have already been published [7,8].

The aim of this study is to investigate to what extent the relationship between the distribution coefficients K_{liver} from the air to the liver [4] could be used for calculating NOAEL values for organic compounds that are responsible for liver toxicity.

MATERIAL AND METHODS

Calculation of the distribution coefficients K_{liver}

Distribution coefficients K_{liver} from the air to the liver were calculated according to the Equation 2 published in the Pharma Algorithms database, ADME Boxes, Version 4.0, 2008. (Pharma Algorithms Inc., Toronto, ON, Canada):

$$\text{Log } K_{liver} = -1.031 + 0.059E + \\ + 0.774S + 0.593A + 1.049B + 0.654L \quad (2)$$

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

No-observed-adverse-effect level (NOAEL) and LOAEL values were obtained from the literature data. Compounds which caused early non-neoplastic effects in the liver, as a result of inhalation or oral exposure, were considered. The increased liver weight was not considered as an adverse effect because it may reflect physiological adaptation to the presence of particular substance. The Abraham's descriptors have been found for 59 compounds.

Abraham's equation describes the transfer of compounds to the liver regardless of their toxicodynamics. Biological activity of a chemical depends on the transport from the site of administration to the site of action and reaction of the unchanged compound or its metabolites with the receptor or target (i.e., biological activity is a function of partition and reactivity). If a structure/activity model is deficient in modelling either partition or reactivity, only a partial correlation with the biological response is likely to be observed [9].

Since it was impossible to evaluate the balance of local bioactivation and detoxication of particular compounds as well as the possible interaction of unchanged compounds and their metabolites with intracellular targets, all compounds were divided into 2 groups: "non-reactive" (alcohols, ketones, esters, ethers, aromatic and aliphatic hydrocarbons, amides) and "possibly reactive" (aldehydes, allyl compounds, amines, benzyl halides, halogenated hydrocarbons, acrylates) [10].

The NOAEL and LOAEL values are presented in Tables 1 and 2.

To obtain the corresponding NOAEL values the LOAEL values were divided by 2 [64]. Then NOAELs obtained both as a result of inhalation and oral exposure in animals have been transformed into concentrations in mg/m^3 for workers according to the procedure described in the REACH document [65].

In the first step oral NOAEL for a given animal was transferred to humans with a factor of 4 for allometric scaling for rats, 7 for mice and 2.5 for other interspecies differences.

Using a standard human body weight (70 kg) and a default human breathing volume of 10 m^3 for workers in 8 h and light activity, this dose was then translated into the air concentration (NAEC) according to the equation:

$$NAEC_{worker\ 8h} = \\ = NOAEL \times 70\ kg/\text{allometric scaling factor} \times 10\ m^3 \quad (3)$$

Where inhalative data are concerned, air concentrations for animal and human exposure are generally compared directly. For workers the air concentration was corrected for the lung ventilation (6.7 m^3 for base level and 10 m^3 for light activity during 8 h):

$$NAEC_{worker\ 8h} = NOAEL_{inh} \times 6.7\ m^3/10\ m^3 \quad (4)$$

Statistical analysis

Statistical analysis was carried out using SPSS version 14. Linear regression analysis was applied to examine the correlation.

