Short-term Toxicity Tests for Non-genotoxic Effects
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CHAPTER 20

Predicting Safe Levels of Chemicals

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20.1 INTRODUCTION

The capacity of existing toxicological laboratories is insufficient to evaluate the toxicity, hazard and safe (permissible) exposure levels of all known chemicals, or all new chemical compounds before they are introduced to the environment. Therefore, there is a need to develop methods of rapidly predicting safe exposure levels in the absence of extensive toxicological information. In the USSR, a variety of methods have been proposed for the rapid prediction of safe levels of chemicals for human exposure. These have been developed for chemicals or families of chemicals with well-known properties and established toxicities. The effectiveness of each approach has been determined by examining the correlation of the properties under investigation with the existing maximum acceptable concentrations (MACs), established by traditional methods, for the chemicals being considered.

20.2 LIMITATIONS IN EXTRAPOLATING THE RESULTS OF TRADITIONAL TOXICOLOGY TO MAN

Traditional toxicology involves experimentation with laboratory animals (generally mammals) with the aim of extrapolating the results to humans. However, there are a number of factors in this approach which limit the validity of data interpretations and extrapolations.

20.2.1 Variation in toxicity with route of exposure

It is often necessary to extrapolate toxicity data for one route of exposure to establish safe levels for a different route of exposure. This may arise, for example, when attempting to set MACs for chemicals in the air of the occupational environment based on data derived from exposure of animals via the diet. However, the toxicity or hazard of a chemical can be markedly different for different routes of exposure, as demonstrated in Table 20.1.

Table 20.1 Degree of toxicity of substances by ingestion and inhalation

Substance	Ingestion		Inhalation	
	LD50 (mg/kg)	Hazard classification*	LC50 (mg/m³)	Hazard classification*
m-aminobenztrifluoride	220	III	440	I
Benzyl chloride	1500	III	390	I
Benzyl chloride	1400	III	210	I
Benztrichloride	1300	III	60	I
Bromacetopropylacetate	600	III	149	I
2-Vinylpyridine	420	III	460	I
Dinitril perfluoroglutaric acid	997	III	58	I
Benzidine	327	III	290	I
2-Chloroethanesulphochloride	240	III	250	I

* Harmful substances are classified into the following four classes of hazard: I, extremely hazardous; II, very hazardous; III, moderately hazardous; IV, slightly hazardous.
These hazard classes are defined and described in detail in the State Standard GOST 12.1.007–76 entitled 'System of Occupational Safety Standards. Harmful Substances. Classification and General Safety Requirements'.

20.2.2 Variation with age and size

There is a concern with regard to variation of toxic response with age and size, not only in the laboratory animals upon which tests are conducted, but also with respect to the workforce for which occupational exposure limits are being established.

To some extent, species differences in response to a toxic chemical may be explained by variation in size. Allometric relationships, such as size and age variation in metabolism, can be correlated to inter- and intraspecies differences in responses to toxic chemicals.

With regard to worker protection, MACs are usually established for a healthy, mature, young adult, whereas increasing numbers of adolescents and older persons are making up the workforce. Variations in the responses of these different subpopulations are seldom considered when MACs are being established.

20.2.3 Variations in species sensitivity

Interspecies differences in sensitivity to specific chemicals can be represented by the coefficient of species sensitivity (CSS):

$$\mathrm{CCS} = \frac{\mathrm{LD50}_{\mathrm{max}}}{\mathrm{LD50}_{\mathrm{min}}}$$

where the $LD50_{max}$ is the LD50 of the most tolerant (i.e. least sensitive) species tested, and the $LD50_{min}$ is the LD50 of the least tolerant (most sensitive) species tested.

Table 20.2 displays CSS values for 52 chemicals tested with four species of laboratory rodents.

