



The ToxBank Compound Wiki was created to support the organisation and presentation of information on reference compounds to SEURAT-1 scientists. The selection of a semantic media wiki to develop this resource enables both the collaborative assembly, annotation and curation of information profiles on compounds and the structured capture of metadata such as on linked toxicological data or biochemical mechanisms.

The wiki provides an extensible high quality information resource servicing the selection and use of reference compounds by researchers during their experimental planning. Compound information pages are linked to sources of repeated-dose toxicity *in vivo* and *in vitro* data, physical and chemical property data, linked biological resources on genes and pathways, and whenever available, human adverse event and epidemiological data.

The wiki is extensible for further development as a critical SEURAT-1 cluster resource for the support of chemical and biological reagents evaluation, selection, quality control, distribution and use.

The general compound selection criteria (shown on left) were developed by the SEURAT-1 Gold Compound Working Group (GCWG) established at the very start of the program. During 2011 these criteria were elaborated further to take into account the emerging strategic goal of the SEURAT-1 cluster to develop a Mechanism of Action (MoA)-based approach to toxicity assessment. This includes evaluation of both on- and off-target effects of compounds, e.g., for marketed NSAID drugs (shown on right),

Information related to the selection criteria on compounds has been organized on the ToxBank wiki for work-in-progress on candidate compounds. When a compound has been approved by the GCWG, the page is published for access by all researchers at the cluster level.

Compounds were selected based on the initiating event and a limiting range of reactivity. Alkylating agents span the range from totally non-selective, diffusion-controlled reaction with virtually any thiol to highly selective alkylation of select proteins, e.g. glyceraldehyde phosphate dehydrogenase. Redox cycling- and free radical-based cyto-toxics were chosen to address the contribution of lipid peroxidation to cytotoxicity. A proteomics experiment that discriminates between reaction of proteins and DNA with lipid peroxidation products vs. depletion of redox potential will provide a quantitative estimate of the importance of lipid peroxidation in cytotoxicity. A key additional question is whether redox cycling agents also reverse the electron transport chain to deplete ATP at high concentrations.



**SEURAT-1**

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Each compound has an associated information profile page on the wiki which contains a summary of all relevant information discovered on that compound. This includes a summary of available knowledge in the literature, calculated and experimental properties, and compound-specific links to many other linked resources providing useful chemical, biological or toxicological information.

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Through using a linked resource approach the compound profiles can be linked to related key biological information available of interest e.g., on genes and pathways associated with the MoA probed by the test compound (Links to Comparative Toxicogenomics Database and Kegg pathways resources shown).

Experimental data and model predictions on physico-chemical properties such as solubility, volatility and partition coefficient are assembled for each compound. Furthermore information on recommended products and suppliers are provided with details on specific product codes, purity, storage conditions and stability.

Lipid regulation is addressed at two levels: inhibitors of specific points in the metabolic system and activation of the nuclear hormone receptor lipid-regulating systems. Steatosis is not necessarily a result of hepatocyte dysregulation but may be a remote effect of adipocyte dysregulation. Activation of some NHRs does not in itself cause hepatotoxicity, but the receptors are so promiscuous that they are included as negative controls.

The Compound Assessment Team prepares detailed assessment of each compound against the acceptance criteria and MoA-based strategic considerations. Compounds are recommended to the SEURAT-1 cluster if they are agreed unanimously by this team. The Gold Compound Working Group consists of representatives of each project team of the SEURAT-1 program plus representatives from the Scientific Expert Panel. These representatives proposed the subset of compounds from which potential standards were drawn and provide a conduit for interaction with the project teams on compound selection.

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