Table 1. NOAEL/LOAEL values for non-reactive compounds

Compound	CAS No.	Critical study [references]	NOAEL/ LOAEL*	NOAEL modified (mg/m^3)	Log NOAEL** modified	log-logK
Acetone	67-64-1	rats – gavage (30–90 days), an increased liver weight and liver-to-body weight ratio [11]	NOAEL: 2 500 mg/kg/day	4 375	3.64	0.055
Tert-Amyl methyl ether	994-05-8	rats, dogs – inhalation (6 h/day, 5 days/week, 90 day), an increased absolute and relative liver weights [12]	NOAEL: 4 180 mg/m^3	2 800	3.44	0.120
2-Butoxyethanol	11-76-2	rats, mice – inhalation (6 h/day, 5 days/week, 14 weeks), an increased number of liver Kupffer cells [13]	LOAEL: 302 mg/m^3 NOAEL: 151 mg/m^3	101	2.00	0.480
Cumene	98-82-8	rats – inhalation (6 h/day, 5 days/week, 13 weeks), an increased liver weight [14]	NOAEL: 2 460 mg/m^3	1 648	3.22	0.390
Cyclohexane	110-82-7	rats – inhalation (6 h/day, 5 days/week, 90 days), an increased liver weight, centrilobular hypertrophy [15]	LOAEL: 24 500 mg/m^3 NOAEL: 12 250 mg/m^3	7 350	3.86	0.120
Cyclohexanol	108-93-0	rabbits – inhalation (6 h/day, 5 days/week, 5–11 weeks), slight degenerative changes in the liver [16]	LOAEL: 593 mg/m^3 NOAEL: 269 mg/m^3	180	2.26	0.370
Cyclohexanone	108-94-1	rabbits – inhalation (6 h/day, 50 days), barely demonstrable degenerative changes in the liver [16]	LOAEL: 762 mg/m^3 NOAEL: 381 mg/m^3	255	2.41	0.370
N,N-Dimethylacetamide	127-19-5	rats – inhalation (6 h/day, 5 days/week, 6 months), focal necrosis of liver [17]	LOAEL: 694 mg/m^3 NOAEL: 347 mg/m^3	233	2.37	0.410
Dimethylformamide	68-12-2	rats – inhalation (6 h/day, 10 days), slightly enlarged livers [18]	NOAEL: 272 mg/m^3	182	2.26	0.370
Ethanol	64-17-5	rats – gavage (12 weeks), a fatty liver and necrosis [19]	LOAEL: 10 000 mg/kg/day NOAEL: 5 000 mg/kg/day	4 375 8 750	3.94	0.060
Ethyl acetate	141-78-6	rabbits – inhalation (65 four-hour exposures), liver damage [20]	LOAEL: 16 020 mg/m^3 NOAEL: 8 010 mg/m^3	3 601	3.55	0.130
Ethyl benzene	100-41-4	rats – inhalation (7 h/day, 5 day/week, 6 months), a cloudy swelling in the liver [21]	LOAEL: 1 736 mg/m^3 NOAEL: 868 mg/m^3	582	2.76	0.340

Table 1. NOAEL/LOAEL values for non-reactive compounds – cont.

Compound	CAS No.	Critical study [references]	NOAEL/ LOAEL*	NOAEL modified (mg/m^3)	Log NOAEL** modified	log-logK
Ethyl tert-Butyl ether	637-92-3	rats – inhalation (6 h/day, 5 days/week, 4 weeks), a relative liver weight increase [12]	NOAEL: 8 360 mg/m^3	5 601	3.74	0.21
Indene	95-13-6	rats – inhalation (six 7.5-hour exposure periods), from slightly fatty degeneration to severe necrosis in the liver [22]	LOAEL: 3 792 mg/m^3 NOAEL: 1 896 mg/m^3	1 272	3.10	0.45
Methyl tert-butyl ether	1634-04-4	rats – inhalation (6 h/day, 5 days/week, 13 weeks), an increased liver weight [23]	NOAEL: 14 400 mg/m^3	9 648	3.98	0.02
Methylcyclohexane (cyclohexylmethane)	108-87-2	rabbits – inhalation (6 h/day, 90 h), a slight cellular liver injury [16]	LOAEL: 11 520 mg/m^3 NOAEL: 5 760 mg/m^3	3 865	3.59	0.16
Methyl isoamyl ketone	110-12-3	rats – inhalation (6 h/day, 5 days/week, 96 days), slight increases in liver weight [24]	NOAEL: 4 660 mg/m^3	3 122	3.49	0.38
Methyl isobutyl ketone	108-10-1	rats – inhalation (24 h/day, 2 weeks), an increased absolute liver weight and an increased organ-to-body-weight ratio [25]	NOAEL: 818 mg/m^3	548	2.73	0.30
Xylene (all isomers)	1330-20-7	rats – inhalation (8 h/day, 6 days/week, 110–130 days), a slight liver congestion [26]	LOAEL: 2 967 mg/m^3 NOAEL: 1 484 mg/m^3	994	2.99	0.33

* NOAEL – no-observed-adverse-effect level.
** LOAEL – lowest-observed and adverse-effect level.

