Chemicals and Materials

What is a LD_{50} and LC_{50}?

On this page

What does LD_{50} mean?

LD stands for "Lethal Dose". LD_{50} is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals. The LD_{50} is one way to measure the short-term poisoning potential (acute toxicity) of a material.

Toxicologists can use many kinds of animals but most often testing is done with rats and mice. It is usually expressed as the amount of chemical administered (e.g., milligrams) per 100 grams (for smaller animals) or per kilogram (for bigger test subjects) of the body weight of the test animal. The LD_{50} can be found for any route of entry or administration but dermal (applied to the skin) and oral (given by mouth) administration methods are the most common.

What does LC_{50} mean?

LC stands for "Lethal Concentration". LC values usually refer to the concentration of a chemical in air but in environmental studies, it can also mean the concentration of a chemical in water.

According to the (Organisation for Economic Cooperation and Development) (OECD) Guidelines for the Testing of Chemicals, a traditional experiment involves groups of animals exposed to a concentration (or series of concentrations) for a set period of time (usually 4 hours). The animals are clinically observed for up to 14 days.

The concentrations of the chemical in air that kills 50% of the test animals during the observation period is the LC_{50} value. Other durations of exposure (versus the traditional 4 hours) may apply depending on specific laws.

Why study LD_{50}'s?

Chemicals can have a wide range of effects on our health. Depending on how the chemical will be used, many kinds of toxicity tests may be required.

Since different chemicals cause different toxic effects, comparing the toxicity of one with another is hard. We could measure the amount of a chemical that causes kidney damage, for example, but not all chemicals will damage the kidney. We could say that nerve damage is observed when 10 grams of chemical A is administered, and kidney damage is observed when 10 grams of chemical B is administered. However, this information does not tell us if A or B is more toxic because we do not know which damage is more critical or harmful.

Therefore, to compare the toxic potency or intensity of different chemicals, researchers must measure the same effect. One way is to carry out lethality testing (the LD_{50} tests) by measuring how much of a chemical is required to cause death. This type of test is also referred to as a "quantal" test because it is measures an effect that "occurs" or "does not occur".

Who invented the idea of an LD_{50}?

In 1927, J.W. Trevan attempted to find a way to estimate the relative poisoning potency of drugs and medicines used at that time. He developed the LD_{50} test because the use of death as a "target" allows for comparisons between chemicals that poison the body in very different ways. Since Trevan's early work, other scientists have developed different approaches for more direct, faster methods of determining the LD_{50}.

What are some other toxicity dose terms that are used?

LD_{01} Lethal dose for 1% of the animal test population

LD_{100} Lethal dose for 100% of the animal test population

LDLO The lowest dose causing lethality

TDLO The lowest dose causing a toxic effect

Why are LD_{50} and LC_{50} values a measure of acute toxicity?

Acute toxicity is the ability of a chemical to cause ill effects relatively soon after one oral administration or a 4-hour exposure to a chemical in air. "Relatively soon" is usually defined as a period of minutes, hours (up to 24) or days (up to about 2 weeks) but rarely longer.

How are LD/LC_{50} tests done?

In nearly all cases, LD_{50} tests are performed using a pure form of the chemical. Mixtures are rarely studied.

The chemical may be given to the animals by mouth (oral); by applying on the skin (dermal); by injection at sites such as the blood veins (i.v.- intravenous), muscles (i.m. - intramuscular) or into the abdominal cavity (i.p. - intraperitoneal).

The LD_{50} value obtained at the end of the experiment is identified as the LD_{50} (oral), LD_{50} (skin), LD_{50} (i.v.), etc., as appropriate. Researchers can do the test with any animal species but they use rats or mice most often. Other species include dogs, hamsters, cats, guinea pigs, rabbits, and monkeys. In each case, the LD_{50} value is expressed as the weight of chemical administered per kilogram body weight of the animal and it states the test animal used and route of exposure or administration; e.g., LD_{50} (oral, rat) - 5 mg/kg, LD_{50} (skin, rabbit) - 5 g/kg. So, the example "LD_{50} (oral, rat) 5 mg/kg" means that 5 milligrams of that chemical for every 1 kilogram body weight of the rat, when administered in one dose by mouth, causes the death of 50% of the test group.

