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Regression Method to Estimate Provisional TLV/WEEL-equivalents for Non-carcinogens

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There is a huge and changing number of chemicals in commerce for which workplace exposure criteria have not been assigned. Assigning an exposure criterion by an expert committee is resource-intensive—not soon available for the large majority of chemicals in current use. In the absence of assigned criteria, we have provided a regression method to estimate a first-screen estimate of a 'TLV/WEEL-equivalent' inhalation time-weighted average exposure criterion for a pure chemical (or chemical group) from a measure of a non-stochastic toxic exposure to elicit a chronic or sub-chronic health effect, known as a lowest observable adverse effect level (LOAEL) or a (highest) no observable adverse effect level (NOAEL). Results are presented for six data sets for which both a threshold limit value (TLV) or workplace environmental exposure level (WEEL) exposure criterion is presently assigned, and a LOAEL or NOAEL measure of toxic health effect was available from the United States Environmental Protection Agency Integrated Risk Information System data base. The results can be applied as a first estimate of exposure to substances for which no TLV or WEEL (TLV/WEEL) exists, and also serve as a mechanism for identifying substances for potential re-evaluation of their exposure limit, based on their relative position about the prediction models. © **2000 British Occupational Hygiene Society. Published by Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

The evaluation and control of chemical hazard to human health at work relies strongly on inhalation exposure criteria—both as professional guidelines and legal standards. Systematic development of exposure criteria began in the late 1800s in Germany (Henschler, 1984), extending to North America in the early 1940s (Weisburger, 1994). Today, there are published workplace airborne exposure criteria (sometimes called 'exposure limits') for about 2000 chemicals. In comparison, about 100 000 chemicals are presently handled in commerce worldwide. Hundreds of new chemicals are added to world commerce each year and the use of others ceases. Hence, the list of chemicals in use without published exposure criteria is an enormous shifting target (Roach, 1994). The task of evaluating all existing chemicals far exceeds the capacity of the toxicology profession worldwide (US EPA, 1986).

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Two of the sets of professional guideline exposure criteria widely used in North America are the Threshold Limit Values (TLVs), published by the American Conference of Governmental Industrial Hygienists (ACGIH), and the Workplace Environmental Exposure Levels (WEELs) published by the American Industrial Hygiene Association (AIHA). These exposure criteria have been used in the authors' present analyses.

Of the 2000 chemicals with airborne exposure criteria, only about 250 such criteria are primary limits, based on human data. The great majority are secondary criteria, based mostly on tests using rodents (Roach, 1994). Exposure to a chemical often results in multiple toxic effects, often appearing at different levels of exposure (US EPA, 1986). The effect of exposure selected by a toxicologist to evaluate a chemical's toxicity quantitatively is called its toxic endpoint, often a sub-lethal effect, which can be used subsequently for developing an exposure criterion for workers. The bases for selecting the endpoint of concern usually include (1) the sensitivity of the endpoint, (2) severity of the response, and (3) whether the endpoint is reversible or irreversible (US EPA, 1986).

A low level of exposure to a chemical may produce an effect which is not clearly adverse (US EPA, 1986). To distinguish those effects from exposures which are adverse (cause overt or clinical damage) from non-adverse effects (sometimes called 'biomarkers of exposure'), a toxicologist will typically select an adverse endpoint (US EPA, 1986). Generally, this endpoint dose is expressed in one of two ways: as a lowest observable adverse effect level (LOAEL), or as a highest no observable adverse effect level (NOAEL). The severity of the endpoint response is reflected in the value of the LOAEL or NOAEL—as severity of response increases, the values of the LOAEL and (highest) NOAEL are reduced. The generic NOAEL is formally defined as the 'highest dose level that does not produce a significantly elevated increase in an adverse response' (Faustmann and Omenn, 1996).

The largest collection of published LOAEL and NOAEL values known to the authors is to be found within the toxicity data of the Integrated Risk Information System (IRIS) published by the United States Environmental Protection Agency (US EPA, 1996). IRIS was created to provide a source of consistent, best available toxicity data for human health risk assessment under the United States Superfund law for cleaning-up contaminated real estate.

Animal tests for chronic toxicity, other than for cancer or germline mutagenicity, typically consist of a few dose groups with several animals at each dose. Generally, oral doses or inhalation concentrations are selected over a range of no observable adverse effect levels, NOAELs, up to a lowest observable adverse effect level, LOAEL, at which the selected toxic endpoint is first seen, as the exposure dose (or concentration) is increased stepwise (US EPA, 1986). The NOAEL reported is typically the highest NOAEL measured, and identified as such. A statistical limitation of using LOAEL or NOAEL values to estimate the selected toxic endpoint threshold is that the measured values for LOAEL and NOAEL will depend on the size of the animal test groups (Faustmann and Omenn, 1996). Another method introduced to estimate toxic thresholds is the benchmark dose, which would be preferred because it is based on more dose–response information than an LOAEL or NOAEL. However, at present, far more LOAEL and NOAEL data than benchmark values are available in IRIS for developing regression equations. Therefore, we used only LOAEL and NOAEL values for this study.

Owing to the lack of published exposure limits for most chemicals to which workers may be exposed, there is clear potential use for a method to provide a rapid screening estimate for a safe exposure level for human exposure at work from inhalation. This report presents a regression method to make such a screening estimate based on LOAEL and NOAEL data, mainly from animal experiments. This work is not intended to apply to carcinogens or mutagens, for which the prevailing model, whether right or wrong, is stochastic. Use of the equations developed here should be restricted to dose-graded toxic effects in test animals or humans, having a toxic LOAEL or NOAEL caused by oral or inhalation exposure.

These equations were developed by regression of the overlap between LOAEL and NOAEL data from the US EPA IRIS data base (October 1996 edition; US EPA, 1996) and the workplace inhalation exposure criteria, mentioned above: (1) the Threshold Limit Values (TLVs); and (2) the Workplace Environmental Exposure Levels (WEELs). For these regressions, only time-weighted average TLVs and WEELs were used. For each type of guideline criterion, TLV or WEEL, the time-weighted average value for that criterion is intended for comparison with the time-weighted average concentration measured in the workplace, either for an eight-hour working day or a 40 h working week. In practice, time-weighted average measurements of exposure are usually made over a representative eight-hour working day, or a representative portion of it. The publishers of these TLVs and WEELs have set the values of these criteria at levels believed to be safe to protect nearly all workers, day after day, without adverse effects over a working lifetime. It is important that TLVs, and presumably WEELs also, are interpreted as upper control limits for each working day average exposure—not an upper limit for long-term or working lifetime average exposures (Hewett, 1997).