Table 2. NOAEL/LOAEL values for reactive compounds

Compound	CAS No	Critical study [references]	NOAEL/ LOAEL*	NOAEL modified (mg/m^3)	Log NOAEL** modified	log-logK
Acetonitrile	1975-05-08	rats – inhalation (6 h/day, 5 days/week, 13 weeks), an increased liver weight [27]	NOAEL: 2 688 mg/m^3	1 800.0	3.25	–0.140
Aldrin	309-00-2	rats – diet (2 days), an increased liver weight [28]	NOAEL: 1.2 mg/kg/day	2.1	0.32	0.822
Allyl alcohol	107-18-6	rats – drinking water (15 weeks), hepatotoxicity [29]	LOAEL: 17 mg/kg/day NOAEL: 8.5 mg/kg/day	14.8	1.17	0.160
Allyl chloride	107-05-1	rats, mice – inhalation (6 h/day, 5 days/week, 3 months), no changes in liver attributable to allyl chloride [30]	NOAEL: 787 mg/m^3	527.0	2.72	–0.250

Table 2. NOAEL/LOAEL values for reactive compounds – cont.

Compound	CAS No	Critical study [references]	NOAEL/ LOAEL*	NOAEL modified (mg/m^3)	Log NOAEL** modified	log-logK
Bromoform	75-25-2	rats – diet (30 days), liver swelling [31]	LOAEL: 56 mg/kg NOAEL: 28 mg/kg	49.00	1.69	0.33
Carbon tetrachloride	56-23-5	rats, mice – inhalation (6 h/day, 5 days/week, 13 weeks), an increased liver weight, fatty changes [32]	LOAEL: 63 mg/m^3 NOAEL: 31.5 mg/m^3	21.10	1.33	0.05
Chlorobenzene	108-90-7	rats – inhalation (7 h/day, 5 days/week, 24 weeks), an increased liver weight, congestion [33]	LOAEL: 346 mg/m^3 NOAEL: 173 mg/m^3	115.00	2.06	0.30
Chloroform	67-66-3	rats – inhalation (7 h/day, 5 days/week, 6 months), a centrilobular granular degeneration [34]	LOAEL: 243 mg/m^3 NOAEL: 121 mg/m^3	81.50	1.91	0.09
Cyclonite	121-82-4	rats – diet (90 days), an enlarged liver [35]	NOAEL: 30 mg/kg/day	52.50	1.72	0.87
o-Dichlorobenzene	95-50-1	rats – gavage (138 doses), an increased liver weight [36]	NOAEL: 188 mg/kg	329.00	2.52	0.42
p-Dichlorobenzene	106-46-7	rats – diet (130 oral doses 192 days), an increased liver weight [37]	NOAEL: 188 mg/kg	3.10	1.90	0.38
1,1-Dichloroethane	75-34-3	rats, guinea pigs, rabbits – inhalation (6 h/day, 5 days/week, 13 weeks) [38]	NOAEL: 2 025 mg/m^3	1 956.00	3.29	–0.21
Dichloromethane	75-09-2	dogs, guinea pigs – inhalation (4 h/day, 5 days/week, 7.5 weeks), a moderate fatty liver degeneration [39]	LOAEL: 35 300 mg/m^3 NOAEL: 17 650 mg/m^3	11 825.00	4.07	–0.45
Diethanolamine	111-42-2	rats – inhalation (6 h/day, 5 days/week, 13 weeks), an increased liver weight [40]	NOAEL: 29 mg/m^3	19.40	1.29	0.60
Diethylamine	109-89-7	rabbits – inhalation (7 h/day, 5 days/week, 6 weeks), a parenhymatous liver degeneration with evidence of cell regeneration [41]	LOAEL: 105 mg/m^3 NOAEL: 52.5 mg/m^3	35.20	1.55	0.25
Diphenylamine	122-39-4	beagle dogs – diet (2 years), a peripherolobular fatty change with a marked increase in liver weight [42]	LOAEL: 110 mg/kg/day NOAEL: 55 mg/kg/day	192.00	2.28	0.68
Endosulfan	115-29-7	rats – diet (5 mg/kg, 30 days), an increased liver weight [43]	NOAEL: 5 mg/kg	8.75	0.94	1.05

