DSSTox Log File:

FDA Maximum (Recommended) Daily Dose Database (FDAMDD)

(last updated 15 February 2008)

Description: Information in this file documents the creation, review, and update process for the DSSTox FDAMDD SDF files and provides summary information on database contents. The first section summarizes the process used for creating the initial DSSTox SDF file and the quality assurance checks and procedures employed. A table providing field and data counts offers summary overview of FDAMDD file contents and chemical composition. The Log Table documents modifications and revisions to the database content or format in version updates. To obtain the most current version of this Log File and a record of any new modifications, a user should periodically consult the DSSTox FDAMDD database page: http://www.epa.gov/ncct/dsstox/sdf_fdamdd.html.

QA and Development Notes for v1a:
FDAMDD SDF file underwent an extensive series of quality review checks prior to publication of initial launch version. The original FDA MRDD database was obtained from the Source website (http://www.fda.gov/cder/Offices/OPS_IO/MRTD.htm), imported into Excel, and was used for cross-referencing and checking of all modified and added fields. We particularly thank Edwin Matthews, Daniel Benz, and Naomi Kruhlak for invaluable assistance in various stages of development and quality review, clarifying numerous issues pertaining to the experimental data and their representation in the original database, and approving changes to field names and contents. Chemical structures were initially obtained by conversion of the FDA Source-provided SMILES codes using CambridgeSoft ChemDraw (ver 8.0 for Windows) for MS Excel. An additional field containing CAS registry numbers was contributed to this effort by the FDA Source collaborators. However, CAS were not provided for all listed chemicals and, in many cases, multiple CAS were provided for single structure records in the original Source database. For the latter, the CAS corresponding to the main SMILES structure was often not apparent since additional CAS often corresponded to salt and complexed forms or different stereoisomer forms of the listed pharmaceutical. Hence, considerable additional effort was invested in the verification, review, and addition of CAS registry numbers to the DSSTox FDAMDD database.

Four sources of CAS registry numbers (CASRN) corresponding to chemical structures were used extensively in the checking of chemical structures and CASRN, identification of missing CASRNs, and identification of derivative forms of structures corresponding to alternate CASRN listed within a structure entry. The ChemFinder website (http://chemfinder.cambridgesoft.com/) and National Library of Medicine's ChemID website (http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp) were the two main public on-line resources used extensively for checking CASRN to structures. Another major resource employed was the Merck Index, 12th Ed. (and Merck Index, 13th Ed., electronic database in CambridgeSoft ChemOffice Ultra 8.0). In addition, therapeutic catories (**Therap_Cat**) were obtained primarily from the Merck Index sources, and secondarily from ACD Labs ChemSketch Dictionary (ver. 8.0) and the on-line literature. In addition, ACD Labs ChemSketch Dictionary (ver. 8.0) was the primary source of structures and corresponding SMILES for all main FDAMDD entries containing stereochemical features (**ChemNote =** "stereochem"). A number of errors (over 80) were found in the original Source FDA MRDD database listing of SMILES, not including the more than 75 cases where we modified Source SMILES to the salt or complex tested form for the main DSSTox FDAMDD. Wherever possible these corrections or changes were verified by more than a single outside CAS/Structure source, all changes were documented and the listing provided to the FDA Source collaborators.

IUPAC systematic chemical names, **ChemName_IUPAC**, were computed by Marc Nicklaus (NCI) using the ACD Labs IUPAC Name-Generation software (ACD/NameBatch, version 8.05). **INChI** codes were automatically generated from the final DSSTox SDF using a pre-release version of the publicly available program, wINChI11b.exe, accessible from the NIST INChI developers (http://chemdata.nist.gov/IChI/INChIv11b.zip).

A total of 15 records were deleted in migrating the original Source-provided FDA MRDD database (1233 records as of 20May04) to the DSSTox FDAMDD (1217 final records in version 1a). These 15 records are listed in a table below along with the original FDA Source SMILES, the problem with the record, and the action taken in creating the initial launch version of the DSSTox FDAMDD.

All records in the DSSTox FDAMDD SDF file are "defined organics" (i.e., no inorganics or organometallics). A file in which all salts and complexes are simplified to the parent structure can be generated easily using commercial and publicly available tools from the information provided in the DSSTox FDAMDD SDF file.

