Median lethal dose

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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 with the same meaning, in particular in translations from non-English-language texts, but can also refer to a *sub*lethal dose; because of this ambiguity, it is usually avoided. LD_{50} is usually determined by tests on animals such as laboratory mice. In 2011 the US Food and Drug Administration approved alternative methods to LD_{50} for testing the cosmetic drug Botox without animal tests.[2][3]

Contents

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).

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}" (dosage 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 $LD_{50}/30$ 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 $\mathbf{LCt_{50}}$, which relates to lethal dosage from exposure, where C is concentration and t is time. It is often expressed in terms of mg-min/m^3. $\mathbf{ICt_{50}}$ 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/m^3 is equivalent to 10 minutes of 10 mg/m^3 ($1 \times 100 = 100$, as does $10 \times 10 = 100$).

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 $\mathbf{LC_{50}}$ 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 minute for a cubic meter (e.g., ICt_{50} is 100 medium doses - min/m^3).

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	>90g/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	10.0	[12]
Aspartame	mice, oral	>10,000 mg/kg	10.0	[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]
JWH-018 (Synthetic cannabinoid)	rat, oral	5,600 mg/kg	5.6	[20]
Taurine	rat, oral	>5,000 mg/kg	5.0	[21]
Melamine cyanurate	rat, oral	4,100 mg/kg	4.1	[15]
Fructose (fruit sugar)	rat, oral	4,000 mg/kg	4	[22]
Sodium molybdate	rat, oral	4,000 mg/kg	4	[23]
Sodium chloride (table salt)	rat, oral	3,000 mg/kg	3	[24]
Paracetamol (acetaminophen)	rat, oral	1,944 mg/kg	1.944	[25]
Delta-9-tetrahydrocannabinol (THC)	rat, oral	1,270 mg/kg	1.27	[26]
Cannabidiol (CBD)	rat, oral	980 mg/kg	0.98	[27]
Methamphetamine	rat, oral	980 mg/kg	0.98	[28]
Metallic Arsenic	rat, oral	763 mg/kg	0.763	[29]
Ibuprofen	rat, oral	636 mg/kg	0.636	[30]
Formaldehyde	rat, oral	600–800 mg/kg	0.600	[31]

Substance	Animal, Route	LD_{50} {LC_{50}}	LD_{50} : g/kg {LC_{50} : g/L} standardized	Reference
Alkyl dimethyl benzalkonium chloride (ADBAC)	rat, oral fish, immersion aq. invertebrates, imm.	304.5 mg/kg {0.28 mg/L} {0.059 mg/L}	0.3045 {0.00028} {0.000059}	[32]
Coumarin (benzopyrone, from *Cinnamomum aromaticum* and other plants)	rat, oral	293 mg/kg	0.293	[33]
Psilocybin (from magic mushrooms)	mouse, oral	280 mg/kg	0.280	[34]
Hydrochloric acid	rat, oral	238–277 mg/kg	0.238	[35]
Ketamine	rat, intraperitoneal	229 mg/kg	0.229	[36]
Aspirin (acetylsalicylic acid)	rat, oral	200 mg/kg	0.2	[37]
Caffeine	rat, oral	192 mg/kg	0.192	[38]
Arsenic trisulfide	rat, oral	185–6,400 mg/kg	0.185–6.4	[39]
Sodium nitrite	rat, oral	180 mg/kg	0.18	[40]
Methylenedioxymethamphetamine (MDMA, ecstasy)	rat, oral	160 mg/kg	0.18	[41]
Uranyl acetate dihydrate	mouse, oral	136 mg/kg	0.136	[42]
Dichlorodiphenyltrichloroethane (DDT)	mouse, oral	135 mg/kg	0.135	[43]
Bisoprolol	mouse, oral	100 mg/kg	0.1	[44]
Cocaine	mouse, oral	96 mg/kg	0.096	[45]
Cobalt(II) chloride	rat, oral	80 mg/kg	0.08	[46]
Cadmium oxide	rat, oral	72 mg/kg	0.072	[47]
Sodium fluoride	rat, oral	52 mg/kg	0.052	[48]
Pentaborane	human, oral	<50 mg/kg	<0.05	[49]
Capsaicin	mouse, oral	47.2 mg/kg	0.0472	[50]
Mercury(II) chloride	rat, dermal	41 mg/kg	0.041	[51]
Vitamin D3 (cholecalciferol)	rat, oral	37 mg/kg	0.037	[52]
Piperidine (from black pepper)	rat, oral	30 mg/kg	0.030	[53]
Heroin (diamorphine)	mouse, intravenous	21.8 mg/kg	0.0218	[54]
Lysergic acid diethylamide (LSD)	rat, intravenous	16.5 mg/kg	0.0165	[55]