Table 2. NOAEL/LOAEL values for reactive compounds – cont.

Compound	CAS No	Critical study [references]	NOAEL/ LOAEL*	NOAEL modified (mg/m^3)	Log NOAEL** modified	log-logK
Ethyl bromide	74-96-4	rats – inhalation (4 h/day, 6 months), hepatic function disruption [44]	LOAEL: 2 410 mg/m^3 NOAEL: 1 205 mg/m^3	807.00	2.91	–0.21
Ethyl chloride	75-00-3	rats – inhalation (6 h/day, 5 days/week, 13 weeks), an increased liver to body weight ratios [45]	NOAEL: 50 540 mg/m^3	33 862.00	4.53	–0.72
Ethylene dichloride	107-06-2	guinea pigs – inhalation (7 h/day, 5 days/week, 226 days), an increased liver weight [46]	NOAEL: 405 mg/m^3	271.00	2.43	–0.01
Halothane	151-67-7	rats, rabbits – inhalation (5 h/day, 5 days/week, 7 weeks), a centrilobular fatty liver infiltration [47]	LOAEL: 4 030 mg/m^3 NOAEL: 2 015 mg/m^3	1 350.00	3.13	–0.10
Heptachlor	76-44-8	rats – in diet (80 days), hepatic necrosis and synthesis of smooth endoplasmic reticulum [47]	LOAEL: 2 mg/kg/day NOAEL: 1 mg/kg/day	1.75	0.24	0.87
Hexachlorobenzene	118-74-1	rats – in diet (21 days), a relative liver weight increase, a centrilobular increase in hepatocyte size [48]	LOAEL: 8 mg/kg/day NOAEL: 4 mg/kg/day	7.00	0.84	0.63
Hexachlorobutadiene	87-68-3	rats – in diet (30 days), minimal hepatocellular swelling [49]	LOAEL: 100 mg/kg NOAEL: 50 mg/kg	87.50	1.94	0.53
Hexachloroethane	67-72-1	rats – diet (16 weeks), an increased liver weight, slight swelling of hepatocytes [50]	LOAEL: 62 mg/kg/day NOAEL: 31 mg/kg/day	54.20	1.73	0.44
Methyl chloroform	71-55-6	rats, guinea pigs – inhalation (1.2–3 h/day, 3 months), pathologic changes in liver [51]	LOAEL: 5 440 mg/m^3 NOAEL: 2 720 mg/m^3	1 842.00	3.26	–0.05
4,4'-Methylene dianiline	101-77-9	rats – oral intubation (16 weeks), a minor liver damage [52]	LOAEL: 8 mg/kg/day NOAEL: 4 mg/kg/day	7.00	0.85	0.88
Picloram	1918-02-1	rats – food (2 years), an increased liver weight, a centrilobular hepatocellular hypertrophy [53]	LOAEL: 60 mg/kg/day NOAEL: 30 mg/kg/day	53.00	1.72	0.85

Table 2. NOAEL/LOAEL values for reactive compounds – cont.

