PERMISSIBLE DAILY EXPOSURE (PDE)
DETERMINATION STRATEGY FOR
DICLOFENAC SODIUM (INJECTION)
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1. BASIC INFORMATION

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<thead>
<tr>
<th>Toxicological Profile, Hazards Identification, Risk Assessment and Permissible Daily Exposure (PDE) Monograph of Diclofenac Sodium (Inj)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDE Value</strong></td>
</tr>
<tr>
<td><strong>Chemical name</strong> (IUPAC Name)</td>
</tr>
<tr>
<td><strong>Drug product</strong></td>
</tr>
</tbody>
</table>
2. HAZARDS IDENTIFIED

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotoxicant</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Carcinogen</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive/developmental toxicity</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly sensitizing potential</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. SUMMARY OF ASSESSMENT PROCESS (CALCULATION OF PDE VALUE)

| PDE value | 0.35 mg/day |

HAZARD IDENTIFICATION

**Pharmacodynamics data**

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. It inhibits both leukocyte migration and the enzyme cyclooxygenase (COX-1 and COX-2), leading to the peripheral inhibition of prostaglandin synthesis.

**Acute toxicity**

Single dose toxicity studies were carried out in mouse, rat, guinea-pig and rabbits. Oral median lethal dose of mouse is 389 mg/kg, rat is 173 mg/kg, guinea-pig is 1110 mg/kg and of rabbit is 194 mg/kg. Intravenous mean lethal dose of mouse is 133 mg/kg, rat is 106 mg/kg and in guinea-pig is 127 mg/kg.

**Repeated dose toxicity**

Studies up to one year were conducted in rodents and non-rodents. The major effect is gastrointestinal ulceration associated mortality.

**Carcinogenicity**

Carcinogenicity studies were conducted in mice and rats. Long term studies revealed no significant increases in tumour incidence. Diclofenac sodium was not carcinogenic to mice.

**Genotoxicity studies**

*In vitro* and *in vivo* studies were carried out. Diclofenac sodium was found to be non-mutagenic.

**Reproductive/Developmental toxicity**

The lowest tested dose is toxic to pregnant rats and maternal toxicity associated foetal effects were observed.

**Highly sensitizing potential**

Diclofenac sodium didn’t show any sensitivity in rabbits and guinea pigs.
IDENTIFICATION OF CRITICAL EFFECTS

<table>
<thead>
<tr>
<th>Sensitive indicator of an adverse effect seen in non-clinical toxicity data</th>
<th>Gastrointestinal (GI) toxicity was reported in the animal species.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical therapeutic and adverse effects</td>
<td>Diclofenac sodium is used to treat eye pain, redness, and swelling in patients who are recovering from cataract surgery and sensitivity to light in patients who are recovering from corneal refractive surgery. Common adverse effects of Diclofenac include burning or stinging in your eye just after you instill the drops, itchy eyes, stomach pain, vomiting, headache, dizziness, fever, chills, runny nose, swelling of the eyes or face, red or bloody eyes, eye pain, sensitivity to light, blurred or decreased vision and teary eyes. Therapeutic dose- 37.5 mg IV bolus over 15 seconds every 6 hours as needed for pain.</td>
</tr>
</tbody>
</table>

Maximum Dose: 150 mg/day

NOAEL | 7 mg/kg/day from 4-week i.v. toxicity study in rats.

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation

<table>
<thead>
<tr>
<th>F1: Extrapolation between species</th>
<th>5</th>
<th>Based on the selection of toxicity study of rats.</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2: Inter-individual variability</td>
<td>10</td>
<td>Conventionally used to allow for differences between individuals in the human population</td>
</tr>
<tr>
<td>F3: Duration of toxicity</td>
<td>10</td>
<td>Short term (4-weeks) toxicity study in rats</td>
</tr>
<tr>
<td>F4: Severe toxicity (1-10)</td>
<td>2</td>
<td>Based on the pre-clinical findings (GI toxicity).</td>
</tr>
<tr>
<td>F5: NOAEL Vs LOAEL (10 if LOAEL)</td>
<td>1</td>
<td>Selection of NOAEL dose.</td>
</tr>
<tr>
<td>PK correction</td>
<td>For PDE calculation, no factor is applied.</td>
<td></td>
</tr>
</tbody>
</table>
4. IDENTIFICATION OF THE ACTIVE SUBSTANCE

Diclofenac sodium is a nonsteroidal anti-inflammatory drug which is used for the therapy of chronic forms of arthritis and mild-to-moderate acute pain.

