

HOMEOPATHIC MEDICINAL PRODUCT WORKING GROUP
(HMPWG)

PREAMBLE
TO THE 1ST LIST OF FIRST SAFE DILUTIONS (FSD)

DISCUSSION IN THE FSD-SUBGROUP	23 - 24 February 2016
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PREAMBLE

The Homeopathic Medicinal Products Working Group (HMPWG) has decided to develop the process of establishing First Safe Dilutions (FSD) and to facilitate the input of data from Member States with national experience. Consequently, a first “List of First Safe Dilutions” has been established based on evaluation of data from Member States. The list is based on the document “Structure of the List of First Safe Dilutions”. The assessment of the homeopathic stocks to establish a FSD follows the standards as elaborated in the documents “Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin” (PtC) and “Questions and Answers on First Safe Dilutions”.

This list is intended as a recommendation to be taken into account by competent authorities of the Member States and applicants. It is a living document. Each entry is based on the current literature available in the public domain. When new relevant and scientifically justifiable information for an entry of the list is available, a re-assessment of this entry could be possible. HMPWG will decide about adequate time-lines for re-assessment. All interested parties are hereby invited to submit data to elaborate this list further.

The FSDs are only valid for triturations or dilutions for oral preparations.¹

The “List of First Safe Dilutions” comprises:

- Stock/raw/starting material: name of the stock; if the stock has a monograph in the European Pharmacopoeia or in a pharmacopoeia officially used in the Member States, the official title of this monograph is used by reference to the Pharmacopoeia where it is published.
- Method of Preparation:
 - manufacturing method of the European Pharmacopoeia or a pharmacopoeia currently used officially in the Member States
 - or
 - possible monograph-specific preparation
- Toxic component concentration: component on which the calculation of FSD is based
 - toxicologically relevant component of the raw material, provided that:
 - the toxicological component can be quantified (e.g. chemicals) or
 - an upper content threshold is specified in a pharmacopoeial monograph or
 - the information is taken from an official regulatory authority document (e.g. HMPC assessment reports) .
 - whole starting material in cases where the relevant toxicological principle is not known or an upper limit is not defined in a pharmacopoeial monograph
- Basis for FSD: approach that was chosen to derive the FSD based on the decision tree (Annex 1 of the PtC)²

¹ For other pharmaceutical dosage forms submitted under article 14 of the Directive 2001/83/EC, the recalculation is explained in the PtC. For submission under article 16 of the Directive, the FSD could act as a starting point for the safety assessment. For this type of submission both the degree of the dilution of each stock in the finished product and the posology of the product should be considered.

- Acceptable amount: the acceptable amount per day, which is safe for all age- and patient-groups; its derivation is based on the entry in the column "Basis for FSD" and data provided by the cited reference in the column "Reference"
- Reference: source of data which are relevant for calculating the acceptable amount
- Calculation method: the calculation of the potency with reference to the value listed in the column "Acceptable amount"
- FSD: the potency deemed safe for all age- and patient-groups, when 10 g of a homeopathic preparation in this potency is administered orally
- Remarks: any remarks relevant for the understanding of the FSD

² E. g.: If the assessment is conducted via PDE route, this means that according to the available data, neither any valid information has been found to establish an ADI (food), nor an LHRD, nor that the (phyto)chemical characterisation is available to establish a TTC.