Compound	CAS No	Critical study [references]	NOAEL/ LOAEL*	NOAEL modified (mg/m^3)	Log NOAEL** modified	log-logK
Propargyl alcohol	107-19-7	rats – inhalation (7 h/day, 5 days/week, 3 months), an increased liver weight [19]	NOAEL: 184 mg/m^3	123.00	2.09	0.140
Propylene dichloride	78-87-5	rats – in diet (5 times weekly, 13 weeks), degenerative effects on the centrilobular hepatocytes [54]	LOAEL: 250 mg/kg/day NOAEL: 125 mg/kg/day	218.00	2.34	0.069
Pyridine	110-86-1	rats – diet (90 days), mild hepatotoxicity, inflammatory lesions, increased liver and liver to body weight ratios [55]	LOAEL: 25 mg/kg/day NOAEL: 12.5 mg/kg/day	21.90	1.34	0.310
1,1,2,2-Tetrachloro-ethane	79-34-5	rats, rabbits – inhalation (3–4 h/day, 11 months), a liver damage [50]	LOAEL: 100 mg/m^3 NOAEL: 50 mg/m^3	33.50	1.53	0.360
Tetrachloroethylene	127-18-4	mice – lavage (5 days/week, 6 weeks), an increased liver weight and triglycerides [56]	LOAEL: 100 mg/kg/day NOAEL: 50 mg/kg/day	50.00	1.70	0.310
1,2,4-Trichloroben-zene	120-82-1	rats – inhalation (7 h/day, 5 days/week, 26 weeks), microscopic changes in liver parenhyma after 4 or 13 weeks of exposure [57]	LOAEL: 185 mg/m^3 NOAEL: 92.5 mg/m^3	62.00	1.79	0.460
1,1,2-Trichloroethane	79-00-5	mice – drinking water (90 day), clinical chemistry indications of adverse effects on the liver [58]	LOAEL: 305 mg/kg/day NOAEL: 153 mg/kg/day	153.00	2.18	0.170
Trichloroethylene	79-01-6	rats – inhalation (7 h/day, 5 days/week, 6 months), an increased liver weight [59]	NOAEL: 2 154 mg/m^3	1 443.00	3.16	0.110
1,2,3-Trichloropro-pane	96-18-4	rats – inhalation (6 h/day,5 days/week, 13 weeks), an increased liver weight [60]	NOAEL: 30 mg/m^3	20.10	1.30	0.340
2,4,6-Trinitrotoluene (TNT)	118-96-7	dogs – gelatin capsules (0.5 mg/kg/day, 6 months), frank hepatotoxicity [61]	LOAEL: 0.5 mg/kg/day NOAEL: 0.25 mg/kg/day	0.87	–0.06	0.800
Vinylidene chloride	75-35-4	rats, rabbits, guinea pigs – inhalation (8 h/day, 5 days/week, 6 months), some hepatic degeneration [62]	LOAEL: 100 mg/m^3 NOAEL: 50 mg/m^3	34.00	1.53	–0.110
Xylidine	1300-73-8	rats – gavage (4 weeks), an increased liver weight [63]	NOAEL: 20 mg/kg	35.00	1.54	0.570

Abbreviations as in Table 1.

RESULTS AND DISCUSSION

The NOAEL values for non-reactive and reactive compounds as well as the respective log-log K_{liver} values are presented in Tables 1 and 2.

The obtained relationships between log-log K and NOAEL values for non-reactive and reactive compounds are presented on Figures 1 and 2. The correlation coefficients between log-log K and log NOAEL for non-reactive (Figure 1) and reactive compounds (Figure 2) amounted to r = –0.8045 and r = –0.8123, respectively, and were statistically significant**.**

The method for calculation of the NOAEL values was validated against the already established OEL values. For this purpose, LOAELs for 17 compounds, where the liver was considered as the critical organ for setting OELs by ACGIH [50], were calculated on the basis of their log-log K_{liver} values according to the regression equations for reactive and non-reactive compounds. To obtain the OELs, the calculated NOAEL's were divided by 12.5 according to the recommendations provided in the REACH document [65] (assessment factors: 2.5 for interspecies differences other than factor for allometric scaling and 5 for intraspecies differences) (Table 3).