**IUPAC name**: sodium; 2-[2-(2,6-dichloroanilino) phenyl] acetic acid

**Chemical Abstracts Service (CAS) registry number**: 15307-86-5

**Chemical description and physical properties**: It is a white to off-white powder which is practically insoluble in aqueous acidic solutions.

**Melting point**: 283-285 °C

**Molecular weight**: 318.1 g/mol

**Molecular formula**: C_{14}H_{11}Cl_{2}NNaO_{2}

**Structure of Diclofenac sodium**

![Structure of Diclofenac sodium](image)
5. OBJECTIVE AND SEARCH STRATEGY

At present, pharmaceutical companies are investing significant effort to assess and control cross-contamination risk of drug products that are manufactured in the shared production facilities (3). Determination of health-based exposure limits for a residual active substance through the derivation of a safe threshold value is employed to identify the risk posed. The derivation of threshold value like permitted daily exposure (PDE) or threshold of toxicological concern is used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of diclofenac sodium have been presented based on the published data. The data were extracted from Pubmed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), MSDS, HSDB, Product monograph, National Toxicology Program (NTP), and FDA.

6. INTRODUCTION

Diclofenac sodium is a phenylacetic acid derivative and non-steroidal anti-inflammatory drug. It is used for the treatment of acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis (1, 2).

Diclofenac sodium is a non-steroidal anti-inflammatory drug. ATC code is M01AB05.

7. HAZARD IDENTIFICATION

a. Pharmacodynamics data

Diclofenac sodium reduces inflammation and by extension reduces nociceptive pain and combats fever. It also increases the risk of developing a gastrointestinal ulcer by inhibiting the production of protective mucus in the stomach (1, 2).

b. Acute toxicity studies

Acute toxicity studies were conducted in mice, rats, mice, guinea pigs, rabbit, dogs and monkeys. Rat is more sensitive to single dose toxicity of diclofenac sodium compared to mice. The estimated LD$_{50}$ is between 106 to 389 mg/kg in rats and mice followed by oral or
intravenous route. Rabbit is more sensitive with intravenous administration (LD$_{50}$ 60 mg/kg) and monkeys considerably less sensitive with an oral LD$_{50}$ of 3200 mg/kg. The observed clinical signs are dyspnea and recumbence in rodents and CNS and gastrointestinal effects in dogs and monkeys. Intravenous administration resulted in death due to respiratory or cardiac failure. Gastrointestinal problems and peritonitis are the observed findings followed by oral administration. The most frequent autopsy findings in animals that died were gastric irritation, perforation and their sequelae (5).

c. Repeated dose toxicity

Table no.1 Toxicity study through oral route (5).

<table>
<thead>
<tr>
<th>Species</th>
<th>Period</th>
<th>Daily dose mg/kg/day P.O.</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>3 months</td>
<td>0.25, 1 and 2 mg/kg/day, from 59 weeks (high-dose groups) to 98 weeks (low and intermediate dose groups)</td>
<td>Mortality was seen in high dose groups due to which it was terminated after 59 weeks. Observation include ulceration of the gastrointestinal tract, with perforated ulcers leading to peritonitis and sequelae. Hematologic patterns showing neutrophilic leucocytosis and anaemia were seen in the high and intermediate dose groups, particularly females at weeks 52 and 98, respectively. In female animals, observations include enlarged adrenals, depressed glucose and elevated alkaline phosphatase levels. Histology studies revealed drug-related changes including mucosal ulceration of the small intestine, lymphangiectasis, lymphoid hypoplasia, and plasma cell hypoplasia of the mesenteric lymph nodes, foci of hepatocytic hyperplasia, adrenal cortical atrophy and prostatitis. No increase in tumour incidence was observed.</td>
</tr>
<tr>
<td>Dog</td>
<td>3 months</td>
<td>0.5 mg/kg/day</td>
<td>Signs of toxicity were observed which were reversible. Mainly GI tract toxicity was observed at the dose level of 0.5 mg/kg/day.</td>
</tr>
</tbody>
</table>
# PERMITTED DAILY EXPOSURE FOR DICLOFENAC SODIUM

