



Unit IV: Pharmacodynamics:

Concept of LD₅₀, LC₅₀, TD₅₀ and therapeutic index

❖ The Median Lethal Concentration, LC₅₀

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 concentration of the chemical in air that kills 50% of the test animals during the observation period is the LC₅₀ value. Other durations of exposure (versus the traditional 4 hours) may apply depending on specific laws.

❖ Therapeutic index (or ratio)

The literature seems to use the terms "therapeutic index" and "therapeutic ratio" in a way which might suggest that they are synonymous, even though there is an SAQ in the local anaesthetic primary exam which asked the candidates to interpret each term separately. Fortunately, CICM examiners have not yet plagiarised this question. In Katzung, the therapeutic index is defined as

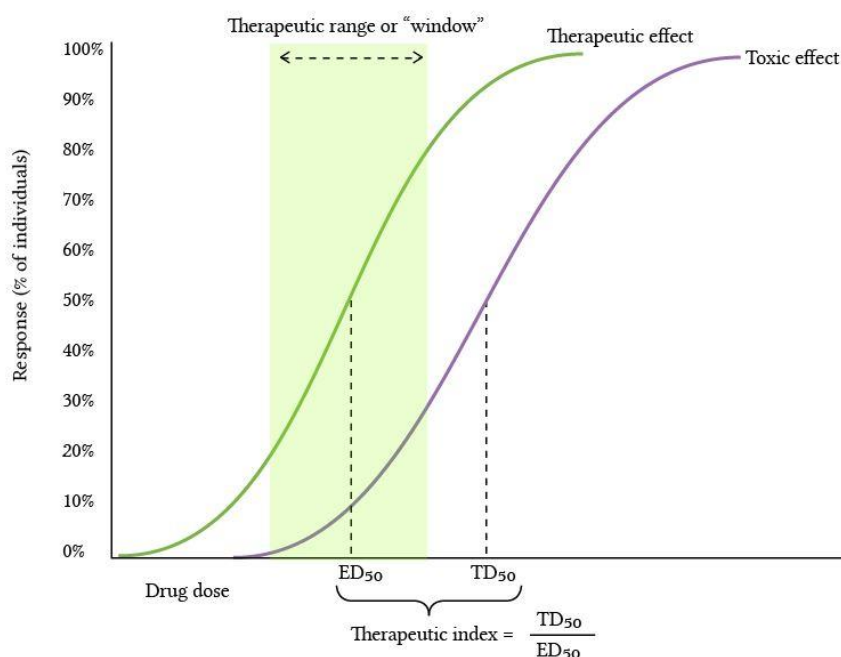
"the ratio of the TD₅₀ to the ED₅₀ for some therapeutically relevant effect"

The official IUPC documents don't seem to have any sort of gospel answer, and every piece of literature seems to have some arbitrary way of defining

this concept. Abughazaleh & Tracy (2007) acknowledge this. "Although the general concept of the therapeutic index is describable by most individuals", they begin their article, all sorts of operational issues (like the lack of a formal definition) "continue to confound determination and clinical utility of the 'therapeutic index.'" These pharmacologists' authority as experts (Wiley gave them a chapter from their *Encyclopedia of Clinical Trials*) suggest that one should at least be vaguely aware of how they define this concept:

"Therapeutic index is most commonly defined as the ratio of the median lethal dose (LD50) to the median effective dose (ED50), as determined in preclinical animal studies, [which] reflects the selectivity of a drug to elicit a desired effect rather than toxicity"

All of these variants are probably valid on some level, but the exam-going CICM trainee would probably be better off treating Katzung as the definitive official source for this sort of thing. As such, the von Zastrow definition is used for the purposes of the diagrams here.