Correlation between the mean OEL values published by at least 2 out of 3 organizations [50,66,67] and those calculated ones was very high (r = 0.897, p < 0.000) (Figure 3). Ratio of the calculated values to the mean OELs depends on the assumed assessment factors. Using the factor of 12.5, according to the REACH document [65], 7 of the calculated OELs were lower and 10 were higher than the mean published values. However, taking into account the divergences between the OELs in different countries, the possibility of practical usage of the proposed way of calculating LOAEL values seems very promising. According to the Setubal-principles developed by the Expert Group of the OECD Work Program on QSARs, the model for regulatory purposes should be associated with the following information: a defined endpoint, an unambiguous algorithm, a defined domain of applicability, appropriate measures of goodness-of-fit, robustness and predictivity

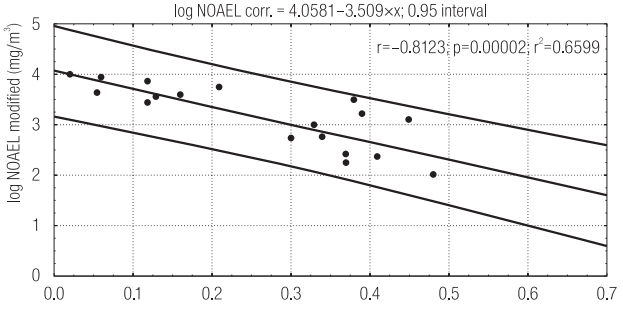

Fig. 1. Relationship between the log-logK and log NOAEL – non-reactive compounds

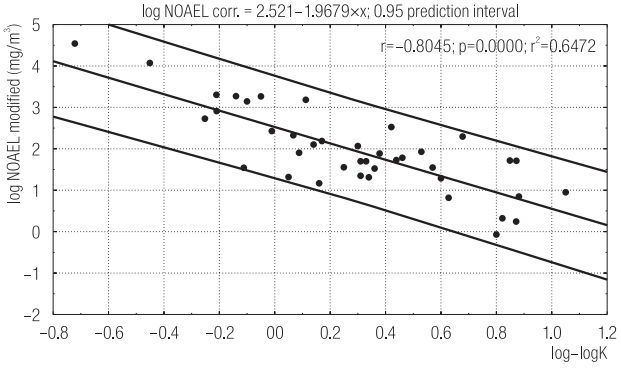

Fig. 2. Relationship between the log-logK and log NOAEL – reactive compounds

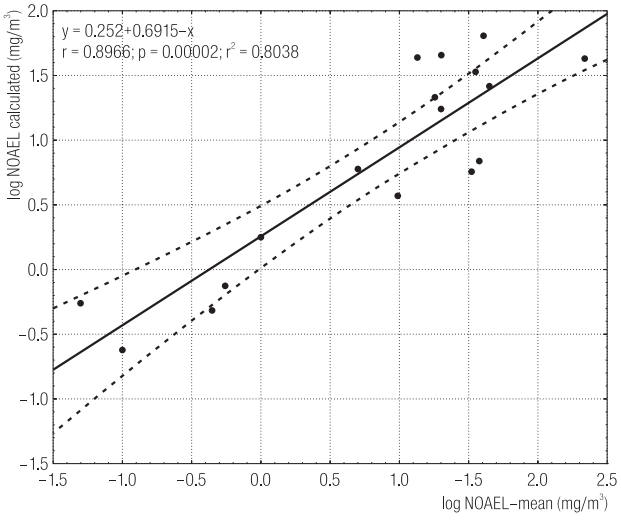

Fig. 3. Relationship between the mean and the calculated NOAEL values

Table 3. Comparison between the published Occupational Exposure Limits (OELs) and the calculated values