<table>
<thead>
<tr>
<th>Species</th>
<th>Period</th>
<th>Daily dose mg/kg/day P.O.</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhesus monkey</td>
<td>6 months</td>
<td>5 and 15 mg/kg/day</td>
<td>Signs of toxicity were observed which were reversible. Mainly GI tract toxicity was observed at the dose level of 5 and 15 mg/kg/day.</td>
</tr>
<tr>
<td>Baboon</td>
<td>12 months</td>
<td>0, 5, 15 (reduced to 10 on day 254) and 50 (reduced to 30 on day 38) mg/kg/day for up to 52 weeks</td>
<td>Diclofenac caused ulceration of the gastrointestinal tract. Ulceration was confined to the colon in the low-dose group but was present in the stomach and small intestine also in the other two groups. Body weights were below controls. Constipation, with occasional episodes of diarrhoea, was a marked feature. In all treated groups, there was a dose-related fall in serum albumin levels. Anaemia and an increased ESR were observed in the high-dose group. Food consumption and body-weight gains were within normal limits. Haematology parameters were comparable and serum albumin levels returned towards normal values.</td>
</tr>
</tbody>
</table>

**Table no. 2** Toxicity studies through intravenous route. (6)
## PERMITTED DAILY EXPOSURE FOR DICLOFENAC SODIUM

| Rats | 4 weeks by i.v. route with 9-week recovery period | i. One high dose (HD) (15 mg/kg/day) male died on Day 6 and 1 HD female was sacrificed on Day 18. Both deaths were associated with poor general condition and peritonitis. In HD females, observations include slight decrease in red blood cell parameters, slight increase in white blood cell count and statistically significant increase in reticulocytes in HD rats were noted (regenerative anaemia).  

ii. In HD females only, slight decreases in total protein and albumin was observed. Increased spleen weights associated with extramedullary haematopoiesis were also noted. There was increased extramedullary hemopoiesis in spleen for all doses and increase of incidence was dose dependent. However, these findings were reversible after recovery period. There were gastro-intestinal (stomach, cecum, colon, duodenum, ileum and Jejunum) histology findings (e.g., peritoneal inflammatory cell infiltration or peritonitis) in HD animals. |
### PERMITTED DAILY EXPOSURE FOR DICLOFENAC SODIUM

<table>
<thead>
<tr>
<th>Species</th>
<th>Duration/dose</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>iii. There were very mild to mild renal tubular vacuolation in low dose (LD) (3 mg/kg/day), MD (7 mg/kg/day) and HD groups. Consistent with higher systemic exposure to diclofenac, female rats appeared more sensitive than male rats to GI toxicity. Due to histopathology, organ weight and haematology findings a dose level of <strong>7 mg/kg/day was considered to be NOAEL</strong>.</td>
</tr>
</tbody>
</table>
| Cynomolgus monkeys       | 4 weeks with a 3-month recovery period Doses include 3, 15 and 60 mg/kg/day | i. Most animal at high dose (HD) produced dark feces and soft/liquid feces in the first week of dosing and a number of these also had red mucoidal material (assumed to be blood) in the feces. Some of the animals in this group appeared hunched, subdued and lethargic.  
 ii. HD animals showed reduced levels of albumin, the albumin-globulin ratio and alkaline phosphatase. Albumin levels and albumin-globulin ratios were reduced at week 4 in both sexes dosed at MD compared with control.  
 iii. In one HD female severe gastrointestinal lesions, including multifocal mucosal necrosis and submucosal edema was seen. Also, pyloric mononuclear-cell infiltrate in stomach was seen in one HD male.  
 iii. Histopathological findings in mid dose (MD) groups included mild inflammatory cell infiltration in the colon in two animals, moderate thymus atrophy in 1 male, polymorphonuclear leukocyte infiltration and ulceration of tail skin, and a very mild to mild granular appearance of the renal tubular cells in the medullary rays.  
**No-observed-adverse-effect-level (NOAEL):** 3 mg/kg/day based on the absence of toxic effects. |