If the lethal effects from breathing a compound are to be tested, the chemical (usually a gas or vapour) is first mixed in a known concentration in a special air chamber where the test animals will be placed. This concentration is usually quoted as parts per million (ppm) or milligrams per cubic metre (mg/m^3). In these experiments, the concentration that kills 50% of the animals is called an LC_{50} (Lethal Concentration 50) rather than an LD_{50}. When an LC_{50} value is reported, it should also state the kind of test animal studied and the duration of the exposure, e.g., LC_{50} (rat) - 1000 ppm/ 4 hr or LC_{50} (mouse) - $5mg/m^3$/ 2hr.

Which LD_{50} information is the most important for occupational health and safety purposes?

Inhalation and skin absorption are the most common routes by which workplace chemicals enter the body. Thus, the most relevant from the occupational exposure viewpoint are the inhalation (LC_{50}) and skin application tests (LD_{50}-skin). Despite this fact, the most frequently performed lethality study is the oral LD_{50}. This difference occurs because giving chemicals to animals by mouth is much easier and less expensive than other techniques. However, the results of oral studies are important for drug studies, food poisonings, and unintentional domestic poisonings. Oral occupational poisonings might occur by contamination of food or cigarettes from unwashed hands, and by unintentional swallowing.

How do I compare one LD_{50} value to another and what does it mean to humans?

In general, the smaller the LD_{50} value, the more toxic the chemical is. The opposite is also true: the larger the LD_{50} value, the lower the toxicity.

The LD_{50} gives a measure of the immediate or acute toxicity of a chemical in the strain, sex, and age group of a particular animal species being tested. Changing any of these variables (e.g., type animal or age) could result in finding a different LD_{50} value. The LD_{50} test was neither designed nor intended to give information on the long-term exposure effects of a chemical.

Once you have an LD_{50} value, it can be compared to other values by using a toxicity scale. Confusion sometimes occurs because several different toxicity scales are in use. The two most common scales used are the "Hodge and Sterner Scale" and the "Gosselin, Smith and Hodge Scale". These tables differ in both the numerical rating given to each class and the terms used to describe each class. For example, a chemical with an oral LD_{50} value of 2 mg/kg, would be rated as "1" and "highly toxic" according to the Hodge and Sterner Scale (see Table 1) but rated as "6" and "super toxic" according to the Gosselin, Smith and Hodge Scale (see Table 2). It is important to reference the scale you used when classifying a compound.

It is also important to know that the actual LD_{50} value may be different for a given chemical depending on the route of exposure (e.g., oral, dermal, inhalation). For example, some LD_{50}s for dichlorvos, an insecticide commonly used in household pesticide strips, are listed below:

- Oral LD_{50} (rat): 56 mg/kg
- Dermal LD_{50} (rat): 75 mg/kg
- Intraperitoneal LD_{50}: (rat) 15 mg/kg
- Inhalation LC_{50} (rat): 1.7 ppm (15 mg/m3); 4-hour exposure
- Oral LD_{50} (rabbit) 10 mg/kg

- Oral LD_{50} (pigeon:): 23.7 mg/kg
- Oral LD_{50} (rat): 56 mg/kg
- Oral (mouse): 61 mg/kg
- Oral (dog): 100 mg/kg
- Oral (pig): 157 mg/kg

Differences in the LD_{50} toxicity ratings reflect the different routes of exposure. The toxicity rating can be different for different animals. The data above show that dichlorvos is much less toxic by ingestion in pigs or dogs than in rats. Using Table 1, dichlorvos is moderately toxic when swallowed (oral LD_{50}) and extremely toxic when breathed (inhalation LC_{50}) in the rat. Using Table 2, dichlorvos is considered very toxic when swallowed (oral LD_{50}) by a rat.