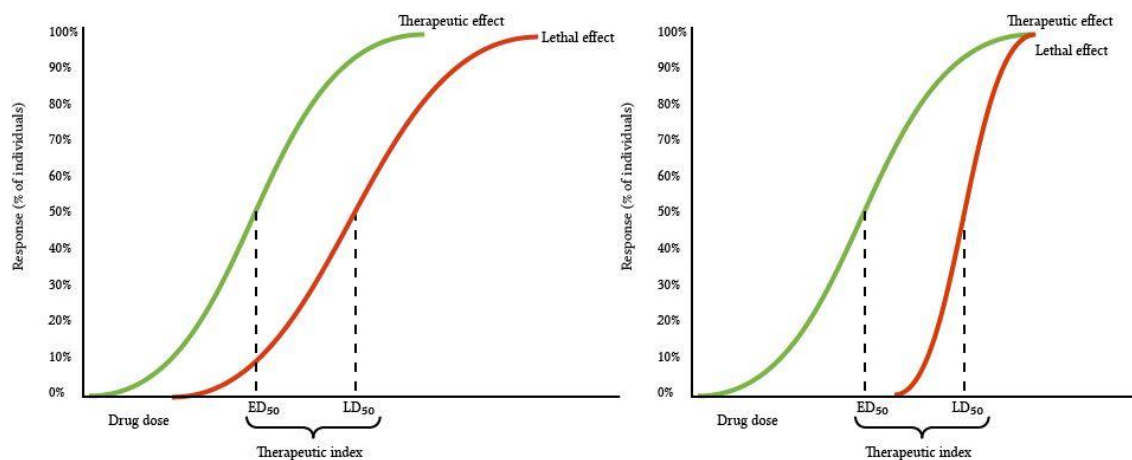
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The point of the therapeutic index

- ◆ **It is a numeric measure of the selectivity of the drug for its desired effect.** The larger the value, the safer the drug, one could crudely say.
- ◆ **It guides the need for therapeutic level monitoring.** Drugs with a narrow therapeutic index should be monitored more closely.
- ◆ **It guides the dosing interval.** Or rather, it theoretically could. The drug with a narrow index would need to be given more frequently and in smaller doses.

For real-life bedside clinical purposes, this therapeutic index concept leaves much to be desired.

- **The original equation calls for a measurement of LD₅₀ (TI = LD₅₀/ED₅₀),** which would be inconvenient to determine experimentally in humans.
- **Comparison between therapeutic indices of different drugs is unreliable.** An infinite number of different therapeutic indices can be calculated for any drug, because different desired or toxic effects can be chosen as endpoints.
- **It is unhelpful in the cases of idiosyncratic reactions,** or where the adverse reaction is completely unrelated to dose (eg. anaphylaxis).
- **It misrepresents risk.** The dose-response curves for the desired effect and the toxic effect may be very different in their slope. In fact, though pharmacology textbooks always draw beautifully parallel curves, there is absolutely no scientific reason for this to be so. Observe two drugs:



As you can see, the drug on the left kills approximately 10% of people at ED_{50} , and in order to achieve full effect reliably in 100% of the population, one would need to tolerate a mortality of 80%. In contrast, drug on the right does not cause any deaths at ED_{50} , but then rapidly becomes lethal. Obviously the "*selectivity of a drug to elicit a desired effect rather than toxicity*" is somewhat different between these substances, but the therapeutic index would remain the same.

Therapeutic index, margin of safety that exists between the dose of a drug that produces the desired effect and the dose that produces unwanted and possibly dangerous side effects. This relationship is defined as the ratio $LD_{50}:ED_{50}$, where LD_{50} is the dose at which a drug kills 50 percent of a test group of animals and ED_{50} is the dose at which the desired effect is produced in 50 percent of a test group. In general, the narrower this margin, the more likely it is that the drug will produce unwanted effects.

The therapeutic index has many limitations, notably the fact that LD_{50} cannot be measured in humans and, when measured in animals, is a poor guide to the likelihood of unwanted effects in humans. Nevertheless, the therapeutic index



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emphasizes the importance of the margin of safety, as distinct from the potency, in determining the usefulness of a drug.

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