

Median lethal dose

In toxicology, the **median lethal dose**, LD_{50} (abbreviation for "lethal dose, 50%"), LC_{50} (lethal concentration, 50%) or LCt_{50} is a measure of the lethal dose of a toxin, radiation, or pathogen. The value of LD_{50} for a substance is the dose required to kill half the members of a tested population after a specified test duration. LD_{50} figures are frequently used as a general indicator of a substance's acute toxicity. A lower LD_{50} is indicative of increased toxicity.

The test was created by J.W. Trevan in 1927.^[1] The term **semilethal dose** is occasionally used in the same sense, in particular with translations of foreign language text, but can also refer to a sublethal dose. LD_{50} is usually determined by tests on animals such as laboratory mice. In 2011, the U.S. Food and Drug Administration approved alternative methods to LD_{50} for testing the cosmetic drug Botox without animal tests.^{[2][3]}

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Conventions

The LD_{50} is usually expressed as the mass of substance administered per unit mass of test subject, typically as milligrams of substance per kilogram of body mass, sometimes also stated as nanograms (suitable for botulinum), micrograms, or grams (suitable for paracetamol) per kilogram. Stating it this way allows the relative toxicity of different substances to be compared, and normalizes for the variation in the size of the animals exposed (although toxicity does not always scale simply with body mass). For substances in the environment, such as poisonous vapors or substances in water that are toxic to fish, the concentration in the environment (per cubic metre or per litre) is used, giving a value of LC_{50} . But in this case, the exposure time is important (see below).

The choice of 50% lethality as a benchmark avoids the potential for ambiguity of making measurements in the extremes and reduces the amount of testing required. However, this also means that LD_{50} is not the lethal dose for all subjects; some may be killed by much less, while others survive doses far higher than the LD_{50} . Measures such as " LD_1 " and " LD_{99} " (dose required to kill 1% or 99%, respectively, of the test population) are occasionally used for specific purposes.^[4]

Lethal dosage often varies depending on the method of administration; for instance, many substances are less toxic when administered orally than when intravenously administered. For this reason, LD_{50} figures are often qualified with the mode of administration, e.g., " LD_{50} i.v."

The related quantities $LD_{30}/60$ or $LD_{50}/60$ are used to refer to a dose that without treatment will be lethal to 50% of the population within (respectively) 30 or 60 days. These measures are used more commonly within Radiation Health Physics, as survival beyond 60 days usually results in recovery.

A comparable measurement is LC_{50} , which relates to lethal dosage from exposure, where C is concentration and t is time. It is often expressed in terms of $\text{mg}\cdot\text{min}/\text{m}^3$. LC_{50} is the dose that will cause incapacitation rather than death. These measures are commonly used to indicate the comparative efficacy of chemical warfare agents, and dosages are typically qualified by rates of breathing (e.g., resting = 10 l/min) for inhalation, or degree of clothing for skin penetration. The concept of Ct was first proposed by Fritz Haber and is sometimes referred to as Haber's Law, which assumes that exposure to 1 minute of 100 mg/m³ is equivalent to 10 minutes of 10 mg/m³ ($1 \times 100 = 100$, as does $t \times 10 = 100$).

Some chemicals, such as hydrogen cyanide, are rapidly detoxified by the human body, and do not follow Haber's Law. So, in these cases, the lethal concentration may be given simply as LC_{50} and qualified by a duration of exposure (e.g., 10 minutes). The Material Safety Data Sheets for toxic substances frequently use this form of the term even if the substance does follow Haber's Law.

For disease-causing organisms, there is also a measure known as the median infective dose and dosage. The median infective dose (ID_{50}) is the number of organisms received by a person or test animal qualified by the route of administration (e.g., 1,200 org/man per oral). Because of the difficulties in counting actual organisms in a dose, infective doses may be expressed in terms of biological assay, such as the number of LD_{50} 's to some test animal. In biological warfare, infective dosage is the number of infective doses per cubic metre of air times the number of minutes of exposure (e.g., IC_{50} is 100 medium doses · min/m³).

Limitation

As a measure of toxicity, LD_{50} is somewhat unreliable and results may vary greatly between testing facilities due to factors such as the genetic characteristics of the sample population, animal species tested, environmental factors and mode of administration.^[5]

There can be wide variability between species as well; what is relatively safe for rats may very well be extremely toxic for humans (cf. paracetamol toxicity), and vice versa. For example, chocolate, comparatively harmless to humans, is known to be toxic to many animals. When used to test venom from venomous creatures, such as snakes, LD_{50} results may be misleading due to the physiological differences between mice, rats, and humans. Many venomous snakes are specialized predators on mice, and their venom may be adapted specifically to incapacitate mice; and mongooses may be exceptionally resistant. While most mammals have a very similar physiology, LD_{50} results may or may not have equal bearing upon every mammal species, such as humans, etc.

Examples

Note: Comparing substances (especially drugs) to each other by LD_{50} can be misleading in many cases due (in part) to differences in effective dose (ED_{50}). Therefore, it is more useful to compare such substances by therapeutic index, which is simply the ratio of LD_{50} to ED_{50} .