The TLV and WEEL criteria are for exposure to single, usually pure, chemical agents. They presume no substantive concurrent exposures to other toxic agents. When there are, in fact, cumulative or otherwise interacting toxic effects due to exposures to multiple chemical agents, industrial hygienists are expected to adjust recommended safe exposure criteria down to lower concentrations, based on professional judgement, to reflect additive or synergistic effects, where there is reason to expect such effects.

The method developed here estimates a preliminary safe workplace exposure limit for inhalation, most useful for chemicals which lack an officially assigned exposure criterion, but have a published LOAEL or NOAEL for a toxic endpoint of concern, which is expressed following a chronic or sub-chronic latency period. This method can serve as a first screen in the iterative process of risk assessment. If a chemical turns out to have a sufficiently low TLV/WEEL-equivalent, this may serve to justify a more detailed, formal risk assessment, or expert committee evaluation, for setting an exposure criterion.

Other potential uses of this estimation method are in use for relative hazard ranking of chemicals (the reason these equations were developed; see Whaley *et al*., 1999), and in identifying outliers among TLV/WEEL—threshold relationships which are several orders of magnitude outside the behaviour of the prevailing data—alerting responsible committees that a review of the TLV or WEEL value previously assigned may be warranted.

METHODS

All chemicals used were individually identified by chemical name and/or Chemical Abstracts Service (CAS) identification number, in at least three sources (Sax and Lewis, 1989; Howard and Neal, 1992; Budavari *et al*., 1996). Chemical names refer to those used in the data sources, IRIS and the TLV/WEEL lists. These are often different from formal chemical names [International Union of Pure and Applied Chemistry, IUPAC, or 9th Collective Index (Howard and Neal, 1992)], accessible through the CAS numbers.

Animal data

The US EPA Integrated Risk Information System (IRIS) data base contains over 600 chemicals of environmental concern, intensively reviewed by the Agency to determine the most credible LOAEL or NOAEL (or, more recently, the occasional benchmark dose), for purposes of conducting consistent human health risk assessments for hazardous waste remediations under the US Superfund law (US EPA, 1996). These data were extracted to our data base. For methyl mercury, measures of LOAEL and NOAEL were obtained from the Mercury Tox Profile, published by the US Agency for Toxic Substances and Disease Registry. A few apparent outliers were rechecked, to verify LOAEL or NOAEL values, again using the EPA IRIS compact disk, read-only memory (CD-ROM); but, for these, only January 1998 IRIS entries were available (details in the footnotes to Table 1).

For oral exposure, the units reported in IRIS (and usually in the primary papers for the LOAEL or NOAEL) reflect an intake rate as milligrams chemical ingested per kilogram body weight per day (mg kg^{-1} day^{-1}). For inhalation exposure, the exposure is expressed either as the concentration of chemical inhaled, as milligram chemical contaminant per cubic metre of contaminated air, mg m^{-3} (primary data), or as an equivalent intake rate. The equivalent intake rate assumes default conversion factors, such as average breathing rate, tidal volume, per cent absorbed (of that inhaled), body mass, etc., characteristic of the test population and test sample of that population. Therefore, the resulting inhalation exposure expressed as an intake rate, namely milligram chemical absorbed per kilogram body weight per day, is derived, or are secondary data.

In IRIS, when there were alternative measures by the same exposure route among which to choose, for example both an LOAEL and an NOAEL, usually from different studies, we chose the lower (more protective) values for the regression data set. Only chronic or sub-chronic LOAEL or NOAEL measures were used. When both inhalation and oral route LOAEL or NOAEL measurements were available from IRIS, segregated data from both routes were entered.

We use the meanings recommended by Eaton and Klaassen for 'acute' (one exposure or continual up to 24 h), 'sub-acute' (one day to one month), 'sub-chronic' (one to three months) and 'chronic' (exceeding three months) for rodent exposure durations (Eaton and Klaassen, 1996).

Exposure limits

As mentioned, two sets of professional guideline exposure limits, the Threshold Limit Values (TLVs), published by the American Conference of Governmental Industrial Hygienists, or ACGIH (1995, 1996) and the Workplace Environment Exposure Levels (WEELs), published by the American Industrial Hygiene Association or AIHA (1995) were examined for inclusion in this study.

The values of 1995–1996 TLVs and 1995 WEELs used were all time-weighted averages. The time-weighted average is the form of inhalation exposure criterion normally used to protect against chronic toxicity, and all of these time-weighted average criteria were unique values. Exposure criteria that

have no unique numeric value were deleted. When the TLV and/or WEEL lists contained one generic compound, but we could only locate IRIS data on specific isomers, all isomers were assigned separate entries in the regression data set. All asbestos values were deleted, because they were based on counts, rather than mass per unit volume. For the few chemicals which have both TLVs and WEELs, the more protective (lower) exposure limit was used. The combined TLV/WEEL 'pruned' list of unique values amounted to 598 TLVs and 68 WEELs, for a total of 666 chemicals.

Statistical methods

Linear regression lines were fitted to the TLV/WEEL values, using the LOAEL and NOAEL data as predictors. Scatter plots indicated that transformation of both TLV/WEEL values and LOAEL and NOAEL values to natural logarithms (ln) linearized the relationship between them and led to distributions consistent with the requirements for linear regression.

The motivation for developing these regressions was to provide a hazard ranking of chemicals for measuring progress in pollution prevention. We have used 'TLV/WEEL-equivalent estimates' obtained from these regression equations (Eqs 1–6, Table 2) for development of this hazard ranking (Whaley *et al.*, 1999).

Six independent variables (LOAELs, NOAELs, segregated by primary versus derived units; Table 1) were correlated with their corresponding TLV or WEEL values. This created six distinct data sets, containing some overlap of chemical identities, but with independent LOAEL or NOAEL values, each data set generating a linear regression equation, to predict TLV/WEEL-equivalent estimates for exposure criteria.