### d. Carcinogenicity

Carcinogenicity studies were conducted in mice and rats. One mouse and two rat long-term carcinogenicity studies were conducted with diclofenac sodium and administered as feed mixture. There was no diclofenac sodium treatment related increase in tumor incidence up to 2 mg/kg in rats. Dose dependent increase in mortality was observed especially in females was observed at 1 and 2 mg/kg/day. Gastrointestinal ulceration and related complications were identified as the main cause of mortality. There was a positive dose-related trend with respect to adrenal medullary hyperplasia, mammary fibroadenomas and subcutaneous tissue fibromas.
in females, as well as of C-cell adenomas of the thyroid in males. The differences in the incidence between the various groups, including control, were small and were considered to reflect the variation in the spontaneous occurrence of these incidental lesions, common in old laboratory rats. In a 2-year mouse study, mice were treated with 0.1, 0.3, 1 and 2 mg/kg/day. Diclofenac sodium caused mortalities at 1 and 2 mg/kg/day particularly in males as a consequence of ulceration and/or perforation of the small intestine and therefore prevented evaluation. The known susceptibility of rodents to non-steroidal anti-inflammatory drugs, resulting in high mortality at dose levels close to the therapeutic dose, is considered to be a rodent-specific effect. Diclofenac Sodium was not carcinogenic to mice under the conditions of this study. (5).

e. Mutagenesis

Diclofenac sodium was not genotoxic in in vitro (reverse mutation in bacteria [Ames], mouse lymphoma thymidine kinase) or in in vivo (including dominant lethal and male germinal epithelial chromosomal aberration in Chinese hamster) assays (5).

f. Reproductive toxicity

Table no. 4 Reproductive toxicity studies were conducted in rats and rabbits (5).

<table>
<thead>
<tr>
<th>Animals</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>2 and 4 mg/kg/day</td>
<td>Doses when given orally to male and female rats showed no noticeable effect on fertility. Dosing was carried out during premating, mating, gestation, and lactation periods. At the higher dose, prolonged gestation and dystocia were observed. Embryotoxicity (low birth weight, failure to survive) was observed at both doses but it was minimal at 2 mg/kg/day. Postnatal survival and growth of pups from drug-treated animals showed slightly retarded growth at the higher dose.</td>
</tr>
<tr>
<td>Mice and rats</td>
<td>2, 3, 10 and 20 mg/kg/day</td>
<td>Teratology studies at oral doses of 2, 3, 10, and 20 mg/kg/day showed no teratogenic effects on foetuses. At the higher doses, pronounced gastrointestinal effects were observed in the dams and a marked toxic effect noted in foetuses (reduced birth weights and increased foetal deaths).</td>
</tr>
</tbody>
</table>
PERMITTED DAILY EXPOSURE FOR DICLOFENAC SODIUM

<table>
<thead>
<tr>
<th>Rabbits</th>
<th>5 or 10 mg/animal/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant females treated with oral doses of 5 or 10 mg/animal/day throughout the gestation period showed a dose-dependent increase in resorption rates, diminished foetus weights, and abnormal skeletal findings. Definite embryotoxicity was observed at the highest dose although there was no evidence to suggest teratogenicity.</td>
<td></td>
</tr>
</tbody>
</table>

Administration of diclofenac inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased foetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors.

g. Highly Sensitizing potential

Local tolerance –

**Primary skin irritation study in rabbits**- Drug produced a very slight erythema. It is considered non-irritating.

**Primary eye irritation study in rabbits**- Drug was found to be non-irritating.

**Phototoxicity in guinea pigs**-

**Determination of phototoxicity in albino guinea pigs**- Drug has irritating effects (erythema and edema) but lacked photo irritating potency.