The following examples are listed in reference to LD_{50} values, in descending order, and accompanied by LC_{50} values, (bracketed), when appropriate.

Substance	Animal, Route	LD_{50} (LC_{50})	$LD_{50} : g/kg$ ($LC_{50} : g/L$) standardized	Reference
Water	rat, oral	>90,000 mg/kg	>90	[6]
Sucrose (table sugar)	rat, oral	29,700 mg/kg	29.7	[7]
Glucose (blood sugar)	rat, oral	25,800 mg/kg	25.8	[8]
Monosodium glutamate (MSG)	rat, oral	16,600 mg/kg	16.6	[9]
Stevioside (from stevia)	mice & rats, oral	>15,000 mg/kg	>15	[10]
Vitamin C (ascorbic acid)	rat, oral	11,900 mg/kg	11.9	[11]
Lactose (milk sugar)	rat, oral	>10,000 mg/kg	>10	[12]
Aspartame	mice, oral	>10,000 mg/kg	>10	[13]
Urea	rat, oral	8,471 mg/kg	8.471	[14]
Cyanuric acid	rat, oral	7,700 mg/kg	7.7	[15]
Cadmium sulfide	rat, oral	7,080 mg/kg	7.08	[16]
Ethanol (Grain alcohol)	rat, oral	7,060 mg/kg	7.06	[17]
Sodium isopropyl methylphosphonic acid (IMPA, metabolite of sarin)	rat, oral	6,860 mg/kg	6.86	[18]
Melamine	rat, oral	6,000 mg/kg	6	[15]
Methanol	rat, oral	5,628 mg/kg	5.628	[19]
Taurine	rat, oral	>5,000 mg/kg	>5	[20]
Melamine cyanurate	rat, oral	4,100 mg/kg	4.1	[15]
Fructose (fruit sugar)	rat, oral	4,000 mg/kg	4	[21]
Sodium molybdate	rat, oral	4,000 mg/kg	4	[22]
Sodium chloride (table salt)	rat, oral	3,000 mg/kg	3	[23]
Paracetamol (acetaminophen)	mouse, oral	338 mg/kg	0.338	[24]
Delta-9-tetrahydrocannabinol (THC)	rat, oral	1270 mg/kg	1.27	[25]
Cannabidiol (CBD)	rat, oral	980 mg/kg	0.98	[26]
Metallic Arsenic	rat, oral	763 mg/kg	0.763	[27]
Ibuprofen	rat, oral	636 mg/kg	0.636	[28]
Formaldehyde	rat, oral	600-800 mg/kg	0.6	[29]
Alkyl dimethyl benzalkonium chloride (ADBAC)	rat, oral fish, immersion aquatic invertebrates, immersion	304.5 mg/kg {0.28 mg/L} {0.059 mg/L}	0.3045 {0.00028} {0.000059}	[30]
Coumarin (benzopyrone, from <i>Cinnamomum aromaticum</i> and other plants)	rat, oral	293 mg/kg	0.293	[31]
Psilocybin (from magic mushrooms)	mouse, oral	280 mg/kg	0.280	[32]
Hydrochloric acid	rat, oral	238-277 mg/kg	0.238	[33]
Ketamine	rat, intraperitoneal	229 mg/kg	0.229	[34]
Aspirin (acetylsalicylic acid)	rat, oral	200 mg/kg	0.2	[35]
Caffeine	rat, oral	192 mg/kg	0.192	[36]
Arsenic trisulfide	rat, oral	185-6,400 mg/kg	0.185-6.4	[37]
Sodium nitrite	rat, oral	180 mg/kg	0.18	[38]
Methylenedioxymethamphetamine (MDMA, ecstasy)	rat, oral	160 mg/kg	0.18	[39]
Uranyl acetate dihydrate	mouse, oral	136 mg/kg	0.136	[40]
Dichlorodiphenyltrichloroethane (DDT)	mouse, oral	135 mg/kg	0.135	[41]
Uranium	mice, oral	114 mg/kg (estimated)	0.114	[42]
Bisoprolol	mouse, oral	100 mg/kg	0.1	[43]
Cocaine	mouse, oral	96 mg/kg	0.096	[44]
Cobalt(II) chloride	rat, oral	80 mg/kg	0.08	[45]
Cadmium oxide	rat, oral	72 mg/kg	0.072	[46]
Thiopental sodium (used in lethal injection)	rat, oral	64 mg/kg	0.064	[47]
Methamphetamine	rat, intraperitoneal	57 mg/kg	0.057	[48]
Sodium fluoride	rat, oral	52 mg/kg	0.052	[49]
Pentobarbital	human, oral	<50 mg/kg	<0.05	[50]
Capsaicin	mouse, oral	47.2 mg/kg	0.0472	[51]
Mercury(II) chloride	rat, dermal	41 mg/kg	0.041	[52]
Vitamin D3 (colecalciferol)	rat, oral	37 mg/kg	0.037	[53]
Piperidine (from black pepper)	rat, oral	30 mg/kg	0.030	[54]
Heroin (dimorphine)	mouse, intravenous	21.8 mg/kg	0.0218	[55]
Lysergic acid diethylamide (LSD)	rat, intravenous	16.5 mg/kg	0.0165	[56]
Arsenic trioxide	rat, oral	14 mg/kg	0.014	[57]
Metallic Arsenic	rat, intraperitoneal	13 mg/kg	0.013	[58]
