

DSSTox Field Definition File:

EPA Estrogen Receptor Ki Binding Study (*Laws et al.*) (KIERBL) Database File

(last updated 17 February 2009)

Description: Information in this file is intended to provide a minimum level of annotation to the DSSTox SDF (Structure Data Format) file created for the EPA Estrogen Receptor Ki Binding Study (*Laws et al.*) (KIERBL) Database File. For further explanation of Source-specific fields and background pertaining to the content of this database, a user is encouraged to consult the Main Citation below. Additional information is provided on the DSSTox KIERBL SDF Download Page http://www.epa.gov/ncct/dsstox/sdf_kierbl.html. The DSSTox KIERBL data file contents approximately correspond to columns in Table 1 published in the Main Citation (*Laws et al.*, 2006) – see below. Fields are represented as pure numeric or text for ease of processing, and footnotes and abbreviations are eliminated. Results for 50 compounds that gave some evidence of binding in initial screening studies were reported in that study, along with follow-up secondary analysis to determine Ki binding constants. The KIERBL file also includes previously unpublished results for an additional 228 compounds that were labeled “non-binders” in initial screening studies. Lastly, the KIERBL file includes the PubChem summary activity fields, **ActivityOutcome_KIERBL** and **ActivityScore_KIERBL**.

Description of **DSSTox Standard Chemical Fields** can be found in the Central Field Definition Table located at:
<http://www.epa.gov/ncct/dsstox/CentralFieldDef.html>

The first section of the Table below lists the **DSSTox Standard Toxicity Fields** employed for this database, followed by the **KIERBL Source-Specific Fields** containing the data field information particular to KIERBL. The **Field Type** indicates the type of the field, such as numeric, integer, defined text, memo, etc. All **Units** and **Descriptions** are extracted from Source reference materials unless otherwise noted. **Allowable Entries** lists allowed field entries occurring in KIERBL, separated by slashes for exclusive entries (i.e., cannot occur with another entry) and semicolons or spaces for non-exclusive entries (i.e., can occur with other values). These are defined and explained in the **Description** section.

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Main Citations: Publications reporting use of the DSSTox SDF file for KIERBL are asked to list the full DSSTox file name(s), including date stamp, and to cite as primary references the following:

Laws SC, Yavanhaxay S, Copper RL, Eldridge JC. 2006. Nature of the binding interaction for 50 structurally diverse chemicals with rat estrogen receptors. *Toxicological Sciences*. 94(1), 46-56; doi:10.1093/toxsci/kfl092.

Download PDF for personal use at <http://toxsci.oxfordjournals.org/cgi/reprint/kfl092?ijkey=qOBz5uEzojlv0zy&keytype=ref>
Published by Oxford University Press 2006 <http://toxsci.oxfordjournals.org/misc/terms.shtml>.

U.S.EPA. 2002. Endocrine Disruptor Screening Program: Chemical Selection Approach for Initial Round of Screening. *Federal Register*, 67(250): 79618; <http://www.epa.gov/fedrgstr/EPA-TOX/2005/September/Day-27/t19260.pdf>

USEPA. 2002. Development of estrogen binding data for approximately 300 chemicals: final data package submittal. EPA Contract No. 68-W-99-033, Work Assignment 3-04.

SDF Usage Notes:

Each DSSTox SDF file contains a single **STRUCTURE** field. For each chemical record, the **STRUCTURE** field entry directly corresponds to the content of the **STRUCTURE_...** fields. The **STRUCTURE_Shown** field documents the relationship between what is displayed in the **STRUCTURE** field and the actual tested chemical substance, i.e. **TestSubstance_...** fields, with the latter corresponding directly to the toxicity data field entries. Commercial chemical relational database (CRD) applications may automatically insert one or more structure identifier fields upon import or export of an SDF file (e.g., Formula, FW or Mol_ID), fields that may augment or duplicate one or more of the DSSTox Standard Chemical Fields. Users are cautioned that fields containing null values in the first record of the SDF will be reordered upon import into most applications; for this reason, the word "blank" has been inserted into null fields in Record 1 of DSSTox SDF files and can be deleted after SDF import. Users are additionally cautioned that some fields (**STRUCTURE_SMILES** and **STRUCTURE_InChI**, in particular) may exceed the 200 character limit specified in the MDL CTFiles SDF standard (see <http://www.epa.gov/ncct/dsstox/MoreonSDF.html>), and that some CRD applications may insert a line break or truncate these fields upon SDF import or export. Finally, CRD application-specific molecular header information in the SDF file is deleted in the final DSSTox SDF files; users running CRD applications requiring a unique molecule header upon import of the SDF can specify either **DSSTox_RID** or the **DSSTox_FileID** be used. Upon SDF import, **DSSTox_CID** can be used to identify and manage chemical structure duplicates and **DSSTox_Generic_SID** can be used to identify common Test Substances across and within DSSTox files (similar to CASRN-substance, but available for all DSSTox substances and further distinguishes among different purity/grade substances).

As an MS Word document, the following table is best viewed onscreen using either Normal or Web Layout View in Landscape page orientation.

Field Name	Field Type	Units	Allowable Entries	Description	Comments
DSSTox Standard Toxicity Fields					
Study Type <i>(no spaces)</i>	defined text		Receptor Binding	Field is used to label all records in the database, generally with the same entry, and is designed to facilitate record identification for cross-database structure searching. Field entry refers to the main type of toxicity study for which data is represented in the database.	Field names and content are being coordinated with the public ToxML standardization effort.
Endpoint	defined text		Estrogen receptor (ER) competitive binding; IC50; Ki	Field is used to label all records in the database, generally with the same entry, and is designed to facilitate record identification for cross-database structure searching. Field entry refers to the type of toxicity measure represented within the database.	Field names and content are being coordinated with the public ToxML standardization effort.
Species	memo		rat	Field is used to label all records in the database, generally with the same entry, and is designed to facilitate record identification for cross-database structure searching. Field entry refers to the species used in the toxicity study represented within the database.	Field names and content are being coordinated with the public ToxML standardization effort.
Assay_Target	memo		Rat uterine cytosol (RUC) estrogen receptor (ER)	Field is used to label all records in the database, generally with the same entry, and is designed to facilitate record identification for cross-database structure searching. Field entry refers to the assay target (tissue and receptor) in the case of receptor-based assays and is intended provide assay-specific annotation for resources such as EPA ACToR and PubChem.	Field names and content are being coordinated with the public ToxML standardization effort.
KIERBL Source-Specific Fields					

Source_ChemicalName <i>(no spaces)</i>	memo		<i>text</i>	Common or trade name of chemical listed in original Source data file, which may or may not agree precisely with the generic DSSTox entry provided in TestSubstance_ChemicalName . Field is provided to offer direct correspondence from DSSTox file to Source documentation, in either on-line or journal publication.	TestSubstance_ChemicalName entry converted to generic chemical name associated with DSSTox_Generic_SID in all files published after January 1, 2009. <i>New field added January 2009.</i>
IC50_microM	numeric	μM	# <i>blank</i>	The concentration of a test chemical that inhibits the maximal specific binding of 0.33 nM radiolabeled (³ H) 17-beta-estradiol (E2) to rat uterine cytosolic (RUC) estrogen receptor (ER) by 50%. IC50 is determined from analysis of the competitive binding curves (for more information see BindingCurves_Group and BindingCurves_Details) <i>"blank"</i> or null value indicates less than 20% binding occurred at maximum tested concentration of 100 microM, or value could not be determined from binding curve.	Additional assumptions of the assay are that: (1) the radio-ligand and the test chemical compete for the same receptor site so that binding of one or the other is mutually exclusive, (2) the reaction is reversible and reaches equilibrium such that the rate of new ER-ligand association equals the rate of dissociation, and (3) neither the ligand nor ER is altered by binding. Refer to Main Citation for further details.