**Cutaneous hypersensitivity**-

**Contact hypersensitivity in albino guinea pigs**- Drug resulted in slight irritation (4)

8. IDENTIFICATION OF CRITICAL EFFECTS

Scientific evaluation of published pharmacological and toxicological data including clinical and non-clinical reports helps to identify the adverse effect of the active substances. The critical effect of the active substance is one that meets the severity and persistence criteria at the lowest intake to define the hazard associated with the intake.

a. **Most sensitive indicator of an adverse effect seen in non-clinical toxicity data**

Gastrointestinal (GI) toxicity was reported in the animal species.

b. **Clinical therapeutic and adverse effects**
Diclofenac sodium is used to treat eye pain, redness, and swelling in patients who are recovering from cataract surgery and sensitivity to light in patients who are recovering from corneal refractive surgery. Common adverse effects of Diclofenac include burning or stinging in your eye just after you instill the drops, itchy eyes, stomach pain, vomiting, headache, dizziness, fever, chills, runny nose, swelling of the eyes or face, red or bloody eyes, eye pain, sensitivity to light, blurred or decreased vision and teary eyes (7).

9. RATIONAL FOR NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL) VALUE SELECTION

The toxicity studies of diclofenac sodium were studied in rodents and non-rodents. The rationale behind the selection of NOAEL dose of 7 mg/kg/day from 4-weeks intravenous toxicity study in rats, because rats are more sensitive to drug (NSAID).

10. APPLICATION OF ADJUSTMENT FACTORS (RATIONALE FOR THE ADJUSTMENT FACTORS)

A series of modifying or safety factors are used when NOEL is based on studies of differing types and duration in different species to provide a risk assessment for human exposure (10,11).

a. F1: interspecies difference

This factor takes into account the comparative surface area: body weight ratios for the species concerned and for man. Surface area is calculated as $S = KM^{0.67}$ where $M$ is the body mass and $K$ is constant, has been taken to be 10 according to the appendices 3 of the ICH guideline. For a 50 kg person, the equation gives a surface area of 64.3 dm$^2$; the surface area: body weight ratio is thus 2.76. The multiples of the human surface area: body weight ration gives factors for the mouse=12, rat=5, monkey=3, rabbit=2.5 and dog=2.

A factor of 5 is selected based on the selection of toxicity study of rats.

b. F2: inter-individual differences

A factor of 10 is conventionally used to allow for differences between individuals in human population.

c. F3: duration of exposure

A variable factor up to 10 is used for duration of exposure factor in the reported studies. For
reproductive studies a factor of 1 is used if the whole period of organogenesis is covered. A factor of 2 is used for a 6-month study in rodents or 3.5-year study in non-rodents. A factor 5 has been used for a 3-month study in rodents or a 2-year study in non-rodents and a factor of 10 for shorter duration studies.

A factor of 10 is used based on short term (4-weeks) toxicity study in rats.

d. **F4: nature of toxicity**

A variable factor is applied when the toxicity produced is irreversible in nature i.e. carcinogenicity, neurotoxicity or teratogenicity. A factor of 10 is used when oncogenic or neurotoxic responses are present. A variable factor is used for reproductive toxicity as follows. 1 for embryo or foetal toxicity or mortality associated with maternal toxicity; 5 for embryo or foetal toxicity or mortality without maternal toxicity; 5 for a teratogenic effect with maternal toxicity and 10 for a teratogenic effect in the absence of accompanying maternal toxicity.

A factor of 2 is selected based on the pre-clinical findings (GI toxicity).

e. **F5: quality of data**

A variable factor of 1 is applied to result in which a NOAEL has been established and the PDE being derived from a NOAEL.

A factor of 1 is used based on selection of NOAEL dose.