Table 20.2 LD50 values for different species under administration into the stomach and the CSS values

No	Substance	Mouse LD50 (mg/kg)	Rat LD50 (mg/kg)	Guinea-pig LD50 (mg/kg)	Rabbit LD50 (mg/kg)	CSS
1	Acetocyanhydrine	2.9	13	9	13	4.4
2	Acetphos	210	45	27	45	7.7
3	Ammonium perchlorate	1 900	4 200	3 310	1 900	2.2
4	Acetonenitrile	48	105	50	19	5.5
5	Butylacetate	7 700	13 100	4 700	3 200	4.0
6	1,4-Butanediol	2 062	1 525	1 200	2 531	2.1
7	1,4-Butinediol	104	104	130	150	1.5
8	Butyphos	179	217	146	242	1.6
9	*N*-Butylpyro-catechol	3 000	4 700	1 400	2 800	3.3
10	Gramoxon	37	188	38.6	49.8	3.2
11	Hydrazine hydrate	83	129	40	55	3.2
12	Hexachlorobutane	2 000	1 413	940	1 071	2.1
13	Hexachloro-butadiene	87	350	90	90	4.0
14	3,4-Dichloroaniline	500–700	500–700	500–700	500–700	1.0
15	2,5-Dichloroaniline	2 500–3 000	2 500–3 000	2 500–3 000	2 500–3 000	1.0
16	Dichlorobutyl-tin	35	112	190	125	5.4
17	DDT	180	400	400	300	2.2
18	α-2,4-Dinitrophenol	46	31	81	30	2.7
19	1,2-Dibrom-3-chloropropane	410	300	210	180	2.2
20	Diethanolamine	3 300	3 460	2 200	2 200	1.5
21	Ammonium dimethyldithio-carbonate	592	1 458	1 680	450	3.7
22	1,2-Dibromoethane	420	117	110	55	7.6
23	Diphenylpropane	2 400	12 000	4 000	4 000	5.0
24	Indalon	11.6	7.4	3.2	5.4	3.6
25	Carbathione	266	700	815	320	3.0
26	Monoethanolamine	1 476	2 050	620	1 000	3.3
27	Monoethanol-ethylenediamide	3 550	3 600	1 500	2 000	2.4

Table 20.2 *(continued)*

28	Methylacetophos	322	380	214	420	1.9
29	Murbetol	50	250	250	200	5.0
30	Melprex	266	1 118	176	535	6.3
31	Nicotine (base)	24	50	220	30	9.1
32	*n*-Nitrotoluene	330	2 400	3 600	2 400	10.9
33	Sodium fluoride	80	200	250	100	3.1
34	Parachlorobenzene	3 220	2 512	7 593	2 812	3.0
35	Pentachlorobutane	2 500	2 108	1 410	1 560	1.7
36	Reglone	79.7	281.9	123.6	227.8	3.5
37	Ethyl alcohol	9 488	13 660	1 600	6 300	8.5
38	Carbon disulphide	2 780	3 188	2 125	2 550	1.5
39	Titanium	150	472	100	100	4.7
40	Tetraethyl-tin	40	15	37	7	5.7
41	1,1,1-Trichloroethane	17 200	12 300	9 470	5 660	3.0
42	Phenylhydrazine	175	188	80	80	2.4
43	Triethanolamine	7 750	8 400	5 160	5 300	1.6
44	2-Phenylcyclo-hexenal	5.4	3.5	1.6	2.7	3.3
45	3-Chloro-4-methylcoumarinyl	28	38	57	75	2.6
46	Chlorobenzene	1 445	2 390	5 060	2 250	3.5
47	Chloroindane	1 000	700	1 000	500	2.0
48	Carbon tetrachloride	9 066	6 200	5 760	5 760	1.5
49	Calcium cyanamide	415	513	415	353	1.4
50	Ethyleneglycol	8 348	6 122	8 213	9 000	1.4
51	Epichlorohydrine	194	141	280	345	2.4
52	Ethoxyphos	375	190	300	375	1.9

It has been shown that a threefold difference in LD50 and LC50 is within the normal limits of experimental error and cannot, therefore, serve as a criterion of species differences in sensitivity. This variability, and its significance compared with experimental error, must be considered when extrapolating this data to human beings.