RESULTS

The numbers of chemicals in each of the six univariate regression data sets are presented in Table 1. The total number of chemicals identified was 168, for which a TLV or a WEEL and at least one of the six variables of Table 1 were located. The data sets based upon oral dosing had 120 and 111 points, respectively, while those based upon inhalation were smaller, each containing between 15 and 38 observations.

In linear–linear space, the plots of the six data sets all showed clustering close to the origin with a minority of points plotted at large deviations from the origin—unacceptable for linear univariate regression analysis. However, when the LOAEL or NOAEL and exposure criteria data were all ln-transformed, the scatter plots suggested reasonably acceptable linear relationships (for example, Fig. 1–3). The adjusted R^2 values ranged between 0.51 and 0.90 (see Table 2 and its footnote).

Linear regression estimates of TLV/WEEL-equivalents

The univariate linear regression equations are presented so as to estimate the TLV/WEEL-equivalent (Table 2), in units of milligram contaminant per

Table 1. Two source data sets and six overlap data sets used to generate regression equations

Name of data set	Unit	No. of chemicals[a]	Source
TLV	mg m^{-3}	598 (unique; chronic, sub-chronic)	ACGIH (1995, 1996)
WEEL	mg m^{-3}	68 (unique; chronic, sub-chronic)	AIHA (1995)
Inhalation:			
LOAEL 1	mg m^{-3}	38	IRIS, July 1995[b,e,g]
LOAEL 2	mg kg^{-1} day^{-1}	23	IRIS, July 1995[g]
NOAEL 1	mg m^{-3}	26	IRIS, July 1995[b,g]
NOAEL 2	mg kg^{-1} day^{-1}	15	IRIS, July 1995[e,g]
Oral:			
LOAEL	mg kg^{-1} day^{-1}	120	IRIS, July 1995[c,e,f]
NOEL	mg kg^{-1} day^{-1}	111	IRIS, July 1995[d,e,f]

[a]These numbers are not mutually exclusive. A chemical can have more than one threshold measurement reported in IRIS.

[b]Chlorodifluoromethane inhalation LOAEL (mg m^{-3}) value was confirmed and inhalation NOAEL (mg m^{-3}) was corrected using IRIS, January 1998.

[c]Hexachlorocyclopentadiene oral LOAEL corrected for dosing schedule using IRIS, January 1998.

[d]Insoluble compounds of Cr(VI) oral NOAEL deleted from data set after checking IRIS, January 1998.

[e]Alkyl mercury values for inhalation LOAEL (mg m^{-3}) and inhalation NOAEL (mg kg^{-1} day^{-1}) deleted and replaced with oral LOAEL and oral NOAEL from ATSDR Tox Profile for Mercury, August 1997.

[f]Oral LOAEL and NOAEL values for soluble compounds of nickel, as Ni, and for phenylaminediamine confirmed using IRIS, January 1998.

[g]Inhalation LOAEL and NOAEL, triethylamine, as mg m^{-3}, were verified, and inhalation LOAEL and NOAEL values (units of mg kg^{-1} day^{-1}) were deleted, based on IRIS, January 1998.

cubic metre of contaminated air. The results in Table 2 are applied as follows to estimate TLV/WEEL-equivalents:

$$\text{TLV/WEEL}(\text{mg m}^{-3})\text{-equivalent} = \exp\{1.30 + 0.635\ln[\text{I-LOAEL}(\text{mg m}^{-3})]\} = e^{1.30} \times \text{I-LOAEL}^{0.635}(\text{mg m}^{-3})$$

where I-LOAEL refers to an inhalation LOAEL.

As an example of the findings, Table 3 compares the 38 chemicals for which inhalation exposure limits could be estimated by univariate regression from an inhalation LOAEL, in concentration units of mg m^{-3} (from Eq 1 in Table 2). In Table 3, the existing assigned TLV or WEEL for each chemical ('observed TLV/WEEL') is compared to the regression estimate, the predicted TLV/WEEL-equivalent. As would be expected, the ratios from the estimates fall about equally above and below 1.0.

Estimates of TLV/WEEL-equivalents from literature values of measured LOAELs and NOAELs—25 Superfund chemicals

Table 4 reports the regression-generated estimates for TLV/WEEL-equivalents of 25 chemicals on the consolidated list of hazardous chemicals regulated under the US Comprehensive Environmental Response Compensation and Liability Act, commonly known as 'Superfund'. These chemicals do not currently have an assigned TLV or WEEL time-weighted average exposure criterion.

Table 4 shows chemical identification (CAS number, common name), information on test species, administration route, and basis for the experimental determination (LOAEL or NOAEL), the actual LOAEL or NOAEL value and units, and the TLV/WEEL predictions. Each prediction is derived from an LOAEL or NOAEL. For example, for chemical 1 (chloral) an LOAEL of 15.7 mg kg^{-1} day^{-1} from 90-day ingestion of drinking water in mice has been established. The predicted TLV/WEEL-equivalent for this substance was determined from $\exp[-0.0686 + 0.641 \times \ln(15.7)] = 5.5$.

Goodness of fit

Distributions of the (TLV/WEEL-equivalent)/observed (assigned) TLV/WEEL were generated for each of the six data sets, and outliers identified. The four inhalation LOAEL and NOAEL data sets had no severe outliers. Among the two oral LOAEL and NOAEL data sets, three outstanding outliers were identified.

In the oral LOAEL data set, only data point 86, soluble compounds of nickel, was an outstanding outlier, with a predicted/observed ratio of 113. In the oral NOAEL data set, only data points 11 (beryllium compounds) and 28 (chromium metal and inorganic Cr(III) compounds) were outstanding outliers. The predicted/observed ratio for estimated TLV/WEEL-equivalents was 620 for data point 11 and 281 for data point 28. For these three cases, we went back to the original data and verified the published values. We also noted that the effect of these outliers on the respective regression equations was trivial, partly because of the large number of data points in each of these data sets.