**PDE CALCULATION**

\[
PDE (\text{mg/day}) = \frac{\text{NOAEL (mg/day)} \times \text{Body weight (kg)}}{F_1 \times F_2 \times F_3 \times F_4 \times F_5}
\]

\[
= \frac{7 \times 50}{5 \times 10 \times 10 \times 2 \times 1} = \frac{350}{1000}
\]

\[= 0.35 \text{ mg/day}\]

**11.PK CORRECTION**

For PDE calculation, no Pharmacokinetic correction was carried out.
12. REFERENCES

   https://www.drugbank.ca/salts/DBSALT000466.


   https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022396Orig1s000PharmR.pdf

   https://medlineplus.gov/druginfo/meds/a606003.html


http://academy.gmp-compliance.org/guidemgr/files/Q3C-R7_DOCUMENT_GUIDELINE_2018_1015.PDF
ANNEXURE I: PHARMACOKINETICS

Absorption

In humans, orally-administered diclofenac sodium is rapidly and almost completely absorbed and distributed to blood, liver, and kidneys.

Distribution

Diclofenac is extensively bound (99%) to serum albumin. The apparent volume of distribution is 0.2 to 0.17 L/kg. Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother.

Metabolism

Diclofenac undergoes single and multiple hydroxylation and methoxylation, producing 3', 4', 5-hydroxy, 4'-5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac. These phenolic metabolites are largely inactive, and (along with the parent compound) are mostly converted to glucuronide conjugates.

Elimination

Plasma clearance of diclofenac is 263 ±56 mL/min. The mean terminal drug half-life in plasma is 1.8 hours after oral doses. In humans about 60% of the drug and its metabolites are eliminated in the urine and the balance through bile in the feces. More than 90% of an oral dose is accounted for in elimination products within 72 hours. About 1% of an oral dose is excreted unchanged in urine.
ANNEXURE II: GLOSSARY

ADI/ADE: Acceptable daily intake/ Acceptable daily exposure

AUC: Area under the curve

GRAS: Generally regarded as safe

GLP: Good laboratory practice

GMP: Good manufacturing practice

LD: Lethal dose

LED: Lowest-effective dose

TDLo (Toxic Dose Low): Lowest published toxic dose

LOAEL: Lowest-observed-adverse-effect level

LOEL: Lowest-observed-effect level

MSDS: Material safety data sheet

MTD: Maximum tolerable dose

MPDD: Maximum permissible daily dose

MTEL: Maximum tolerable exposure level

NEL: No-effect level

NOAEL: No-observed-adverse-effect level

NOEL: No-observed-effect level

OEL: Occupational exposure limit

QSAR: Quantitative structure–activity relationship

SDS: Safety data sheet

ADI: Acceptable daily intake. Estimate by JECFA; the amount of a food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk.

Area under the curve (AUC): Area between a curve and the abscissa (horizontal axis), i.e., the area underneath the graph of a function; often, the area under the tissue (plasma) concentration curve of a substance expressed as a function of time.
**Bioaccumulation**: progressive increase in the amount of a substance in an organism or part of an organism that occurs because the rate of intake exceeds the organism’s ability to remove the substance from the body.

**Bioavailability**: biological and physiological availability. Extent of absorption of a substance by a living organism compared to a standard system.

**Biological half-life**: for a substance, the time required for the amount of that substance in a biological system to be reduced to one-half of its value by biological processes, when the rate of removal is approximately exponential.

**Carcinogen**: agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer.

**Clastogen**: agent causing chromosome breakage and (or) consequent gain, loss, or rearrangement of pieces of chromosomes.

**Clearance**: volume of blood or plasma or mass of an organ effectively cleared of a substance by elimination (metabolism and excretion) divided by time of elimination.

**Cmax**: used in pharmacokinetics referring to the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area after the drug has been administered and before the administration of a second dose.

**Critical dose**: dose of a substance at and above which adverse functional changes, reversible or irreversible, occur in a cell or an organ.

**Critical effect**: for deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ:

Adverse effects with no defined threshold concentration are regarded as critical. Dose (of a substance): total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue.

**Draize test**: evaluation of materials for their potential to cause dermal or ocular irritation and corrosion following local exposure; generally using the rabbit model (almost exclusively the New Zealand White) although other animal species have been used.