20.2.4 Extrapolation of animal results to man

When differences in species sensitivity are strongly manifested, the extrapolation of test results to humans must be done with caution. Extrapolation is most valid when differences in interspecies sensitivity are small (i.e. CSS≤3). If the CSS value for a substance is less than or equal to 3, then the data suggest that there is a 2:1 probability that the sensitivity of humans to that substance will be in the same range (within error limits; i.e. animal:human CSS(K_2)≤3). For 34 substances for which

Table 20.3 LD50 values (mg/kg) and their ratio for different species of laboratory animals and for man

No	Substance	Mouse	Rat	Guinea-pig	Rabbit	Man	$LD50_{max}/LD50_{min}$	$LD50_{min}/LD50_{man}$
1	Barium carbonate	200	125	235	—	12.1	1.9	10.3
2	Barium chloride	350	350	—	170	5.0	2.1	34.0
3	Sodium chloride	—	12 000	—	10 000	4 285	1.2	2.3
4	Mercury dichloride	17.5	80	—	30	4.2	4.6	4.2
5	Zink sulphite	—	2 200	—	2 057	107.1	1.1	19.2
6	Calcium cyanamide	415	513	415	353	642.5	1.4	0.5
7	Cichloremethane	5 600	—	—	1 896	2 385	3.0	0.8
8	Chloroform	1 750	2 180	1 750	—	856.5	1.2	2.0
9	Carbon tetrachloride	9 066	6 200	5 760	5 760	428	1.6	13.4
10	Dichlorethane	910	770	—	910	671	1.2	1.1
11	Phenol	—	415	—	510	140	1.2	3.0
12	Methyl alcohol	8 712	12 880	—	9 029	338.5	1.5	25.7
13	Ethyl alcohol	9 488	13 660	2 400	7 900	4 514.2	5.7	0.5
14	Butyl alcohol	2 835	4 360	—	1 750	2 892.8	2.5	0.6
15	Ethyleneglycol	8 348	7 331	8 213	9 000	1 667.5	1.2	4.4
16	Chloralhydrate	—	650	—	1 300	142	2.0	4.6
17	Formaldehyde	—	800	260	—	142	3.1	1.8
18	Paraldehyde	1 790	1 650	—	5 000	1 715	3.0	0.96
19	Malathione (carbophos)	1 187.5	3 000	570	—	17.8	5.3	32.0
20	Octamethyl	22.5	16	—	—	12.5	1.4	1.3
21	Parathione (thiophos)	17	10.5	18.5	50	1.7	4.8	6.2
22	Tricresyl-phosphate	—	—	400	100	7.1	4.0	14.1
23	Chlorophos	377.5	525	—	—	40	1.4	9.4
24	Luminal	325	660	—	150	71	4.4	2.1
25	Barbitol (veronal)	600	200	—	262.5	100	3.0	2.0
26	Mephenizine	150	110	—	50	17.5	3.0	2.8
27	DDT	190	500	400	300	107.1	2.6	1.8
28	Aldrin	20	49	—	—	27.5	2.4	0.7
29	Dieldrin	25	68.5	—	—	27.5	2.7	0.9
30	Salicylic acid	430	900	—	1 100	214	2.3	2.2
31	Aniline	1 075	—	2 500	1 000	285	2.5	3.5
32	Nitrobenzene	—	640	—	660	21.4	1.0	29.9
33	Dinitroorthocresol	47	28	—	—	11.4	1.7	2.4
34	Sodium fluoride	80	200	250	150	87.5	3.1	0.9

Table 20.4 Biological activity (l_i) values of chemical bonds of standardized compounds belonging to different homologous series