Substance	Animal, Route	LD_{50} {LC_{50}}	LD_{50} : g/kg {LC_{50} : g/L} standardized	Reference
Arsenic trioxide	rat, oral	14 mg/kg	0.014	[56]
Metallic Arsenic	rat, intraperitoneal	13 mg/kg	0.013	[57]
Nicotine	human, oral	6.5–13.0 mg/kg (estimated)	0.0065–0.013	[58]
	mice, oral	3.34 mg/kg	0.0034	[59]
Sodium cyanide	rat, oral	6.4 mg/kg	0.0064	[60]
Hydrogen cyanide	mouse, oral	3.7 mg/kg	0.0037	[61]
Chlorotoxin (CTX, from scorpions)	mice	4.3 mg/kg	0.0043	[62]
White phosphorus	rat, oral	3.03 mg/kg	0.00303	[63]
Strychnine	human, oral	1–2 mg/kg (estimated)	0.001	[64]
Cantharidin (from blister beetles)	human, oral	500 µg/kg	0.0005	
Aflatoxin B1 (from *Aspergillus flavus* mold)	rat, oral	480 µg/kg	0.00048	[65]
Plutonium	dog, intravenous	320 µg/kg	0.00032	[66]
Amatoxin (from *Amanita phalloides* mushrooms)	rat	300-700 µg/kg	0.0007	[67]
Tetrodotoxin (TTX, from blue-ringed octopus)	mice, oral	334 µg/kg	0.334	[68]
Bufotoxin (from Bufo toads)	cat, intravenous	300 µg/kg	0.000300	[69]
Robustoxin (from Sydney funnel-web spider)	mice	150 µg/kg	0.000150	[70]
Venom of the Brazilian wandering spider	rat, subcutaneous	134 µg/kg	0.000134	[71]
Uranium	mice, oral	114 µg/kg (estimated)	0.000114	[72]
Venom of the Inland Taipan (Australian snake)	rat, subcutaneous	25 µg/kg	0.000025	[73]
Ricin (from castor oil plant)	rat, intraperitoneal rat, oral	22 µg/kg 20–30 mg/kg	0.000022 0.02	[74]
2,3,7,8-Tetrachlorodibenzodioxin (TCDD, in Agent Orange)	rat, oral	20 µg/kg	0.00002	[75]

Substance	Animal, Route	LD_{50} {LC_{50}}	LD_{50} : g/kg {LC_{50} : g/L} standardized	Reference
Sarin	mouse, subcutaneous injection	17.23 µg/kg (estimated)	0.0000172	[76]
CrTX-A (from box jellyfish venom)	crayfish, intraperitoneal	5 µg/kg	0.000005	[77]
Latrotoxin (from widow spider venom)	mice	4.3 µg/kg	0.0000043	[78]
VX	human, oral, inhalation, absorption through skin/eyes	2.3 µg/kg (estimated)	0.0000023	[79]
Batrachotoxin (from poison dart frog)	human, sub-cutaneous injection	2–7 µg/kg (estimated)	0.000002	[80]
Abrin (from rosary pea)	mice, intravenously human, inhalation human, oral	0.7 µg/kg 3.3 µg/kg 10–1000 µg/kg	0.0000007 0.0000033 0.00001–0.001	
Maitotoxin (from ciguateric fish)	mouse, intraperitoneal	0.13 µg/kg	0.00000013	[81]
Polonium-210	human, inhalation	10 ng/kg (estimated)	0.00000001	[82]
Diphtheria toxin	mice	10 ng/kg	0.00000001	[83]
Shiga toxin (from dysentery)	mice	2 ng/kg	0.000000002	[84]
Tetanospasmin (tetanus toxin)	mice	2 ng/kg	0.000000002	[85]
Botulinum toxin (Botox)	human, oral, injection, inhalation	1 ng/kg (estimated)	0.000000001	[86]
Ionizing radiation	human, irradiation	5 Gy		[87]

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

- IDLH
- Certain safety factor
- Therapeutic index
- Protective index
- Fixed Dose Procedure to estimate LD50
- Median toxic dose (TD50)
- Lowest published toxic concentration (TCLo)
- Lowest published lethal dose (LDLo)
- EC_{50} (half maximal effective concentration)
- IC_{50} (half maximal inhibitory concentration)
- Draize test
- Indicative limit value
- No-observed-adverse-effect level (NOAEL)
- Lowest-observed-adverse-effect level (LOAEL)
- Up-and-down procedure

Related measures

- $TCID_{50}$ Tissue Culture Infective Dosage
- EID_{50} Egg Infective Dosage
- ELD_{50} Egg Lethal Dosage
- Plaque forming units (pfu)

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External links

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