Bivariate equations

Since predictor variables within the inhalation group or within the oral group would be expected to be collinear to some extent, we avoided most multivariate regressions, with one exception. We selected the eight possible combinations of two predictor variables representing measured LOAEL or NOAEL values for the same chemical by different exposure routes, one oral and the other by inhalation, assuming these would have been measured in separate experiments. We then ran these eight direct bivariate regressions, to see if the strength of correlations, expressed as R^2-adj, might be improved over those by univariate regression (see footnote, Table 2). However, in this data set, the number of

Table 2. Correlations: univariate regressions of ln-transformed TLV/WEELs with each of six categories of ln-transformed LOAELs and NOAELs

Equation number	Constant intercept	Slope	R^2 (adjusted)[a]	P-value	No. of pairs (n)
Inhalation:					
1 LOAEL (mg m^{-3})	1.30	0.635	0.698	< 0.0001	38
2 LOAEL (mg kg^{-1} day^{-1})	0.18	0.722	0.606	< 0.0001	23
3 NOAEL (mg m^{-3})	1.52	0.730	0.870	< 0.0001	26
4 NOAEL (mg kg^{-1} day^{-1})	0.00092	0.771	0.898	< 0.0001	15
Oral:					
5 LOAEL (mg kg^{-1} day^{-1})	−0.0686	0.641	0.555	< 0.0001	120
6 NOAEL (mg kg^{-1} day^{-1})	0.585	0.689	0.513	< 0.0001	111

[a]The adjusted R^2, is a goodness of fit measure similar to R-squared (R^2), but adjusted for degrees of freedom (that is the number of parameters in the model) (SAS Institute, 1990).

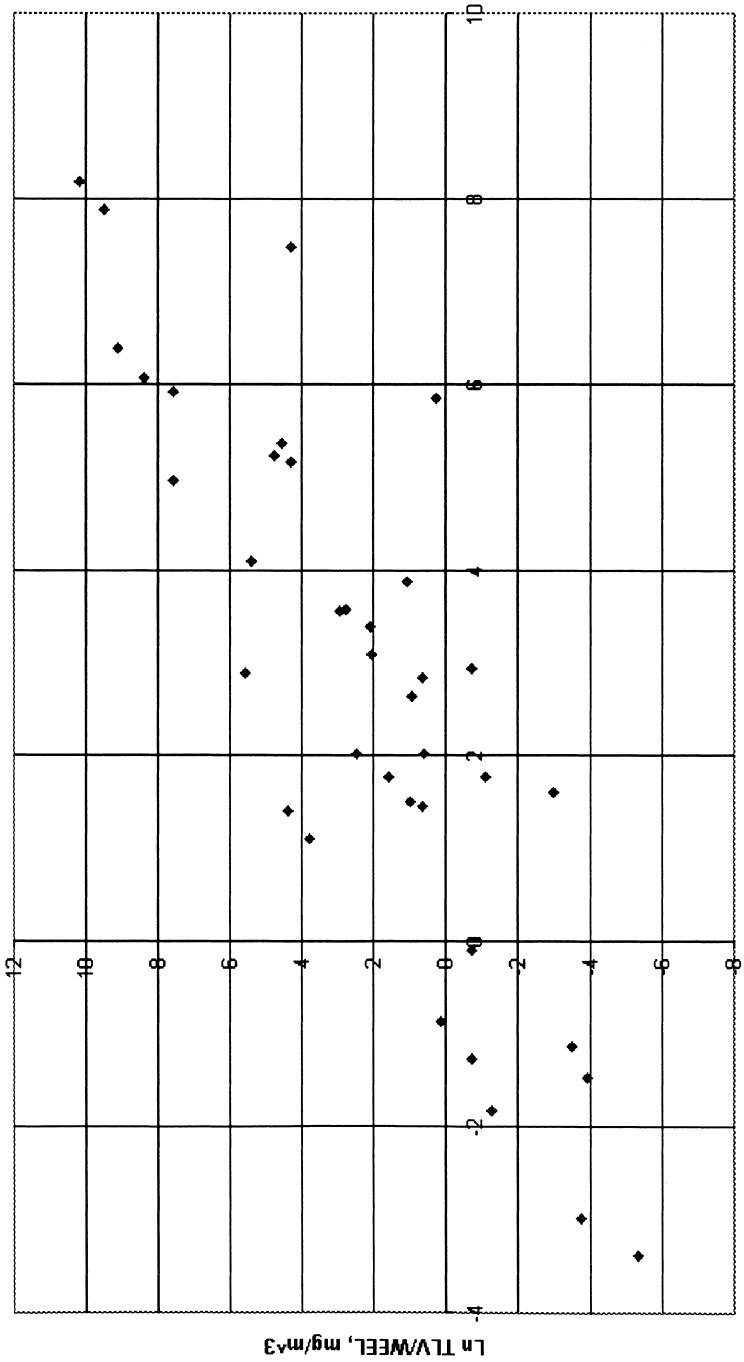

Fig. 1. First example scatterplot: ln TLV/WEEL by ln inhalation LOAEL, both variables in units of mg m^{-3} ($n = 38$).