Bond	l_i(litres/μmol)	Series
C–H	0.8	Saturated and unsaturated, cyclic and non-cyclic and mixed hydrocarbons
C–H	21 273.9	Saturated aldehydes (joined to the carbonyl group)
C–C	51.4	Saturated non-cyclic hydrocarbons
C–C	173.7	Saturated cyclic hydrocarbons
C=C (conjugated bond)*	242.4	Unsaturated cyclic hydrocarbons
C=C	451.8	Unsaturated non-cyclic hydrocarbons
C=C	1 126.5	Unsubstituted aromatic hydrocarbons
C=C	507.9	Substituted aromatic hydrocarbons with one and two side chains
C=C	7 057.9	Substituted aromatic hydrocarbons with an unsaturated side chain
C≡C	2 097.1	Unsaturated hydrocarbons containing a triple bond
C–N	–6 242.7	Aliphatic nitro compounds (one C–N bond joined to carbon)
C–N	154 446.3	Aliphatic nitro compounds (four C–N bonds joined to carbon) from tetranitromethane
C–N	119 027.8	Cyclic mono-nitro compounds
C–N	27 970.0	Aromatic mono-nitro compounds
C–N	77 851.5	Aromatic di-nitro compounds
C–N	66 442.0	Aromatic tri-nitro compounds
C–N	6 113.5	Aliphatic primary amines
C–N	1 565.7	Aliphatic secondary amines
C–N	3 266.2	Aliphatic tertiary amines
C–N	35 914.6	Aliphatic diamines
C–N	97 551.4	Cyclic amines
C–N	33 302.0	Aromatic amines
C–N	16 680.8	Amides
C–N	4 817.6	Heterocyclic compounds
C=N	9 635.2	Heterocyclic compounds
C≡N	97 856.8	Cyanides
C–O	21 987.7	Non-cyclic oxides
C–O	2 465.7	Heterocyclic oxides
C–O	68.1	Aliphatic ethers
C–O	6 535.3	Esters of saturated alcohols
C–O	10 306.9	Esters of unsaturated alcohols
C=O	213.8	Saturated ketones
C=O	8 753.8	Cyclic saturated ketones
C=O	–12 517.8	Saturated aldehydes (joined to the carbonyl group)

Table 20.4 *(continued)*

O–H	8 507.9	Organic acids
O–H	–21 648.2	Monohydric saturated alcohols
O–H	100 223.6	Unsaturated alcohols
O–H	–5 214.5	Aromatic alcohols
N–H	283.3	Ammonia
N–O	2 230.3	Oxides of nitrogen
N=O	4 460.6	Oxides of nitrogen
N=C	1 644 538.3	Aliphatic isocyanides
N=C	139 778.4	Aromatic isocyanides
N–N	318 864.8	Inorganic amines

* The conjugated bond (C=C) differs from an unconjugated bond in that, in the molecule of the compound, it alternates with (C–C) bonds.

human lethality data was available, it was found that about two thirds of those substances with low interspecies variability (CSS ≤3; 26 substances) also had low animal/human variability in toxic response (K_2 ≤3; 16 substances) (Table 20.3). The parameter K_2, is calculated as follows:

$$K_2 = \frac{LD50_{min}}{LD50_{man}}$$

where $LD50_{min}$ is the LD50 for the most sensitive (least tolerant) species tested, and the $LD50_{man}$ is the LD50 for man.

Therefore, generally, when CSS is ≤3, there is a strong probability (i.e. 2:1) that K_2 will be ≤3.

The validity of extrapolation to humans is greater when the threshold of chronic action (Lim_{ch}) is considered instead of the LD50. Therefore, the probability of establishing an adequately safe human exposure level based on animal lim_{ch} data is greater than when using lethal toxicity data.

20.3 METHODS FOR ESTABLISHING SAFE LEVELS OF OCCUPATIONAL EXPOSURE VIA INHALATION

There have been three basic approaches for the rapid determination of safe levels of occupational exposure to chemicals:

(1) derivation on the basis of molecular structure;
(2) derivation on the basis of physicochemical properties;
(3) derivation on the basis of biological activity.