Notes for v2a,b:
Revised DSSTox Standard Chemical Fields are included (see http://www.epa.gov/ncct/dsstox/MoreonStandardChemFields.html) along with updated InChI codes (version 1.0), recomputed IUPAC chemical names (ACDLabs ACD/Name, version 8.0), and many regenerated 2D structures with stereochemistry of steroidal compounds rendered in more standardized form. Additionally, an extensive quality review of all DSSTox chemical records was performed, resulting in numerous corrections and modifications to chemical structures and added information (CASRN, representative structures for mixtures, etc) throughout DSSTox data files. For more information on current review procedures, see http://www.epa.gov/ncct/dsstox/ChemicalInfQAProcedures.html

Notes for v3a:
FDAMDD_v3 has one fewer chemical records (diuron), a few activity changes, and minor QA corrections, field entry revisions, field changes, added CASRN, etc. Changes to DSSTox Standard Chemical Fields include new ID fields: **DSSTox_RID**, **DSSTox_Generic_SID** and **DSSTox_FileID** (replacing **DSSTox_SID** and **DSSTox_ID_FileName**) (see http://www.epa.gov/ncct/dsstox/MoreonStandardChemFields.html). All FDAMDD-specific information has been removed from the standard **ChemicalNote** field and moved to the new **Note_FDAMDD** field (replaces **ToxicityNote**). Contents of **TestSubstance_CASRN_Other** and **TestSubstance_ChemicalName_Other** fields have been moved to the Source-specific **Note_FDAMDD** field and these two fields are discontinued as DSSTox Standard Chemical Fields. In addition, the **ChemicalReplicateCount** field only occurs in FDAMDD and, therefore, has been reclassified as a Source-specific field.

Notes for v3b:
FDAMDD_v3b includes minor structure changes/modifications (stereochemistry) and two new summary activity fields for use in PubChem and structure-activity relationship studies: **ActivityOutcome_FDAMDD** (entries of active, inactive, or inconclusive) and **ActivityScore_FDAMDD** (INTEGER[0-100]). In addition, the new **STRUCTURE_InChIKey** field (25 character abbreviated InChI for use in structure-indexing applications) has been added as a DSSTox Standard Chemical Field to all DSSTox files

Log of SDF Modifications and Version/revision updates:

Date	DSSTox SDF File Names	Modifications from previous version	Additional Notes
1Mar05	FDAMDD_v1a_1217_1Mar05	Initial launch publication; no previous published versions.	FDAMDD is considered a "static" historical database, although further alterations or expansion of the database is possible. Future updates will primarily correct reported errors provided by users or incorporate DSSTox format changes.
10Apr2006	FDAMDD_v2b_1217_10Apr2006	Updated with new DSSTox Standard Chemical Fields and entries (*revised Aug 2005*). Updated InChI codes (version 1.0). Updated IUPAC chemical names (ACDLabs Name to Structure,	Numerous structure modifications and changes in stereochemical rendering throughout DSSTox data files following major quality review.

		version 8.0). Expanded “ddmmmyear” format for dates in DSSTox file names (e.g., 15Dec2005). Modified Source-related field names: **TherapeuticCategory** **ChemClass_MRDD_grouping** **ActivityCategory_MRDD_mmol** **ActivityCategory_MCASE_mg** Deleted field **SMILES_Parent_nostereo**	FDAMDD_v2a_1217_22Oct2005: Note: earlier version of this file was provided to PubChem, with identical format to v2b but latter has undergone additional QA review and has small number of corrections/modifications.
25Jul2007	FDAMDD_v3a_1216_25Jul2007	**Record Deleted** for diuron [330-54-1], formerly DSSTox_ID=418 **Dose_MRDD_mg** activity and related fields corrected for: #18 Adenine [(changed from 0.5 to 15) **TestSubstance_CASRN** changed for DSSTox_FileIDs: #164 from retired to current CAS #602 from retired to current CAS #595 from alternate (possibly retired) CAS to current CAS common to other DSSTox files #1083 to correspond to Chemical Name **STRUCTURE** was changed for DSStox_FileIDs: #95 Azapropazone dihydrate (Chemical name changed to dihydrate – known drug form, same CAS as previously listed) #1083 Sulfonamide CS61 (error reported by Source, old CAS 63-74-1 changed to 1230-33-7, **STRUCTURE** corrected) Revised Standard Fields: **DSSTox_SID** has been replaced by two new ID fields **DSSTox_RID** and **DSSTox_Generic_SID**. **DSSTox_ID_FileName** has been replaced by new ID field: **DSSTox_FileID**. Entries in **TestSubstance_Description** field have been simplified. Entries in **ChemicalNote** that pertained specifically to FDAMDD have been moved to Source-Specific field: **Note_FDAMDD** Deleted fields **TestSubstance_ChemicalName** and **TestSubstance_CASRN_Other** and moved contents to **Note_FDAMDD** **Endpoint** entry changed from “MRDD” to “Maximum Recommended Daily Dose”	

