
Most of the maximum recommended daily dose (MRDD) values in the database were determined from pharmaceutical clinical trials that employed an oral route of exposure and daily treatments, usually for 3-12 months. The pharmaceuticals were given as single or divided dose treatment regimens to achieve desired pharmacological effects. In contrast, roughly 5% of the pharmaceuticals in the FDAMDD database were antineoplastics and anesthetics and were administered intravenously and/or intramuscularly.

When separate MRDDs were reported for different routes of exposure, only the oral MRDD was included in the database. In addition, some pharmaceuticals have different MRDD values for male and female adults, children, or elderly patients. In this situation, only MRDD values for the average adult patient were used. Pharmaceuticals that are administered orally are usually tested over a limited range of doses and have MRDDs reported as mg/day. The mg/day unit was converted to mg/kg-body weight (bw)/day based upon an average adult weighing 60 kg. In
contrast, the dose unit for most antineoplastic drug MRDDs is reported as mg/m2, which was converted to mg/kg-bw/day using the formula mg/kg-bw/day = mg/m2/37 for an average adult. Additionally, a few drugs had MRDDs reported in parts per million (ppm), which were converted to mg/kg-bw/day on the basis that 1000 ppm equals 25 mg/kg-bw/day for an average 60 kg adult. MRDD values for the over 1200 chemicals in this dataset range from 0.00001 to 1000 mg/kg-bw/day.

Some classes of chemicals were excluded from the FDAMDD database due to their unsuitability for most QSAR modeling programs. These were inorganic chemicals, high molecular weight polymers (>5000 Daltons), fibers, salts, mixtures of organic chemicals, and small molecules (<100 Daltons). FDAMDD is the non-proprietary portion of the database that was used in the QSAR analysis.

The DSSTox FDAMDD database is an enhanced and modified version of the original FDA Source MRDD database posted on the FDA Source Website, the latter of which included 3 fields: Generic Chemical Name, MRTD (mg/kg-bw/day), and SMILES code. Although labeled as "maximum recommended therapeutic dose" (MRTD) in the original study, the term "maximum recommended daily dose (MRDD)" was indicated by the Source authors (private communication) to provide a more precise and accurate description. In addition to providing a STRUCTURE field for a specified pharmaceutical, DSSTox FDAMDD includes a STRUCTURE_CASRN registry number for all displayed structures. Additional CASRN are provided along with a brief description of the pharmaceutical derivative for over 900 entries in the Note_FDAMDD field. FDAMDD also includes Merck therapeutic categories (The Merck Index, 12th ed., Merck & Co., Inc.), TherapeuticCategory, for nearly all data records along with the original Source Dose_MRDD_mg activity values. DSSTox FDAMDD has 16 fewer records than the original MRDD Source database due to consolidation of partial structures (i.e., complexed entities) into a single record and elimination of duplicate entries. DSSTox FDAMDD also differs from the MRDD Source database in presenting complete structural information pertaining to the actual salt or complexed form corresponding to the listed TestSubstance_ChemicalName and TestSubstance_CASRN. According to the Source authors, there are a number of cases where multiple related forms or derivatives of a drug were listed as separate records but were assumed to fall under the same clinical toxicity assessment and, therefore, assigned the same Dose_MRDD_mg.
Several features of DSSTox FDAMDD have the potential to impact on SAR analysis and should be taken into account in any future use of these data. Most prominent among these is the imprecise nature of the reported MRDD value, both in terms of the wide range of adverse or toxic effects that would be considered in assigning the MRDD, and in terms of the ambiguous chemical structure association with this dose measure. In DSSTox FDAMDD and the corresponding Source FDA MRDD database, there are several cases where a single Dose_MRDD_mg value is assigned to multiple related structural derivatives of a pharmaceutical, i.e., the same activity is assigned to multiple Structure/CASRN records in the database. In theory, an MRDD value will reflect the lowest dose of a drug producing adverse effects but for the FDA MRDD database this value has been derived from pooled clinical reports where more than one form of a drug may have been administered. When MRDD mg mass units are converted to mmol units
for SAR analysis, a single

Dose_MRDD_mg

is converted to a range of mmol doses, taking into account the different molecular weights of the various drug derivatives. Assuming that these various drug derivatives have similar or equal molar potencies, the reported

Dose_MRDD_mg

could be presumed to reflect the dose of the smallest

STRUCTURE_MolecularWeight
derivative that would register as the highest molar content and, therefore, most potent for a given mass dose.

This variation in MRDD mmol doses for derivatives within a drug family (with the same reported MRDD mg) should be considered an additional source of imprecision and variability in the MRDD measure. The categorical activity, ActivityCategory_MCASE_mg, based on the mass measure,

Dose_MRDD_mg

and used in the Main Citation study is also impacted by these considerations and, therefore, cannot be directly compared to the FDAMDD categorical activity ( ActivityCategory_MRDD_mmol ), which is based on the molar measure,

Dose_MRDD_mmol

.

The original MRDD database was designed and used by the Main Citation authors to construct MCASE toxicity prediction models (MCASE, Inc.). MCASE does not process complexed structures or salts, and its objective is to identify significant associations of activity with chemical structure fragments. Hence, the Main Citation authors in some cases assigned MRDD values to partial structures in separate records, and in other cases where multiple isomers or derivatives were known to exist, these were assigned identical MRDD values. In many other cases, only a single derivative of a known family of drugs is represented in the database. The implication for MCASE study, or any type of fragment-based SAR analysis, is that some drug frameworks (i.e., parent structures) will be more or less heavily weighted within the database depending on the number of structurally related derivatives represented. Our listing of additional CAS numbers (in TestSubstance_CASRN_Other and ChemicalNote) provides a user with an approximate sense for the number of derivatives that may exist. Converting the Source FDA MRDD database to the DSSTox FDAMDD, we consolidated records for complexes that had been split, but otherwise we mirrored the Source database, i.e., we did not collapse multiple derivative drug listings to a single record, nor did we expand a drug listing to multiple records when multiple derivative CAS numbers were known. The

ChemClass_MRDD_grouping

and

ChemicalReplicateCount
fields in FDAMDD have been added to aid in the identification of cases where multiple derivatives sharing the same

**Dose MRDD mg**

are listed as separate records within the database.

*Get the full article and download the database (Updated version: FDAMDD_v3b_1216_15Feb2008)*

[here](http://www.epa.gov/ncct/dsstox/sdf_fdamdd.html)