Substances	Published OELs (mg/m^3)					Calculated OELs	Log
	TLV	MAK	NDS	M	Log-x		
Bromoform*	5.20	–	5.00	5.10	0.70	5.93	0.77
Carbon tetrachloride*	31.00	3.20	20.00	18.10	1.26	21.00	1.32
Chlorobenzene*	46.00	47.00	23.00	38.70	1.58	6.80	0.83
Chloroform*	49.00	2.50	8.00	19.80	1.30	17.50	1.24
Diethanoloamine*	1.00	1.00	–	1.00	0.00	1.75	0.24
N,N-Dimethyl acetamide**	36.00	36.00	35.00	35.60	1.55	33.30	1.52
Dimethylformamide**	30.00	15.00	15.00	20.00	1.30	45.00	1.65
Endosulfan*	0.10	–	0.10	0.10	–1.00	0.23	–0.63
Ethyl bromide*	22.00	50.00	50.00	40.60	1.61	68.70	1.80
Ethylene dichloride*	40.00	–	50.00	45.00	1.65	25.90	1.41
Halothane*	404.00	41.00	–	222.00	2.34	41.80	1.62
Heptachlor*	0.05	0.05	–	0.05	–1.30	0.53	–0.27
Hexachloro ethanol*	9.70	9.80	10.00	9.80	0.99	3.60	0.56
4,4'-Methylene dianiline*	0.81	–	0.08	0.45	–0.35	0.48	–0.32
Trichloropropane*	60.00	–	7.00	33.50	1.52	5.66	0.75
Trinitrotoluene*	0.10	–	1.00	0.55	–0.26	0.72	–0.14
Vinylidene chloride*	20.00	8.00	12.50	13.50	1.13	42.80	1.63

TLV – ACGIH – USA – treshold limit value – American Conference of Governmental Industrial Hygienists [50].
MAK – DFG – Germany – Maximum Concentrations – Deutsche Forschungsgemeinschaft [66].
NDS (MAC) – CIOP-PIB – maximum admmisible concentrations time weighed [67].
OEL – occupational exposure limits.
M – model at the prediction of safe OELs.
* Reactive compounds.
** Non-reactive compounds.

and a mechanistic interpretation, if possible [68]. In the proposed model, aiming at the prediction of safe OELs, the first 4 points have been fulfilled.

About 45% of the Threshold Limit Values (TLV), established by the American Conference of Governmental Industrial Hygienists, 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. Other effects include inhibition of the acetylocholinoesterase activity, methaeminoglobinaemia, and other, mainly in a form of cancer and reproductive toxicity. In total, about 70% of TLV's are based on sensory irritation and disturbances in the liver or CNS functions [50].

The results showing the possibility of OELs prediction based on sensory irritation by means of the same general algorithm have already been published [8]. It is still necessary to verify the possibility of application of the same general algorithm in the case of the central nervous system [5]. If the results are positive, then it would be possible to predict safe occupational exposure limits for the majority of compounds, which can be potentially used in industry, except for the compounds

responsible for effects such as cancer and reproductive toxicity, inhibition of acetylocholinoesterase activity or methaeminoglobinaemia.

CONCLUSIONS

The obtained results suggest that NOAELs and consequently OELs for organic compounds responsible for liver toxicity can be predicted based on the $\log K_{liver}$ values calculated according to the Abraham's Eq. Also validation of the proposed method gave satisfactory results. Correlation between the mean OEL values published by at least 2 out of 3 organizations [50,66,67] and those calculated ones was very high ($r = 0.897$, $p < 0.000$). 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 guidelines for the unstudied compounds.

In the presented publication the Abraham equation gives positive results. Please remember that the equation refers only to the toxicokinetics. The results are valid only for the toxicokinetic characteristics of the chemical compound, i.e. they depend solely on the speed of their deposition in a specified system or organ. In the future, some basic correction to account for the reactivity of individual toxicodynamics of the compounds may be necessary.

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