20.3.1 Molecular structure

The derivation of safe exposure levels in air (maximum acceptable concentration (MAC)) on the basis of chemical structure and the biological activity of chemical bonds was proposed by G. N. Zaeva. In this approach, an index of biological activity (l_i) was established for various chemical bonds (Table 20.4). The MAC for a compound could be calculated as follows:

$$\text{MAC} = \frac{\text{M}(1000)}{\Sigma l_i}\ (\text{mg/m}^3)$$

For example, the MAC for valerianic acid would be calculated as:

$CH_3CH_2CH_2CH_2COOH$ Valerianic acid

$$\text{MAC} = \frac{102(1000)}{9(\text{C–H}) + 4(\text{C–C}) + 1(\text{C} = \text{O}) + 1(\text{C–O}) + 1(\text{O–H})}$$

$$= \frac{102(1000)}{9(0.8) + 4(51.4) + 1(-12517.8) + 1(2197.7) + 1(8507.9)}$$

$$= 5.6\ \text{mg/m}^3.$$

The MAC for valerianic acid legislated by the USSR is 5 mg/m^3. MAC values calculated by this approach generally agree with MACs established for saturated organic acids and alcohols of aliphatic series.

20.3.2 Physicochemical properties

Extensive studies have been carried out on the correlation of physicochemical properties of chemicals and their toxicity by E. I. Ljublina and co-workers at the Leningrad Institute of Industrial Hygiene and Occupational Diseases. Their work examined the relationships of various properties (Table 20.5) of chemicals with the two hour LC50, the two-hour NC50 (NC = narcotic concentration) and with C_{lim} (the threshold concentration causing changes in the bending reflex of rabbits after a 40-minute exposure). The physicochemical properties most closely associated with biological activity were molecular weight, density, refractive index and melting point.

A variety of equations were developed for the calculation of an MAC for inhalation exposure based on correlations with physicocheical properties. These equations included the following:

Table 20.5 Physicochemical properties correlated with biological activity

No.	Name	Units
1	Molecular weight	
2	Density	g/cm^3
3	Molar volume	cm^3/mol
4	Refractive index	
5	Molar refraction	cm^3/mol
6	Melting point	°C
7	Boiling point	°C
8	Saturated vapour pressure	mm Hg
9	Equilibrium temperature	°C
10	Rate of change of t_{boil} with pressure	°C/mm Hg
11	Critical density	g/cm^3
12	Critical temperature	°C
13	Critical pressure	atm
14	Latent heat of fusion	kcal/mol
15	Latent heat of vaporization	kcal/mol
16	Heat of combustion	kcal/mol
17	Heat of formation of gas	kcal/mol
18	Helmholtz energy of formation of gas	kcal/mol
19	Logarithm of distribution coefficient (olive oil/water)	
20	Logarithm of distribution coefficient (water/air)	
21	Surface tension	dyne/cm
22	Kinematic viscosity	centistokes
23	Dynamic viscosity	centipoise
24	Solubility	mmol/litre
25	Specific heat capacity	cal/mol °K
26	Specific heat of vapour	cal/mol °K
27	Themal conductivity	cal/cm s °K
28	Atomic polarization	cm^3
29	Electric dipole moment	Debye
30	Dielectric constant	
31	Specific dispersion	cm^3/g
32	Absolute dispersion	
33	Primary ionization potential	electronvolt
34	Entropy of liquid	cal/mol °C
35	Entropy of gas	cal/mol °C

$$\log(\mathrm{MAC}) = 0.4 - 0.01M + \log M \ (\mathrm{mg/m^3})$$
$$\log(\mathrm{MAC}) = 1.6 - 2.2(p) + \log M \ (\mathrm{mg/m^3})$$
$$\log(\mathrm{MAC}) = 14.2 - 10(n_D) + \log M \ (\mathrm{mg/m^3})$$
$$\log(\mathrm{MAC}) = 0.6 - 0.01(t_{boil}) + \log M \ (\mathrm{mg/m^3})$$
$$\log(\mathrm{MAC}) = -1.2 - 1.012\ (t_{melt}) + \log M \ (\mathrm{mg/m^3})$$
$$\log(\mathrm{MAC}) = 0.48 \log(v) - 1.0 + \log M \ (\mathrm{mg/m^3})$$

where p is the density (g/cm^3), n_D is the refractive index, t_{boil} is the boiling point (°C), t_{melt} is the melting point (°C), and v is the saturated vapour pressure (mm Hg).