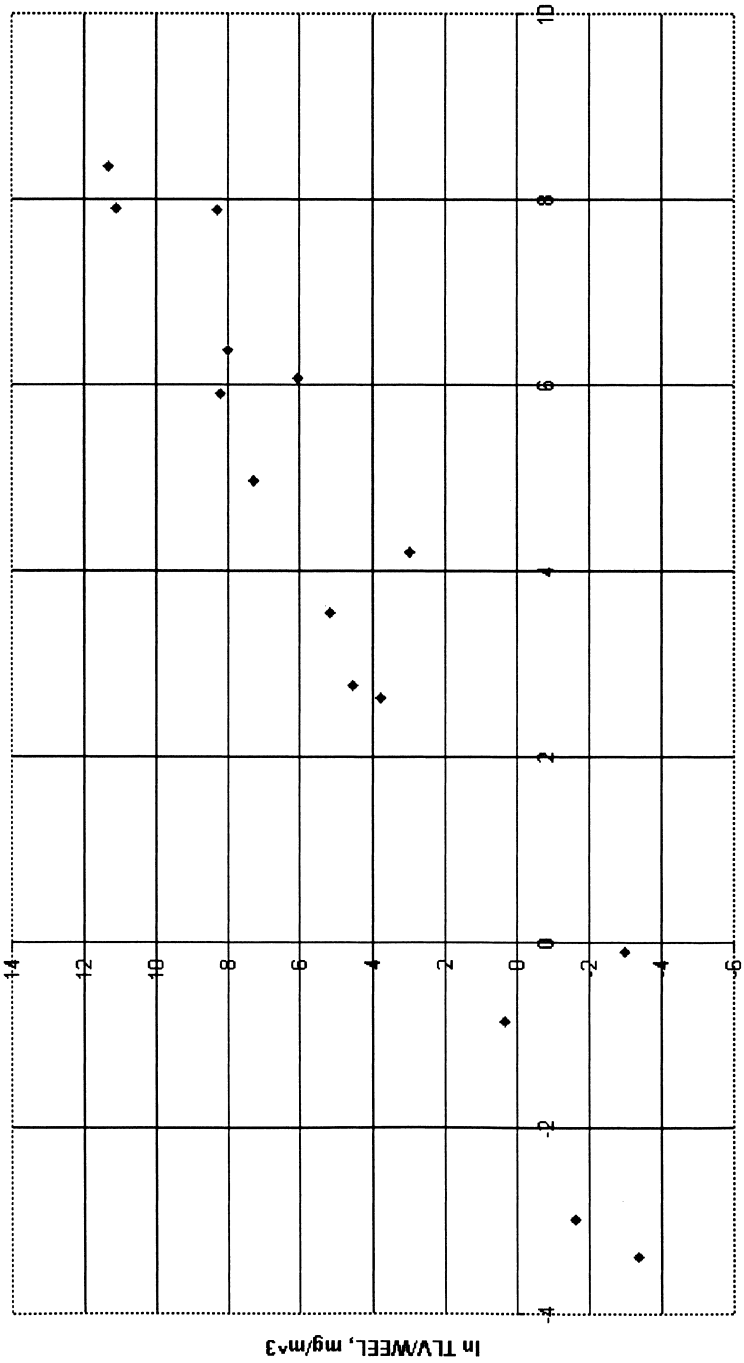

Fig. 2. Second example scatterplot: ln TLV/WEEL, in units of mg m^{-3}, by ln inhalation NOAEL, in units of mg kg^{-1} day^{-1} ($n = 15$).

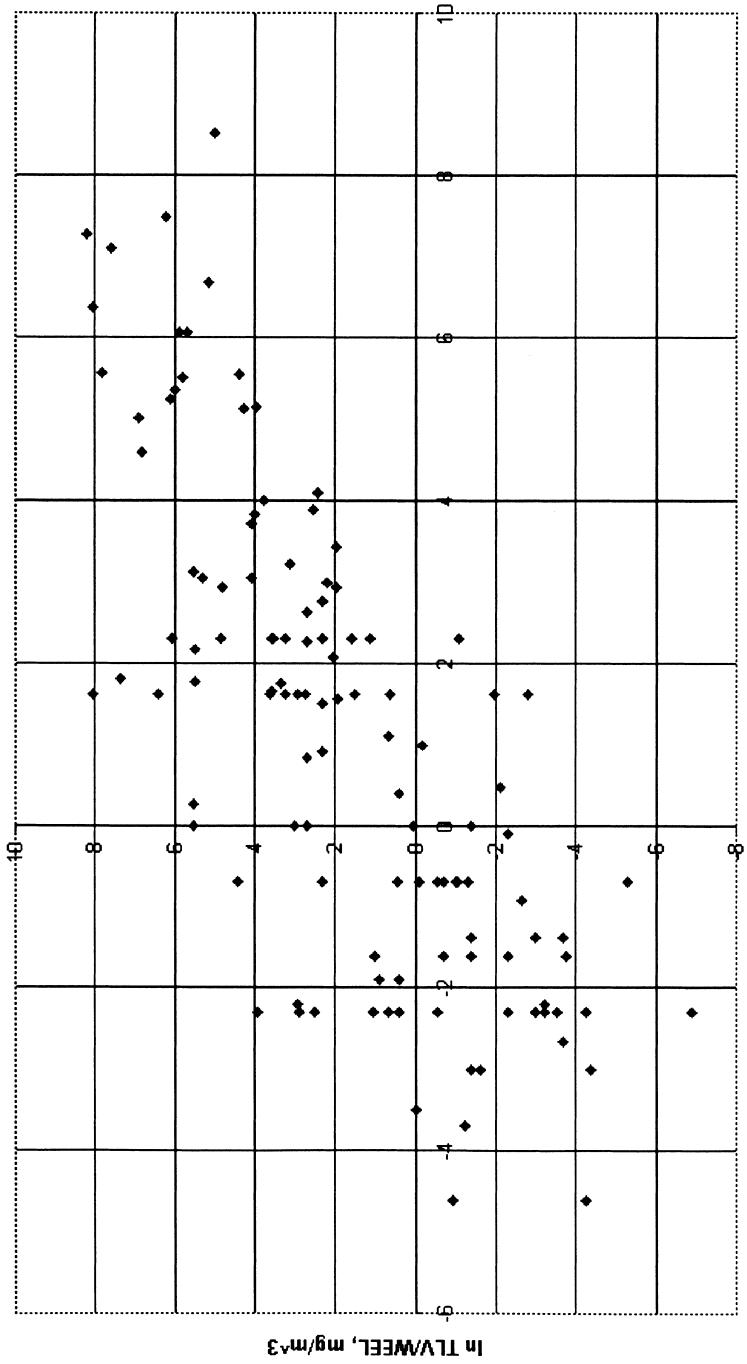

Fig. 3. Third example scatterplot: ln TLV/WEEL, in units of mg m^{-3}, by ln oral LOAEL, in units of mg kg^{-1} day^{-1} ($n = 120$).