Ki_microM_mean	numeric	μM	# <i>blank</i>	<p>Ki is the inhibition constant for the test chemical, i.e., the concentration of the test chemical that will bind to half the binding sites at equilibrium (displacing half of the probe-bound receptors), in the absence of radioligand or other competitors;</p> <p>Ki reported as Mean ± Standard Error from n=2 experiments, see StandardError_Ki_n2;</p> <p>Ki determined from Lineweaver-Burk plots over the tested dose range (TestedRange_microM);</p> <p>For more information see BindingCurves_Group and BindingCurves_Details.</p> <p>If Ki is reported, ActivityOutcome_KIERBL value is "active" and ActivityScore_KIERBL ranges from 10-100.</p> <p>"<i>blank</i>" or null value indicates either non-binder status (when no IC50 was reported or when confirmed by secondary analysis) or that Ki could not be determined due to solubility limitations that prevented secondary analysis.</p>	Refer to Main Citation for further details.
ActivityOutcome_KIERBL (no spaces)	defined text		active/ inactive/ inconclusive/	<p>Categorical activity measure based on reported Ki_microM_mean:</p> <p>"active" = Ki_microM_mean value is reported and true competitive binding and inhibition was confirmed by secondary Ki experiments;</p> <p>"inactive" = no binding was observed when tested to the concentration limit of 100uM, or some binding was observed in initial screening but secondary analysis confirmed non-binder status;</p> <p>"inconclusive" = some binding was observed, but Ki could not be determined due to solubility limitations that prevented the secondary Ki experiment.</p>	Summary activity for use in PubChem and structure-activity relationship studies.
ActivityScore_KIERBL (no spaces)	integer		INTEGER [0-100]	<p>Mapping of LOG₁₀ (Ki_microM_mean) activity values spanning activity range [MAX, MIN] onto Integer 10-100 Activity range. ActivityScore 100 corresponds to the natural ligand for ER (17-β-estradiol), which has the lowest Ki value indicative of the strongest binder. ActivityScore 10 corresponds to largest Ki value indicative of the weakest binder.</p> <p>If ActivityOutcome_KIERBL is "active": $\text{ActivityScore} = \text{INTEGER}(100 * ((-\text{LOG}_{10}(\text{Ki}) + \text{MAX}) / (\text{MAX} - \text{MIN})) * (0.9) + 10)$</p> <p>If ActivityOutcome_KIERBL is "inconclusive": ActivityScore = 5</p> <p>If ActivityOutcome_KIERBL is "inactive": ActivityScore = 0</p>	Summary activity ranking for use in PubChem and structure-activity relationship studies.
StandardError_Ki_n2	numeric	μM	#	Ki reported as Mean ± Standard Error from n=2 experiments (see Ki_microM_mean)	Refer to Main Citation for further details.

			<i>blank</i>	" <i>blank</i> " or null entry if no Ki_microM_mean value reported.	
TestedRange_microM	memo	μM	## <i>blank</i>	Tested dose range for determination of IC50_microM and Ki_microM_mean values, in uM. " <i>blank</i> " or null entry for most instances of inconclusive or inactive determinations of ActivityOutcome_KIERBL .	Refer to Main Citation for further details.
BindingCurve_Group	defined text		Complete/ Partial/ Limited/ Incomplete/ Irregular/ None/	General classification of competitive binding curves based on secondary Ki analysis (see Ki_microM_mean). See BindingCurve_Details for further details pertaining to this classification.	Abbreviated text entries corresponding to Groups A-E in Table 1 of Main Citation.
BindingCurve_Details	memo		<i>text</i>	Additional details pertaining to BindingCurve_Group classification of competitive binding curves based on secondary Ki analysis. Note that binding curve classification factors into final determination of Ki_microM_mean (i.e., true competitive binding determination required complete or partial binding curves), but even a complete binding curve did not necessarily correspond to true competitive binding as determined by secondary analysis. Confounding results may be due to chemicals that: alter the stability of the assay by changing the buffer pH, denature the estrogen receptor (ER), or disrupt ER-binding kinetics.	Expanded text entries corresponding to Groups A-E in Table 1 of Main Citation.
Note_KIERBL	memo		<i>text</i>	Field used to provide supplementary Source-specific information pertaining to the chemical and toxicity fields.	Note contains additional comments pertaining to final determination of binding status, or any discrepancies of KIERBL entries with Table 1 (Main Citation) entries.