**Elimination (in toxicology)**: disappearance of a substance from an organism or a part thereof, by processes of metabolism, secretion, or excretion.
**Embryotoxicity:** production by a substance of toxic effects in progeny in the first period of pregnancy between conception and the fetal stage.

**Fetotoxicity:** production by a substance of toxic effects in progeny in the second period of pregnancy between fetal stage and delivery.

**First-pass effect:** biotransformation and, in some cases, elimination of a substance in the liver after absorption from the intestine and before it reaches the systemic circulation.

**Gavage:** administration of materials directly into the stomach by esophageal intubation.

**Generally regarded as safe (GRAS):** phrase used to describe the USFDA philosophy that justifies approval of food additives that may not meet the usual test criteria for safety but have been used extensively and have not demonstrated that they cause any harm to consumers.

**Genotoxic:** capable of causing a change to the structure of the genome.

**Good laboratory practice (GLP) principles:** fundamental rules incorporated in OECD guidelines and national regulations concerned with the process of effective organization and the conditions under which laboratory studies are properly planned, performed, monitored, recorded, and reported.

**Good manufacturing practice (GMP) principles:** fundamental rules incorporated in national regulations concerned with the process of effective organization of production and ensuring standards of defined quality at all stages of production, distribution, and marketing.

**Hazard identification:** determination of substances of concern, their adverse effects, target populations, and conditions of exposure, taking into account toxicity data and knowledge of effects on human health, other organisms, and their environment.

**Hypersensitivity:** state in which an individual reacts with allergic effects following exposure to a certain substance (allergen) after having been exposed previously to the same substance.

**In silico:** phrase applied to data generated and analyzed using computer modeling and information technology.

**In vitro:** in glass, referring to a study in the laboratory usually involving isolated organ, tissue, cell, or biochemical systems.

**In vivo:** In the living body, referring to a study performed on a living organism.
Lethal dose (LD): amount of a substance or physical agent (e.g., radiation) that causes death when taken into the body.

Lowest-effective dose (LED): lowest dose of a chemical inducing a specified effect in a specified fraction of exposed individuals.

Lowest published toxic dose (Toxic Dose Low, TDLo): the lowest dosage per unit of bodyweight (typically stated in milligrams per kilogram) of a substance known to have produced signs of toxicity in a particular animal species.

Lowest-observed-adverse-effect level (LOAEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

Lowest-observed-effect level (LOEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.


Maximum permissible daily dose (MPDD): maximum daily dose of substance whose penetration into a human body during a lifetime will not cause diseases or health hazards that can be detected by current investigation methods and will not adversely affect future generations.

Maximum tolerable dose (MTD): highest amount of a substance that, when introduced into the body, does not kill test animals (denoted by LD0).

Maximum tolerable exposure level (MTEL): maximum amount (dose) or concentration of a substance to which an organism can be exposed without leading to an adverse effect after prolonged exposure time. Maximum tolerated dose (MTD): high dose used in chronic toxicity testing that is expected on the basis of an adequate sub-chronic study to produce limited toxicity when administered for the duration of the test period.
Median lethal dose (LD50): statistically derived median dose of a chemical or physical agent (radiation) expected to kill 50% of organisms in a given population under a defined set of conditions.

Mutagenicity: ability of a physical, chemical, or biological agent to induce (or generate) heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof).

No-effect level (NEL): maximum dose (of a substance) that produces no detectable changes under defined conditions of exposure.

No-observed-adverse-effect level (NOAEL): greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

No-observed-effect level (NOEL): greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Quantitative structure–activity relationship (QSAR): quantitative structure–biological activity model derived using regression analysis and containing as parameters physicochemical constants, indicator variables, or theoretically calculated values.

Safety data sheet (SDS): single page giving toxicological and other safety advice, usually associated with a particular preparation, substance, or process.

Target (in biology): any organism, organ, tissue, cell or cell constituent that is subject to the action of an agent.

Temporary acceptable daily intake: value for the acceptable daily intake proposed for guidance when data are sufficient to conclude that use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. Note: A higher-than-normal safety factor is used when establishing a temporary ADI and an expiration date is established by which time appropriate data to resolve the safety issue should be available.