Table 3. Ratios of predicted to assigned TLV/WEEL values, inhalation-LOAEL (mg m^{-3})

Datum number	CAS No.	Chemical name	Inhalation-LOAEL (mg m^{-3})	TLV/WEEL (mg m^{-3})	Predicted/observed (TLV/WEEL-equivalent)
1	107-2-8	Acrolein	0.02	0.23	1.02
2	79-10-7	Acrylic acid	0.33	5.9	0.26
3	107-13-1	Acrylonitrile	1.9	4.3	1.1
4	107-5-1	Allyl chloride	44	3.0	13
5	7664-41-7	Ammonia	1.9	17	0.29
6	62-53-3	Aniline	11.6	7.6	2.2
7	7784-42-1	Arsine	0.28	0.16	8.5
8	10049-4-4	Chlorine dioxide	0.49	0.28	7.1
9	532-27-4	*a*-Chloroacetophenone	0.03	0.32	0.96
10	75-45-6	Chlorodifluoromethane	26 300	3540	0.80
11	106-46-7	*p*-Dichlorobenzene	225	60	2.0
12	542-75-6	1,3-Dichloropropene	2.7	4.5	1.4
13	62-73-7	Dichlorvos	0.48	0.9	2.2
14	68-12-2	Dimethylformamide	7.9	30	0.42
15	106-89-8	Epichlorohydrin	1.82	7.6	0.63
16	110-80-5	2-Ethoxyethanol (EGEE)	265	18	7.3
17	100-41-4	Ethyl benzene	4340	434	2.0
18	75-0-3	Ethyl chloride	13 000	2640	0.67
19	822-6-0	Hexamethylene diisocyanate	0.005	0.034	2.7
20	110-54-3	*n*-Hexane	73	176	0.32
21	110-54-3	Hexane (other isomers)	73	1760	0.032
22	7783-6-4	Hydrogen sulphide	2.6	14	0.43
23	7439-96-5	Manganese: dust, compounds, as Mn	0.05	5	0.087
24	74-83-9	Methyl bromide	0.48	19	0.10
25	1634-4-4	Methyl tert-butyl ether	1946	144	3.5
26	101-68-8	Methylene bisphenyl isocyanate	0.024	0.051	5.2
27	101-93-3	Methyl ethyl ketone	8906	590	2.3
28	79-46-9	2-Nitropropane	16	36	0.56
29	7803-51-2	Phosphine	1.12	0.42	8.2
30	78-87-5	Propylene dichloride	1.3	347	0.011
31	107-98-2	Propylene glycol monomethyl ether (PGME)	1975	369	1.4
32	75-56-9	Propylene oxide	2.9	48	0.14
33	100-42-5	Styrene monomer	95	213	0.31
34	108-88-3	Toluene	119	188	0.41
35	121-44-8	Triethylamine	79	4.1	14
36	108-5-4	Vinyl acetate	19	35	0.65
37	593-60-2	Vinyl bromide	7.7	22	0.57
38	106-88-7	1,2-Butylene oxide	4.8	5.9	1.5

Table 4. Estimates of TLV/WEEL-equivalents, calculated from published LOAEL and NOAEL values in IRIS (US EPA)

CAS number	Chemical name	Species route (I/O), LOAEL/NOAEL (L/N)[a]	LOAEL/ NOAEL value	LOAEL/ NOAEL units	Intercept	Slope (coeff.) ln space	Calculated TLV/ WEEL-equivalent
75-87-6	Chloral, or trichloroacetaldehyde	Mouse O-L	15.7	mg kg^{-1} day^{-1}	−0.0686	0.641	0.22
133-90-4	Chloramben	Mouse O-L	15.0	mg kg^{-1} day^{-1}	−0.0686	0.641	0.21
106-47-8	4-Chlorobenzeneamine	Rat O-L	12.5	mg kg^{-1} day^{-1}	−0.0686	0.641	4.7
510-15-6	Chlorobenzilate	Rabbit O-N	5.0	mg kg^{-1} day^{-1}	0.585	0.689	5.4
124-48-1	Chlorodibromomethane	Rat O-N-adj[b]	21	mg kg^{-1} day^{-1}	0.585	0.689	15
91-58-7	2-Chloronaphthalene	Rat O-N	250	mg kg^{-1} day^{-1}	0.585	0.689	81
95-57-8	2-Chlorophenol	Rat O-N	5.0	mg kg^{-1} day^{-1}	0.585	0.689	5.4
131-89-5	2-Cyclohexyl dinitrophenol, or Dinex	Human O-L	2.0	mg kg^{-1} day^{-1}	−0.0686	0.641	1.5
1918-00-9	Dicamba	Rabbit O-N	3.0	mg kg^{-1} day^{-1}	0.585	0.689	3.8
75-27-4	Bromodichloromethane	Mouse O-L	17.9	mg kg^{-1} day^{-1}	−0.0686	0.641	5.9
120-83-2	2,4-Dichlorophenol	Rat O-N	0.3	mg kg^{-1} day^{-1}	0.585	0.689	0.78
75-71-8	Dichlorodifluoromethane	Rat O-N	15	mg kg^{-1} day^{-1}	0.585	0.689	12
105-67-9	2,3-Dimethylphenol	Mouse O-N	50	mg kg^{-1} day^{-1}	0.585	0.689	27
88-85-7	Dinoseb	Rat O-L	1.0	mg kg^{-1} day^{-1}	−0.0686	0.641	0.9
96-45-7	Ethylene thiourea	Rat O-L	0.25	mg kg^{-1} day^{-1}	−0.0686	0.641	0.38
206-44-0	Fluoranthene	Rat O-N	125	mg kg^{-1} day^{-1}	0.585	0.689	50
765-34-4	Glycidaldehyde	Rat O-N-adj	1.09	mg kg^{-1} day^{-1}	0.585	0.689	1.9
70-30-4	Hexachlorophene	Dog O-L	0.75	mg kg^{-1} day^{-1}	−0.0686	0.641	0.78
123-33-1	Maleic hydrazide	Rat O-L	500	mg kg^{-1} day^{-1}	−0.0686	0.641	50
608-93-5	Pentachlorobenzene	Rat O-L	8.3	mg kg^{-1} day^{-1}	−0.0686	0.641	3.6
23950-58-5	Pronamide	Dog O-N	7.5	mg kg^{-1} day^{-1}	0.585	0.689	7.2
2312-35-8	Propargite	Dog O-N	22.5	mg kg^{-1} day^{-1}	0.585	0.689	15
95-95-4	2,4,5-Trichlorophenol	Rat O-N	100	mg kg^{-1} day^{-1}	0.585	0.689	43
99-35-4	1,3,5-Trinitrobenzene	Rat O-N	0.51	mg kg^{-1} day^{-1}	0.585	0.689	1.1
1314-84-7	Zinc phosphide	Rat O-L	3.48	mg kg^{-1} day^{-1}	−0.0686	0.641	2.1

[a]I/O refers to inhalation or oral route of exposure. L/N refers to LOAEL or NOAEL.
[b]The '-adj' following a LOAEL or NOAEL means a value adjusted for an average daily value, if chronic (or sub-chronic) dosing is not consistent throughout the week. For example, if an animal were dosed at X for 5 days per week, the adjusted daily value would be $5X/7$.

points to generate each such equation was, in our judgement, too small to develop meaningful regressions, with *n* ranging from only 5 to 10.