15Feb2008	FDAMDD_v3b_1216_15Feb2008	70 structures were modified: 7 of the modifications resulted in molecular weight changes but no change in ActivityCategory; 8 CASRN were changed- CASRN RID's 23091 and 23092 were swapped. CASRN RID 23158 was changed to CASRN for stereospecific compound CASRN RID 22995 was changed from deleted CASRN CASRN RID 23294 was changed from CASRN for 3-O-methyl to 4-O-methyl CASRN RID 23358 was changed from CASRN for a mixture of neomycins to specific neomycin CASRN RID 23393 was changed from deleted CASRN CASRN RID 23590 was changed to sterospecific CASRN New Standard Field added: **STRUCTURE_InChIKey** Two new summary activity fields added in coordination with PubChem deposits: **ActivityOutcome_FDAMDD** **ActivityScore_FDAMDD**	All corrections or changes to structure information noted in **Note_FDAMDD** field, searchable by version (e.g., v3b).

Field and Data Counts in Older Versions of DSSTox FDAMDD SDF File:

DSSTox SDF	Standard Chemical Fields	Standard Toxicity Fields	Source-specific fields	Chemical records total	STRUCTURE_ ChemicalType:	STRUCTURE_TestedForm_ DefinedOrganic:		
					Defined organic	Parent	Salt	Complex
FDAMDD_v1	20	3	8	1217*	1217	1137	58	22

* One pair of replicate parent structures (Bephenium), and two pairs of replicate CAS (Iophendylate, m and o and Iodinated Glycerol A and B) exist in the database.

FDAMDD SDF Content*	Totals_v2b	Totals_v3a	Totals_v3b

# Records	1217	1216	1216
DSSTox Standard Chemical Fields	20	18	19
DSSTox Standard Toxicity Fields	3	3	3
FDAMDD Source Fields	8	10	10
Total # Fields	31	31	32
Chemical Content	**Counts_v2b**	**Counts_v3a**	**Counts_v3b**
STRUCTURE_ChemicalType:			
defined organic	1217	1216	1216
inorganic	0	0	0
organometallic	0	0	0
no structure	0	0	0
STRUCTURE_TestedForm_DefinedOrganic:			
parent	1136	1133	1131
complex	24	26	27
salt	57	57	58
salt complex	0	0	0
TestSubstance_Description:			
single chemical compound	0	1215	1215
defined mixture or formulation	1216	* (NA)	* (NA)
undefined mixture	0	* (NA)	* (NA)
macromolecule	1	1	1
mixture or formulation	* (NA)	0	0

** (NA) = field entry not applicable for DSSTox file version indicated*

Records Deleted from FDA Source MRDD Database (20May04) to create DSSTox FDAMDD_v1a:

Source Chemical Name	Source SMILES	Reason for deletion of record	Action

Acetyldigitoxin	C1C(O)CC2C(C)(C1)C3C(CC2)C5(O)C(C)(CC3)C(C4=CC(=O)OC4)CC5, C1(C)C(O)C(O)CC(O)O1	Original Source database listed two records with this ChemName, each containing only a portion of the full structure SMILES.	List full structure in single record of FDAMDD.
Carbinoxamine	C2=CC=C(C(OCCN(C)C)C1=CC=C(Cl)C=C1)N=C2, S(=O)(=O)(OS(=O)(=O)OC1=CC=CC=C1)OC2=CC=CC=C2	Original Source database listed two records with this ChemName, the first Carbinoxamine and the second resembling besylate. No CAS or Merck entry located for any form resembling source SMILES complex; CAS provided by source was for maleate complex.	List parent form in FDAMDD with correct CAS.
Cisatracurium (2 records deleted)	C1(OC)=C(OC)C=C6C(=C1)CC[N+](C)(CCC(=O)OCCCCCCOC(=O)CC[N+]3(C)C(CC2=CC=C(OC)C(OC)=C2)C4=C(CC3)C=C(OC)C(OC)=C4)C6CC5=CC(OC)=C(OC)C=C5, C1=CC=CC=C1S(O)(=O)=O	Original Source database listed two records with this ChemName, the first Cisatracurium and the second a partial representation of besylate. Atracurium is same chemical as Cisatracurium, but incorrect structure SMILES was listed in original Source database (extra CH3).	Delete both Cisatracurium records and replace Atracurium parent with besylate complex form in FDAMDD.
Deanol aceglumate	C(C)(=O)NC(CCC(O)=O)C(=O)O	Source indicated that **Dose_MRDD_mg** dose value corresponds exclusively to Deanol listing.	Delete record.
Dichloralphenazone	C(Cl)(Cl)(Cl)C(O)O, C2=CC=CC(N1C(=O)C=C(C)N1C)=C2	Original Source database listed two records with this ChemName, the first entry corresponding to single chloral entity, the second to phenazone portion.	List as single record in complex form with 2 chlorals.
Difluoromethylornithine, alpha-	NCCCC(N)(C(O)O)C(F)F	Structure appears incorrect and no CAS provided by Source; name is synonym for Eflornithine, which is listed as separate record.	Delete record as duplicate of Eflornithine.
Diminazenediaceturate	OC(=O)CNC(C)=O, C2(C(=N)N)=CC=C(NN=NC1=CC=C(C(N)=N)C=C1)C=C2	Original Source database listed two records with this ChemName, the first the diaceturate moiety and the second the parent diminazene.	List as single record in complex form.
Homatropine	C3=CC=CC(C(O)C(=O)OC1CC2N(C)C(C1)CC2)=C3	Source indicated that **Dose_MRDD_mg** dose value corresponds exclusively to Homatropine, dl methylbromide listing.	Delete record.
Mebrobamate	NC(=O)OCC(C)(CCC)COC(N)=O	Name appears incorrect and no CAS provided by Source. Also, Source SMILES only slightly different from SMILES for Meprobamate record; latter is presumed correct.	Delete record for Mebrobamate.
Methyclothiazide	C1(S(=O)(=O)N)=C(C)C=C2C(=C1)S(O)(O)N(C)C(CCl)N2	Structure from Source SMILES appears incorrect; correct structure but incorrect name listed for Metychlothiazide record.	Delete record for Methyclothiazide and correct name in Metychlothiazide record (to Methyclothiazide).

Phenylsemicarbazide, 1-	NC(NNC1=CC=CC=C1)=O	Original Source database listed wrong structure for this name; structure the same as for Phenicarbazide.	Delete record.
Pyruvinium Pamoate	C3(C(O)=O)=CC4C(C(CC1C(O)=C(C(=O)O)C=C2C=1C=CC=C2)=C3O)=CC=CC=4	Original Source database listed two records with this ChemName, the first the neutral Pamoate moiety and the second the parent Pyruvinium.	List as single record in complex form.
Sulbactam, t-butanoic acid	C1C(=O)N2C1S(=O)(=O)C(C)(C)C2C(=O)OCOC(=O)C(C)(C)C	Source indicated that **Dose_MRDD_mg** dose value corresponds exclusively to Sulbactam listing.	Delete record.
Thioquanine	N1C(N)=NC2=C(C1=S)NC=N2	Name appears incorrect and no CAS provided by Source. Structure is tautomeric form of Thioguanine listed as separate record.	Delete record for Thioquanine.
Tribromoethanol, 1,2,2	C(Br)(Br)C(O)Br	Source indicated that **Dose_MRDD_mg** dose value corresponds exclusively to Tribromoethanol, 2,2,2 listing.	Delete record.