Additional equations were developed to more accurately predict MACs for chemicals in homologous series (Table 20.6). However, an intermediate method is still required for the accurate calculation of MACs or other toxicity indices which, although not necessarily all-embracing, would not be limited to particular homologous series.

Table 20.6 Reliability of correlations between the existing maximum allowable concentration (in mmol/m^3) and equations for the calculation of the MAC based on the molecular weight (M), the boiling point (t_{boil}) and the melting point (t_{melt})

Substances	No. of pairs (n)	Correlation coefficient (r)	Probability (p)	Mean deviation (S_{yx})	Equation log MAC =
Hydrocarbons	42	–0.65	<0.001	0.70	0.99–0.012 M
	42	–0.71	<0.001	0.65	0.41–0.006 t_{boil}
	34	–0.62	<0.001	0.73	–0.72–0.007 t_{melt}
Saturated	18	–0.56	<0.02	0.85	1.00–0.015 M
monohydric	17	–0.68	<0.01	0.77	1.41–0.012 t_{boil}
alcohols	10	–0.66	<0.05	0.77	–0.47–0.008 t_{melt}
Nitro compounds	25	–0.72	<0.001	0.71	0.15–0.013 M
without unsaturated	16	–0.70	<0.001	0.69	–0.01–0.008 t_{boil}
bonds in open chains	21	–0.67	<0.001	0.71	–1.67–0.009 t_{melt}
Amines, nitroamines	40	–0.50	=0.001	0.56	–1.04–0.006 M
and other derivatives	31	–0.49	<0.01	0.61	–1.18–0.003 t_{boil}
of amines	27	–0.52	<0.01	0.58	–1.62–0.004 t_{melt}
Chlorinated	35	–0.61	<0.001	0.77	0.12–0.011 M
hydrocarbons	32	–0.51	<0.01	0.83	–0.57–0.007 t_{boil}
	22	–0.65	<0.01	0.58	–1.60–0.009 t_{melt}

20.3.3 Biological activity

K. K. Sidorov proposed a method for deriving MACs based on the threshold of chronic action (lim_{ch}):

$$MAC = \frac{lim_{ch}}{\text{safety factor}}$$

lim_{ch} is based on a chronic exposure by inhalation for four months (4 hours/day; 5 days a week). Alternatively, lim_{ch} (in units of mg/m^3) can be calculated by one of the following two equations:

$\log(\text{lim}_{ch})\ (\text{mg/m}^3) = 0.62 \times \log[\text{LC}_{50}\ (\text{mg/m}^3)] - 1.08;$
$\log(\text{lim}_{ch})\ (\text{mg/m}^3) = 0.77 \times \log[\text{lim}_{ac}\ (\text{mg/m}^3)] - 1.56.$

The safety factor is determined from differences in interspecies sensitivity (CSS; see Table 20.7) and the 'degree of cumulative effects' (see Table 20.8) as the product of points attributed to the values for CSS and Z_{biol} or Z_{ch} determined from the toxicity data. For example, the MAC for bromobenzene would be calculated as follows:

Table 20.7 Coefficient of species sensitivity (CSS)

Degree	CSS	Points
Low	<3	2
Moderate	3.1–9	3
High	>9	4

Table 20.8 Degree of cumulative effects

Degree of cumulation	Z_{biol} = LC50/lim_{ch}	Z_{ch} = $\text{lim}_{ac}/\text{lim}_{ch}$	Points
Low	<10	<2.5	2
Moderate	11–100	2.5–4.9	3
High	101–1000	5–10	4
Very high	>1000	>10	5