DISCUSSION

There is a huge number of chemicals in commerce for which exposure limits have not been assigned. Until now, there has been no systematic way to estimate such an exposure limit. This paper presents regression equations that allow a first screen estimate for an inhalation time-weighted average exposure limit for chemicals with a published measure of LOAEL or NOAEL, or for which an LOAEL or NOAEL may be estimated, for example, using quantitative structure–activity relationship software to estimate oral LOAELs (Mumtaz *et al*., 1995).

The input to these prediction models consists of data derived for different purposes, and measuring different aspects of toxicity or health effect. The most frequent toxicity test performed on laboratory rodents, in order to estimate hazard to human health, is an acute lethality test, by oral or inhalation exposure. Lethality is the toxic endpoint least costly to measure and simplest to document (Roach, 1994). A response to a toxic chemical presented at high dose over a short time can be quite different if exposure to that same chemical occurs at much lower doses over a long time; the resulting acute and chronic health effects may well be expressed in entirely different body systems (Roach, 1992).

The concern for workplace health risk is more often from chronic exposure to low concentrations of contaminants, especially when such agents can cause significant non-lethal toxic effects. Chronic animal testing is slow and costly (Roach, 1994). As a compromise, sub-chronic testing (for example, over a 90-day exposure period) is often conducted as a substitute for chronic (usually lifetime) testing, and the sub-chronic results extrapolated to estimate chronic results. This extrapolation introduces further uncertainty into attempts to estimate the actual chronic toxic threshold by measuring an LOAEL or highest NOAEL.

Two laboratories of which we are aware have attempted to predict TLVs from acute adverse health effect data in rodents. First, for 40 gas and vapour respiratory irritants Alarie was able to determine the inhaled concentration which caused a 50% reduction in respiratory rate in mice, which was directly proportional to the assigned TLV for these respiratory irritants—within an order of magnitude (see Roach, 1992). However, there are many substances for which the TLV is based on health effects other than respiratory irritation, for which this method could not be used.

Roach (1992) recognised that measures of acute lethality in rodents, as oral dose to kill 50% of a test group (LD_{50}) and inhalation concentration to kill 50% of a test group exposed over a specified duration (commonly four hours) are available for a large number of chemicals in commerce. Therefore, he proposed a generic method, applicable to a wide range of chemicals, by which to extrapolate from these widely available measures of acute lethality to a time-weighted average inhalation TLV, which is designed to protect against chronic health effects due to much longer duration sub-chronic or chronic exposures. This method provides different ratios for calculation of the predicted median TLV, depending on whether the inhaled toxic material is a gas or vapour or aerosol, or whether the ingested toxic material is a liquid or solid.

The method presented in this paper is different from that of Roach (1992) in at least two respects:

1. We do distinguish between inhalation and oral exposure, but do not differentiate between the several possible physical phases of the toxic material, because the number of data points in several of our data sets was too small for such resolution.
2. We suggest that an experimental estimate of sub-chronic or chronic toxicity, that is a measured LOAEL or highest NOAEL, may be a more realistic and useful starting point than a measure of acute lethality, in order to predict an exposure criterion as the average daily (eight hour) upper limit for workplace exposure, continued over a working lifetime.

Quality of animal data

Our review of the quality of the data cited in IRIS suggests some lack of consistency. The consistency of the data in the TLV documentation, on which the TLVs are based, has also been questioned (Henschler, 1984; Roach and Rappaport 1990).

As already discussed, neither the LOAEL nor the NOAEL is a precise measure of the real threshold dose, for a given set of experimental conditions. In any test group, biological variability of response introduces a further component to the overall uncertainty within the measure of the LOAEL or NOAEL.

Yet, given such limitations, the regression data sets in this study are comprised of the best data of their types available when the equations were generated (1996). The authors expect to publish a follow-up set of equations, taking into account new published exposure criteria and measures of LOAEL or NOAEL, to compare with this set of equations. Presumably, the appearance of sufficient such new data will not be available until well into the future (see Validation below).

Quality of the exposure limit data

The analysis by Roach and Rappaport of the documentation of the TLVs argues that TLV values have actually been set, based not on toxic threshold, as is reported by the American Conference of Governmental Industrial Hygienists, which publishes the TLVs, but rather based on the level of exposure control available in industry at the time the TLVs were established (Roach and Rappaport, 1990). This may explain the explicit warning in the TLV Documentation *not* to use the TLVs as a measure of relative toxicity (ACGIH, 1995, 1996). No corresponding analysis of the historical documentation of the WEELs has been located.

The toxic effect of concern may not be the toxic effect used to determine an exposure criterion. Often a significant but less serious effect appearing at a lower level, has sometimes been used to select the exposure criterion value (Henschler, 1984); Roach, 1992). However, it is imperative that some relative measure of toxic potential to workers be used which is based on a toxic endpoint far more protective than acute lethality. Therefore, as a compromise for now, until better harm-based data are available, the authors and others (for example Horvath *et al*., 1995) argue that the use of exposure limit guidelines is far more useful than measures of acute lethality in determining relative toxic potential—for both workplace and environmental exposures.

For all their limitations, the TLVs (and presumably also the WEELs) appear to be among the best evaluated and most widely used exposure limit guidelines we have at present. In fact, the US Occupational Safety and Health Administration has used TLV values, in past years, to determine its legal exposure limits and carcinogenic status of hazardous chemicals (Permissible Exposure Limits, or 'PELs') (OSHA, 1989; Paxman and Robinson, 1990).

Apparent strong contribution from animal toxicity data to 1996 TLVs used for these regressions

Roach and Rappaport (1990) examined the correlation between TLV values and incidence of adverse effects from industrial (human) experience—which was very poor. Since our toxicity data used for this analysis are derived primarily from experimental animal LOAEL and NOAEL values, we looked at the overlap between the TLV chemicals used by Roach and Rappaport and ourselves. By our count, the overlap accounts for 46% of the Roach and Rappaport data, but only 23% of the data used for these regressions. That is, the majority of the compounds used for these regressions were different from the ones examined by Roach and Rappaport, for which human experience was the basis for assigning the TLV.