Abbreviations mentioned in the List of FSD table

- ADI: Acceptable Daily Intake (FDA)
- AI: Adequate Intake
- ATSDR: Agency for Toxic Substances and Disease Registry
- BAT: occupational toxicology (Biologische Arbeitsstoff- Toleranz)
- BfR (DE): Bundesinstitut für Risikobewertung, www.bfr.bund.de
- CCRIS: Chemical Carcinogenesis Research Information System, CCRIS - Toxnet – NIH
- COT: Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- CPDB: Carcinogenic Potency Database, <http://potency.berkeley.edu/index.html>
- CPSC: U.S. Consumer Product Safety Commission, <http://www.cpsc.gov/library/library.html>
- CCRIS: Chemical Carcinogenesis Research Information System
- DART / ETIC: Developmental & Reproductive Toxicology / Environmental Teratology Information Centre
- EAFUS: Everything Added to Food in the United States
<http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?filter=977088-41-7&sortColumn=&rpt=eafusListing>
- ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals,
<http://www.ecetoc.org/publications>
- EDI: estimated daily intake
- EED: estimated exposure dose
- EFSA: European Food Safety Authority, EFSA Comprehensive European Food Consumption Database
- EMBASE: Excerpta Medica Database
- EPA: Environmental Protection Agency, U.S. EPA-OPP List of Chemicals Evaluated for Carcinogenic Potential
- ERNA: European Responsible Nutrition Alliance
- ESCOP: <http://www.escop.com/>
- FAO: see JECFA
- FSD: First Safe Dilution
- GRAS: Generally recognized as safe
- HAB: German Homoeopathic Pharmacopoeia
- HMPWG: Homeopathic Medicinal Product Working Group
- HMP: Homeopathic Medicinal Product
- HMPC: Committee on Herbal Medicinal Products
- JECFA (FAO/WHO): Joint FAO/WHO Expert Committee on Food Additives, FAO Food and Agriculture Organisation of the UN
- IARC: International Agency for Research on Cancer
- ICH: International Conference on Harmonisation
- ILSI: International Life Sciences Institute; Europe Concise Monographs,
<http://www.ilsilife.org/Europe/Pages/ConciseMonographSeries.aspx>
- IPCS: International Programme on Chemical Safety, Chemical Safety Information from Intergovernmental Organizations
- IRIS: EPA's Integrated Risk Information System
- LC50: median lethal concentration

- LD50: median lethal dose
- LC100: absolute lethal concentration
- LD100: absolute lethal dose
- LHRD: Lowest Human Recommended Dose
- LOEL: Lowest Observable Effect Level
- LOAEL: Lowest Observable Adverse Effect Level
- MAK: occupational toxicology (Maximale Arbeitsplatz Konzentration)
- MT: mother tincture
- MTC: maximum tolerable concentration
- MTD: maximum tolerated dose
- MCL: Maximum Contaminant Level
- MRL: Minimal Risk Level (ATSDR, for chronic oral exposure)
- MRL: Maximum Residue Limit for pesticide residues
- NOAEL: no observed adverse effect level
- NOEL: No Observable Effect Level
- NRC: National Research Council
- NTP: National Toxicology Program, U.S. National Toxicology Program (NTP) Carcinogen List; reports, evaluations (ranking and designation, allocation to categories); for NTP Reports <http://ntpsearch.niehs.nih.gov/index.html?col=010stat>
- OSHA: Occupational Safety and Health Administration; List of Hazardous Chemicals, List of Highly Hazardous Chemicals, Toxics and Reactives, <http://www.osha.gov>
- PDE: Permitted Daily Exposure
- Ph. Eur.: European Pharmacopoeia
- Ph. Franç.: Pharmacopée française
- PMTD: Provisional Maximum Tolerable Daily Intake
- POD: point of departure
- PubMed (a service of the National Library of Medicine and the National Institutes of Health)
- PTWI: Provisional tolerable weekly Intake
- RDA: Recommended Dietary Allowance
- RfD: Reference Dose (EPA)
- RIVM: Rijksinstituut voor Volksgezondheid en Milieu; National Institute of Public Health and the Environment of the Netherlands
- RTECS: Registry of Toxic Effects of Chemical Substances
- SCF: Scientific Committee on Food
- TADI: temporary acceptable daily intake
- TTC: Threshold of toxicological concern
- TDI: Tolerable Daily Intake (WHO)
- Toxline/Toxnet, <http://toxnet.nlm.nih.gov/>; including: HSDB - Hazardous Substances Data Bank, IRIS - Integrated Risk Information System, ITER - International Toxicity Estimates for Risk, GENE-TOX - Genetic Toxicology (Mutagenicity), CCRIS - Chemical Carcinogenesis Research Information System, TOXLINE - Toxicology Bibliographic Information, TRI - Toxics Release Inventory
- UF: uncertainty factors
- UL: Tolerable Upper Intake Level
- WHO: World Health Organization