From experimental data:
LC50 = 21 000 mg/m^3
LD50 = 2700 mg/kg (mouse)
= 3200 mg/kg (rat)
= 1500 mg/kg (guinea-pig)
= 3300 mg/kg (rabbit)

$$\log \text{lim}_{ch} = 0.62 \times \log(21\ 000) - 1.08$$
$$= 0.62 \times 4.32 - 1.08$$
$$= 1.60$$

$$\text{lim}_{ch} = 40\ \text{mg/m}^3$$

$$Z_{biol} = \text{LC}_{50}/\text{lim}_{ch}$$
$$= 21\ 000/40$$
$$= 525.$$

From Table 20.8, a Z_{biol} value of 525 corresponds to 4 points.
CSS = 3300/1500 = 2.2
From Table 20.7, a CSS value of 2.2 corresponds to 2 points. Finally:

$$MAC = lim_{ch}/\text{safety factor}$$
$$= 40/(4 \times 2) = 40/8 = 5 \text{ mg/m}^3.$$

(The MAC for bromobenzene legislated in the USSR is 3 mg/m³.)

To derive MACs for substances with irritation effects, two equations were proposed by N. G. Ivanov. These were:

$\log(MAC) = 0.69 \log(lim_{ac(rat)}) - 0.18 \log(lim_{ac(man)}) - 0.7 \log(Z_{ir}) - 0.51$ (r=0.96; $S_{xy} = \pm 0.27$; when correlated with established MAC values)

$\log(MAC) = 0.11 \log(LC50) + 0.65 \log(lim_{ir(rat)}) - 0.72 \log (Z_{ir}) - 0.65$
($r = 0.97$; $S_{zy} = \pm 0.27$; when correlated with established MAC values)

where $Z_{ir} = lim_{ac}/lim_{ir}$. Some values for Z_{ir} are listed in Table 20.9.

Table 20.9 Limits of acute and irritative action for rats

Substance	lim_{ac} (mg/m³)	lim_{ir} (mg/m³)	Z_{ir}
1. Ammonia	462	228	2
2. Nitrogen dioxide	58	20	2.9
3. Bromine	50	10	5
4. 2-Chloroethanesulphchloride	97	12	8
5. Tributyl hydroperoxide	340	180	1.9
6. Phosphorus chloroxide	8	0.8	10
7. Sulphur monochloride	90	8.7	10
8. Bromoacetopropylacetate	13.5	4.3	3.1
9. Acetoperopylacetate	150	470	0.3
10. Glycidole	98	98	1
11. Pyromellite acid dianhydride	70	106	0.66
12. Chlorine	20	10	2
13. Sulphur anhydride	500	80	6.2

Responses considered when identifying an end-point for detection of lim_{ir} include respiration rate, olfactory responses, cellular reactions of the lungs and upper respiratory tract, and vital staining of lung tissue. For lim_{ac}, responses include body temperature, motor activity, muscular strength, orientation and oxygen consumption.

20.4 CONCLUSION

Although significant correlations do exist, on the whole, deriving occupational exposure limits based on chemical structure and physicochemical properties is not sufficiently exact for use with all chemicals. However, the establishment of equations specific to homologous or analogous series of chemicals can significantly increase the validity of calculated MACs.

Deriving MACs based on measures of biological activity appears to be the most valid approach, particularly when thresholds of action (either acute—lim_{ac}—or chronic—lim_{ch}) are used. The widespread use of rapid methods for deriving safe exposure levels is a necessity, but toxicological investigations should continue after an MAC has been established and the MAC should be recalculated as more and better data become available. It is also recommended that rapid methods of evaluating MACs only be used for classes of compounds with well understood properties and which do not have delayed or long-term effects, especially if manifested through limited contact with the substance.

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