Table 1: Toxicity Classes: Hodge and Sterner Scale

		Routes of Administration			
		Oral LD_{50}	**Inhalation LC_{50}**	**Dermal LD_{50}**	
Toxicity Rating	**Commonly Used Term**	**(single dose to rats) mg/kg**	**(exposure of rats for 4 hours) ppm**	**(single application to skin of rabbits) mg/kg**	**Probable Lethal Dose for Man**
1	Extremely Toxic	1 or less	10 or less	5 or less	1 grain (a taste, a drop)
2	Highly Toxic	1-50	10-100	5-43	4 ml (1 tsp)
3	Moderately Toxic	50-500	100-1000	44-340	30 ml (1 fl. oz.)
4	Slightly Toxic	500-5000	1000-10,000	350-2810	600 ml (1 pint)
5	Practically Non-toxic	5000-15,000	10,000-100,000	2820-22,590	1 litre (or 1 quart)
6	Relatively Harmless	15,000 or more	100,000	22,600 or more	1 litre (or 1 quart)

Table 2: Toxicity Classes: Gosselin, Smith and Hodge		
Probable Oral Lethal Dose (Human)		
Toxicity Rating or Class	**Dose**	**For 70-kg Person (150 lbs)**
6 Super Toxic	Less than 5 mg/kg	1 grain (a taste – less than 7 drops)
5 Extremely Toxic	5-50 mg/kg	4 ml (between 7 drops and 1 tsp)
4 Very Toxic	50-500 mg/kg	30 ml (between 1 tsp and 1 fl ounce)
3 Moderately Toxic	0.5-5 g/kg	30-600 ml (between 1 fl oz and 1 pint)
2 Slightly Toxic	5-15 g/kg	600-1200 ml (between 1 pint to 1 quart)
1 Practically Non-Toxic	Above 15 g/kg	More than 1200 ml (more than 1 quart)

Can animal LD_{50} data be applied to humans?

In general, if the immediate toxicity is similar in all of the different animals tested, the degree of immediate toxicity will probably be similar for humans. When the LD_{50} values are different for various animal species, one has to make approximations and assumptions when estimating the probable lethal dose for man. Tables 1 and 2 have a column for estimated lethal doses in man. Special calculations are used when translating animal LD_{50} values to possible lethal dose values for humans. Safety factors of 10,000 or 1000 are usually included in such calculations to allow for the variability between individuals and how they react to a chemical, and for the uncertainties of experiment test results.

How should an LD_{50} value be used?

The LD_{50} can be used:

- As an aid in developing emergency procedures in case of a major spill or incident.
- To help develop guidelines for the use of appropriate safety clothing and equipment. For example, if the dermal LD_{50} value for a chemical is rated as extremely toxic, it is important to protect the skin with clothing, gloves (etc.) made of the right chemical-resistant material before handling. Alternatively, if a chemical has an inhalation LC_{50} value which indicates that it is relatively harmless, respiratory protective equipment may not be necessary (as long as the oxygen concentration in the air is in the normal range – around 21%).
- For the development of transportation regulations.

- As an aid in establishing occupational exposure limits.
- As a part of the information in Safety Data Sheets. Remember, the LD_{50} is only a estimate so that lethal toxicity can be compared. It says nothing about levels at which other acute toxic, but non-lethal, effects might occur.

The LD_{50} is only one source of toxicity information. For a more thorough picture of the immediate or acute toxicity of a chemical, additional information should be considered such as the lowest dose that causes a toxic effect (TDLO), the rate of recovery from a toxic effect, and the possibility that exposure to some mixtures may result in increasing the toxic effect of an individual chemical.

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