Toxicological Approaches – Who is Who

The term toxicology is derived from the ancient Greek word, toxikologia, and describes the study of toxicants. The Greek word toxikon in turn stems from toxon, meaning the 'bow' of the archer that is used to shoot off a (poisonous) arrow.

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When it comes to estimating the toxicity of a substance, the concentration of the substance in question is usually the determining factor. Some substances have a beneficial effect on the human body in low doses but pose a potential health risk at higher concentrations. However, all substances are fatal as of a certain application-related dose. In this connection, a historic guiding motto of toxicology is as follows:

> "All things are poison and nothing is without poison; only the dose makes a thing not a poison."
> (Paracelsus, 1538)

Assessing or determining the toxicological effect of a substance is achieved using certain toxicological approaches. In doing so, a differentiation is made between an acute (short-term) or chronic (long-term) effect. These effects can be negative or positive (pharmacological effect) for the human body.

Deriving a toxicologically relevant dose-response relationship – mostly from cell cultures, animal studies, or other models – is paramount in toxicology. A host of sometimes very different toxicological approaches have been defined for this purpose. A selection of these is to be more closely detailed in the following.

NOAEL (No Observed Adverse Effect Level)

One of the key toxicological indicators is the so-called NOAEL. The NOAEL is the dose or concentration level at which no adverse effects are observable in the model organisms in question. The model organisms used may be mice, rats, or cell cultures, etc. These are exposed to various concentration levels of the substance under examination. Subsequently a defined end point is determined (e.g. formation of cancer cells). The NOAEL is a substance-related indicator and is always based on a measuring method (e.g. vitality measurement) for a certain form of application (oral, inhaling) and animal species or cell culture system.

ADI (Acceptable Daily Intake)

Another key approach in toxicology is the so-called ADI, i.e. the Acceptable Daily Intake of a food additive, a pesticide, etc. that is deemed harmless over a person's entire lifetime. The ADI is calculated from the experimentally determined NOAEL. In transferring the results to the human body, a certainty factor of 100 is taken into account to be on the safe side in acknowledging the differences between the test organisms and human.

TDI (Tolerable Daily Intake)

As the key counterpart to the ADI, the TDI applies to undesirable impurities or contaminants and – just like the ADI – states the amount of a substance which can be ingested daily over an entire lifetime without having noticeable effects on the health of consumers. Hence the TDI states the maximum level of an undesirable food contaminant and, exactly like the ADI, is calculated from the NOAEL. In addition to the TDI, maximum levels can be defined for a weekly (TWI = Tolerable Weekly Intake) or monthly (TMI = Tolerable Monthly Intake) level.

ARfD (Acute Reference Dose)

Among the abovementioned toxicological approaches, the relatively new Acute Reference Dose sets a maximum level for short-term exposure of consumers to a substance and is mainly used to assess pesticides and food additives. With regard to residual substances in foods, the ARfD is

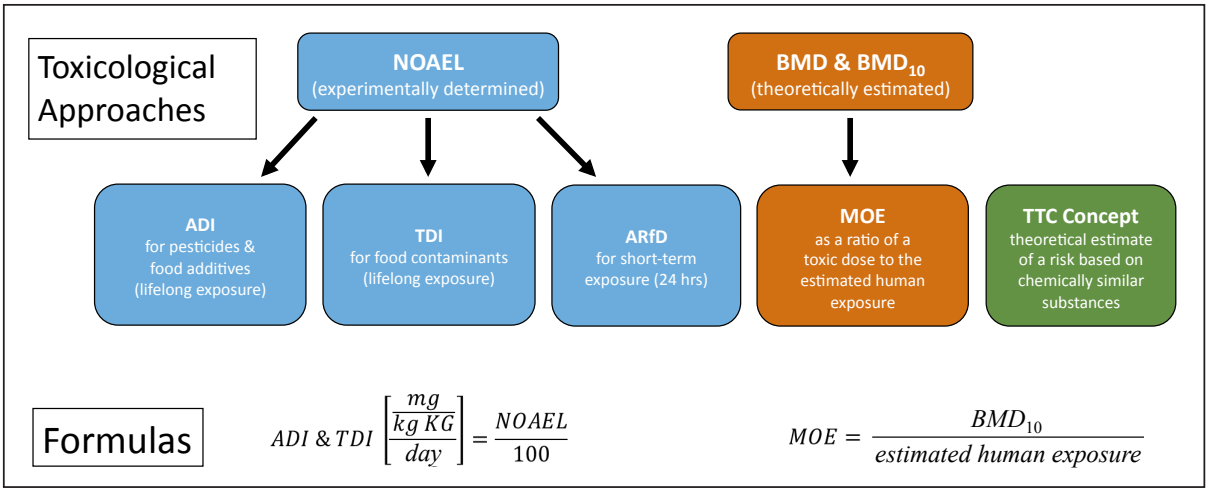

Figure 1: Overview of described toxicological approaches and their respective calculation

the amount a consumer may ingest in one or several meals over a period of 24 hours without this posing a measurable health risk. The ARfD is derived from the NOAEL using a certainty factor (usually a factor of 100).

Benchmark Method

As opposed to the experimentally determined NOAEL, purely mathematical calculations of statistical data can be made from a dose-response relationship. The probably most well-known procedure in this respect is the so-called Benchmark Method. In this case, a statistics-aided analysis of existing dose-response relationships is used to estimate the level at which a defined additional effect occurs. The thereby derived dose is termed the "benchmark dose" (BMD). In the case of substances causing cancer or reproductive toxicity, the dose which (compared to the control group) leads to a 10% higher tumour formation is also calculated (benchmark dose 10%, BMD_{10}).

MOE (Margin of Exposure)

The Margin of Exposure (MOE) is a risk assessment tool used in weighing up possible safety concerns about substances occurring in foodstuffs and feedstuffs which are both genotoxic (i.e. potentially harmful to DNA) and carcinogenic (causing cancer). The MOE is the ratio between two factors: the dose at which a small but measurable harmful effect is first observable and the exposure level of a certain population to the substance in question. Hence the lower the anticipated exposure, the bigger is the MOE. The calculation basis is provided, for example, by the already described BMD_{10}. An MOE of greater than 10,000 (BMD_{10}, tumorigenic in 10% of tested animals) is – in the light of current scientific knowledge – of little concern and takes several (un)certainty factors into consideration.

TTC Concept (Threshold of Toxicological Concern)

Due to improved analyses procedures, more and more substances occurring at low and very low concentrations in foodstuffs and feedstuffs can meanwhile be detected. However, there is little or no toxicological data for many of these substances. The TTC Concept was developed to evaluate the risk of these substances in terms of their harmful effects. In this case, substances with a known chemical structure are evaluated and a maximum level is set based on chemically similar substances which have already undergone a toxicological assessment. This level is kept very low, following the principle of precaution. Subsequently conducted toxicological examinations may confirm or newly define this notional maximum level.

An overview of the toxicological approaches discussed above is provided in figure 1.

Over the last few years, a harmonised risk assessment system for toxicologically relevant substances has been established throughout the EU and this is under constant development and modification to ensure preventive consumer health protection.

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