Nicotine	human, oral mice, oral	6.5-13 mg/kg (estimated) 3.34 mg/kg	0.0065-0.013 0.0034	[59][60]
Sodium cyanide	rat, oral	6.4 mg/kg	0.0064	[61]
Hydrogen cyanide	mouse, oral	3.7 mg/kg	0.0037	[62]
Chlorotoxin (CTX, from scorpions)	mice	4.3 mg/kg	0.0043	[63]
White phosphorus	rat, oral	3.03 mg/kg	0.00303	[64]
Strychnine	human, oral	1-2 mg/kg (estimated)	0.001-0.002	[65]
Cantharidin (from blister beetles)	human, oral	500 µg/kg	0.0005	
Aflatoxin B1 (from <i>Aspergillus flavus</i> mold)	rat, oral	480 µg/kg	0.00048	[66]
Plutonium	dog, intravenous	320 µg/kg	0.00032	[67]
Amatoxin (from <i>Amanta phalloides</i> mushrooms)	rat	300-700 µg/kg	0.0007	[68]
Tetrodotoxin (TTX, from blue-ringed octopus)	mice, oral	334 µg/kg	0.000334	[69]
Fentanyl	monkey	300 µg/kg	0.0003	[70]
Bufoxin (from Bufo toads)	cat, intravenous	300 µg/kg	0.0003	[71]
Sarin	mouse, subcutaneous injection	172 µg/kg	0.000172	[72]
Robustoxin (from Sydney funnel-web spider)	mice	150 µg/kg	0.000150	[73]
VX	human, oral, inhalation, absorption through skin/eyes	140 µg/kg (estimated)	0.00014	[74]
Venom of the Brazilian wandering spider	rat, subcutaneous	134 µg/kg	0.000134	[75]
Venom of the Inland Taipan (Australian snake)	rat, subcutaneous	25 µg/kg	0.000025	[76]
Ricin (from castor oil plant)	rat, intraperitoneal rat, oral	22 µg/kg 20-30 µg/kg	0.000022 0.02	[77]
Carfentanil	human, oral	20 µg/kg	0.00002	[78]
2,3,7,8-Tetrachlorodibenzodioxin (TCDD, in Agent Orange)	rat, oral	20 µg/kg	0.00002	[79]
CrTX-A (from box jellyfish venom)	crayfish, intraperitoneal	5 µg/kg	0.000005	[80]
Latrotoxin (from widow spider venom)	mice	4.3 µg/kg	0.0000043	[81]
Batrachotoxin (from poison dart frog)	human, sub-cutaneous injection	2-7 µg/kg (estimated)	0.000002	[82]
Abrin (from rosary pea)	human, oral	10-1000 µg/kg	0.00001-0.001	
Maitotoxin (from ciguateric fish)	mouse, intraperitoneal	130 ng/kg	0.0000013	[83]
Polonium-210	human, inhalation	10 ng/kg (estimated)	0.0000001	[84]
Diphtheria toxin	mice	10 ng/kg	0.0000001	[85]
Shiga toxin (from dysentery)	mice	2 ng/kg	0.00000002	[86]
Tetanospasmin (tetanus toxin)	mice	2 ng/kg	0.00000002	[87]
Botulinum toxin (Botox)	human, oral, injection, inhalation	1 ng/kg (estimated)	0.00000001	[88]
Ionizing radiation	human, irradiation	5 Gy		[89]

Animal rights concerns

Animal-rights and animal-welfare groups, such as Animal Rights International,^[88] have campaigned against LD_{50} testing on animals. Several countries, including the UK, have taken steps to ban the oral LD_{50} , and the Organisation for Economic Co-operation and Development (OECD) abolished the requirement for the oral test in 2001 (see Test Guideline 401, *Trends in Pharmacological Sciences* Vol 22, February 22, 2001).

See also

- Animal testing
- Reed-Muench method

Other measures of toxicity

31 <http://biology.umn.edu/tools/biotox/presentations/2013ALPHA-LATROTOKIN%20POWERPOINT.pptx>

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34. Topic 2 Toxic Chemicals and Toxic Effects (<http://agrippina.deakin.edu.au/occ-hyg/sbc312/sbc312-07/SBC312-Topic2-07.htm>) Archived (<https://web.archive.org/web/20070929131217/http://agrippina.deakin.edu.au/occ-hyg/sbc312/sbc312-07/SBC312-Topic2-07.htm>) at the Wayback Machine.

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External links

- Canadian Centre for Occupational Health and Safety (<http://www.ccohs.ca/oshanswers/chemicals/d50.html>)

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