International exposure limit data

This analysis has used exposure criteria from the United States. It may be useful to repeat this process using, for example, European exposure criteria, to compare with the results presented here. Examples are the German MAKs (CIHHCCWA, 1997), British OESs (HSE, 1999), and values from other countries (Henschler, 1984; ILO, 1991; ACGIH, 1999).

The prediction equations

Despite the different assumptions and methods used in the development of the mainly animal LOAEL and NOAEL data and the exposure limit data used in these equations, it is noteworthy and reassuring that the correlations between the two sets are so strong. Certainly, some relationship is to be expected, owing to the developers of the exposure limits presumably consulting available animal data when deriving the TLVs or WEELs. However, other sources of pertinent information, including animal data other than those employed here, human data, and economic and feasibility information were almost certainly brought into the decision making (Roach and Rappaport, 1990), affecting the final value of the chosen exposure limit. This would naturally lead to increased variability around the regression line, and decrease the reliability of predictions from the animal data. However, as can be seen for the log-based scatter plots, this was not a major problem in our analysis, since clear and distinct relationships were observed.

In particular, we have shown graded toxicity by an oral route correlates well with, and therefore can be used to predict, inhalation exposure criteria. This could be very useful, since we found far more oral measures of LOAEL or NOAEL than inhalation measures among the data available in IRIS.

In this study, it is not only the prediction equations that are of interest (though they are the main focus of this paper). The residuals around the regression line potentially supply interesting and useful information as well. Large positive residuals indicate chemicals for which the observed exposure limit is substantially greater than that predicted. It would be of interest to explore these chemicals further in order to determine possible reasons for this disparity, and to explore whether the existing limits are truly protective. Similarly, large negative residuals provide *prima facie* evidence that existing limits are unduly conservative; further research might be done to examine if this is really so. Hence, an interesting potential use of this method is to flag chemicals for re-assessment by expert committees. For example, these results may indicate that TLV values assigned to (1) beryllium and compounds, (2) chromium metal and compounds of Cr(III), and (3) soluble compounds of nickel may warrant re-assessment, since the predicted/observed exposure ratios

for these three groups of materials (by oral exposure) are clearly different from the rest of the data. It may be noteworthy that all of these apparent outliers are metals.

Although the authors believe there is value in a first screen estimate for a time-weighted average exposure limit provided by these univariate equations, there is also potential for misuse of this method. For example, it would be unwise for a company starting to market a new chemical to use *only* this method to recommend an exposure limit for that substance. For a chemical which appears to be particularly hazardous, or which is to be widely used, a higher level of toxic evaluation should always be conducted. Our method offers only a first screen, for example, for provisional or emergency use.

As already mentioned, the stimulus for this work was design of a chemical hazard scoring system for measuring progress in pollution prevention (Whaley *et al*., 1999). For such hazard scoring, the authors needed an exposure limit equivalent for chemicals not assigned such a limit by an expert committee. For this purpose, we have used LOAEL and NOAEL values from IRIS, or software estimates of the rat oral LOAEL (Mumtaz *et al*., 1995), plus these linear regression estimates of the TLV/WEEL-equivalent (Eqs 1–6).

Protection against most chemicals, versus protection for most workers

The TLV/WEEL-equivalent values obtained from the models developed in this paper provide objective estimates (employing minimum variance unbiased estimators) of relative toxicity given the overall relationships observed between the animal study data and published TLV/WEELs. If, however, the derived estimates were to be used to protect workers in the absence of other data indicating risk, the uncertainty in the predicted exposure criterion could unwittingly subject some workers to an unacceptable level of risk. Each estimate is subject to the uncertainty caused by the variability in the data and in the resulting regression coefficients. Therefore, for protection of workers, for example in emergencies or provisionally (until the chemical can receive a careful toxicological evaluation), a user could employ these estimates conservatively. Various approaches to this are possible. For example, a TLV/WEEL prediction could be divided by a factor representing a margin of safety. This is analogous to the Superfund risk assessment process for non-carcinogens (US EPA, 1989). Alternatively, a probabilistic approach could be adopted, whereby the lower confidence interval bound of an estimate could be employed. If a conservative approach were deemed necessary, we would prefer the latter approach, as it takes better account of the variability inherent in the data used to derive the estimates. The choice of the lower percentage bound to use, as with any safety factor, must balance the potential risks to humans with the feasibility of attaining and maintaining such levels of exposure control. Even using the safety factor approach, our TLV/WEEL-equivalent estimates are protective against most chemicals, but not necessarily protective of most workers, since the biological inter-individual variability in response is not explicitly addressed in these equations. Since the TLV and WEEL values apparently incorporate safety factors designed to protect most workers, our TLV/WEEL-equivalent estimates should also incorporate this protection indirectly. Therefore, we believe our assumption is reasonable, that protecting against most chemicals in the combined TLV/WEEL-IRIS data set also serves to protect most workers.

Assumption of no co-operative toxic effects

All well-accepted current exposure limits, to our knowledge, assume no co-operative toxic effects. An industrial hygienist aware of an additive, synergistic or antagonistic effect should use professional judgement to adjust the advised maximum exposure. This limitation applies to our results also.

Validation

Validation of any method of prediction is important. However, neither the TLV nor WEEL lists, nor the IRIS lists of chemicals are likely to grow rapidly and substantially over the next few years. Therefore, validation with new data by major expansion of these lists is not likely to be possible for some time.

CONCLUSIONS

We have successfully generated univariate linear regressions to estimate TLV/WEEL-equivalent values from measures of the LOAEL or NOAEL for non-carcinogens to which an exposure limit has not been assigned by an expert committee. These estimated exposure limit values are only first screen estimates, which will often require further toxicity evaluation. These first screen estimates should not be misused as final exposure limits. Because of the uncertainty in these regression estimates, the authors recommend using them to protect workers only in special circumstances, for example, in a provisional or emergency way. Such a precautionary approach may impose exposure controls greater than necessary for some chemicals. Results from this modelling may provide leads in re-evaluating the existing exposure limits for certain substances which appear to fall distinctly above or below the fitted regression lines.

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