



有害性評価支援システム統合 プラットフォーム（HESS）の概要と 操作説明

(独)製品評価技術基盤機構
化学物質管理センター
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HESSとは

- 化学物質をグルーピングし、未試験化学物質の反復投与毒性をリードアクロスにより評価することを支援するシステム
- OECD QSAR Toolboxと類似のシステム構成
- 反復投与毒性試験データ及び毒性発現のメカニズムに関する情報などを収載。詳細なデータベースであるHESS DBとリンクが可能
- NITEのHPから無料で公開
(<https://www.nite.go.jp/chem/qsar/hess.html>)

反復投与毒性試験

目的: 動物に被検物質を一定期間毎日反復投与したときに現れる生体の機能及び形態の変化を観察することにより、被検物質の毒性を明らかにする。

齧歯類(原則ラット)

投与期間 (28日~90日)

回復期間 (14日)

検査項目 体重・摂餌量・摂水量・一般状態
血液学的検査
血液生化学的検査
神経学的検査
尿検査
病理学的検査 臓器重量
剖検所見
組織学的検査

↑
検査

↑
検査

無影響量(NOEL)
No Observed Effect Level

無毒性量(NOAEL)
No Observed Adverse Effect Level

反復投与毒性とリードアクロス

- 反復投与毒性は、全身を対象とした多くの観測事項があり、毒性発現のメカニズムも複雑。よって、化学構造との毒性の相関関係が得られにくく、統計的なQSARモデルの作成は困難
- 反復投与毒性を予測する最も実用的な手法は、メカニズム情報を用いたリードアクロス(カテゴリーアプローチ)と考えられている※
- 反復投与毒性のリードアクロスは、各国の研究開発プロジェクト等において検討が進められている
 - HESSプロジェクト (2007-2011、日本)
 - SEULAT-1 (2011-2015、EU)
 - EU ToxRisk (2016-2021、EU)
 - OECD IATA Case Studies Project (2015-、OECD)

※ OECD Series on Testing and Assessment No. 138, Report of the Workshop on Using Mechanistic Information in Forming Chemical Categories (8-10 December 2010, Crystal City VA, USA) ENV/JM/MONO(2011)8.

「構造活性相関手法による有害性評価手法開発」

実施期間：平成19年度～平成23年度

基本計画：化学物質のリスク評価におけるヒト健康影響の評価において、安全性試験データがない化学物質に、類似物質からのカテゴリーアプローチ等の手法により反復投与毒性を推定できるよう必要となる判断材料を評価者（専門家）に提供するデータベース及び評価支援システムを開発する。

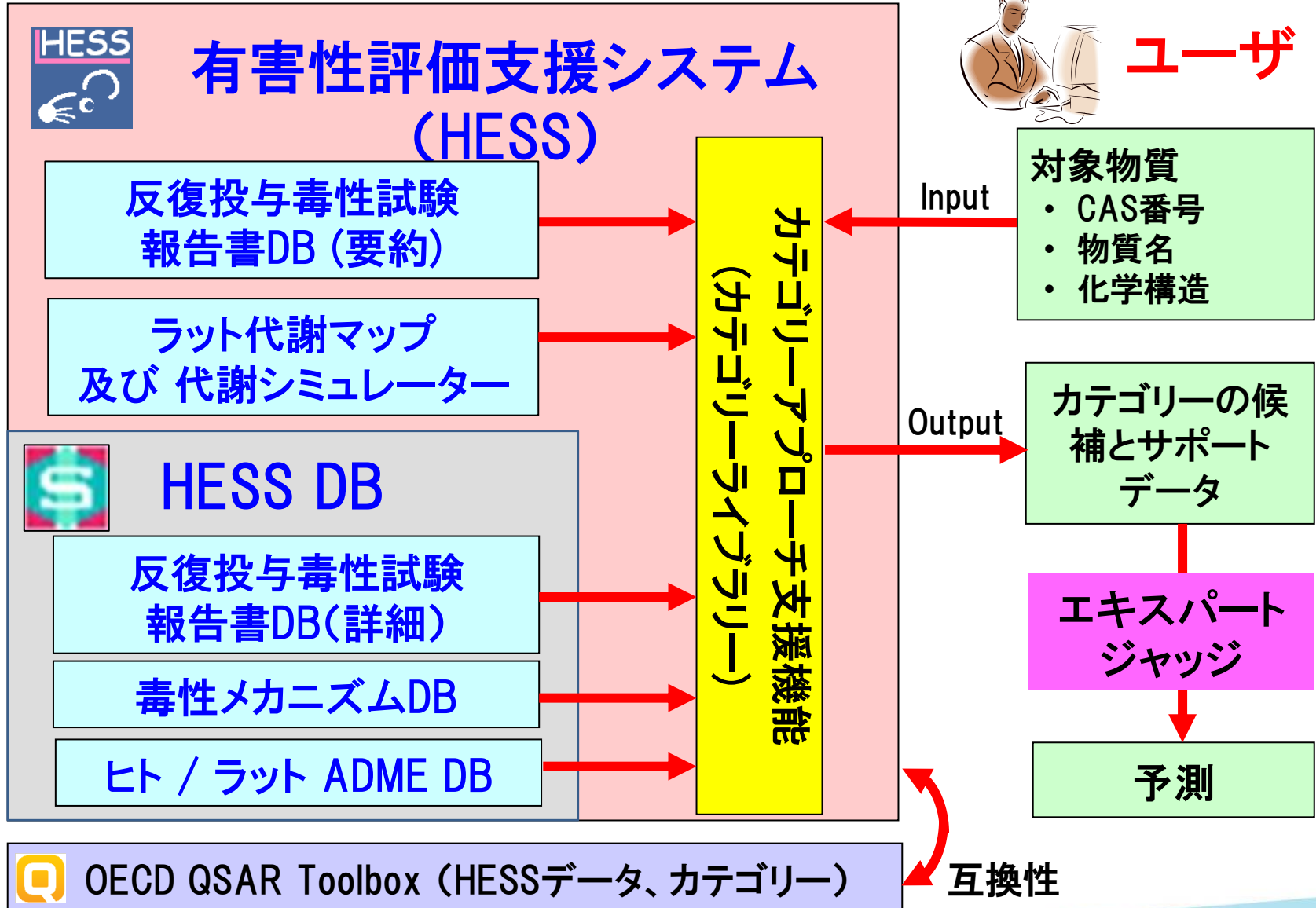
開発方針：

- ・ 専門家の判断をサポートするためのシステムを開発する。
- ・ 毒性、病理の専門家の主導によりシステムを開発する。
- ・ 国際的に利用されるシステムの開発を目指す（OECDと連携）。

HESSの構成



ユーザ



HESSに収載されている情報

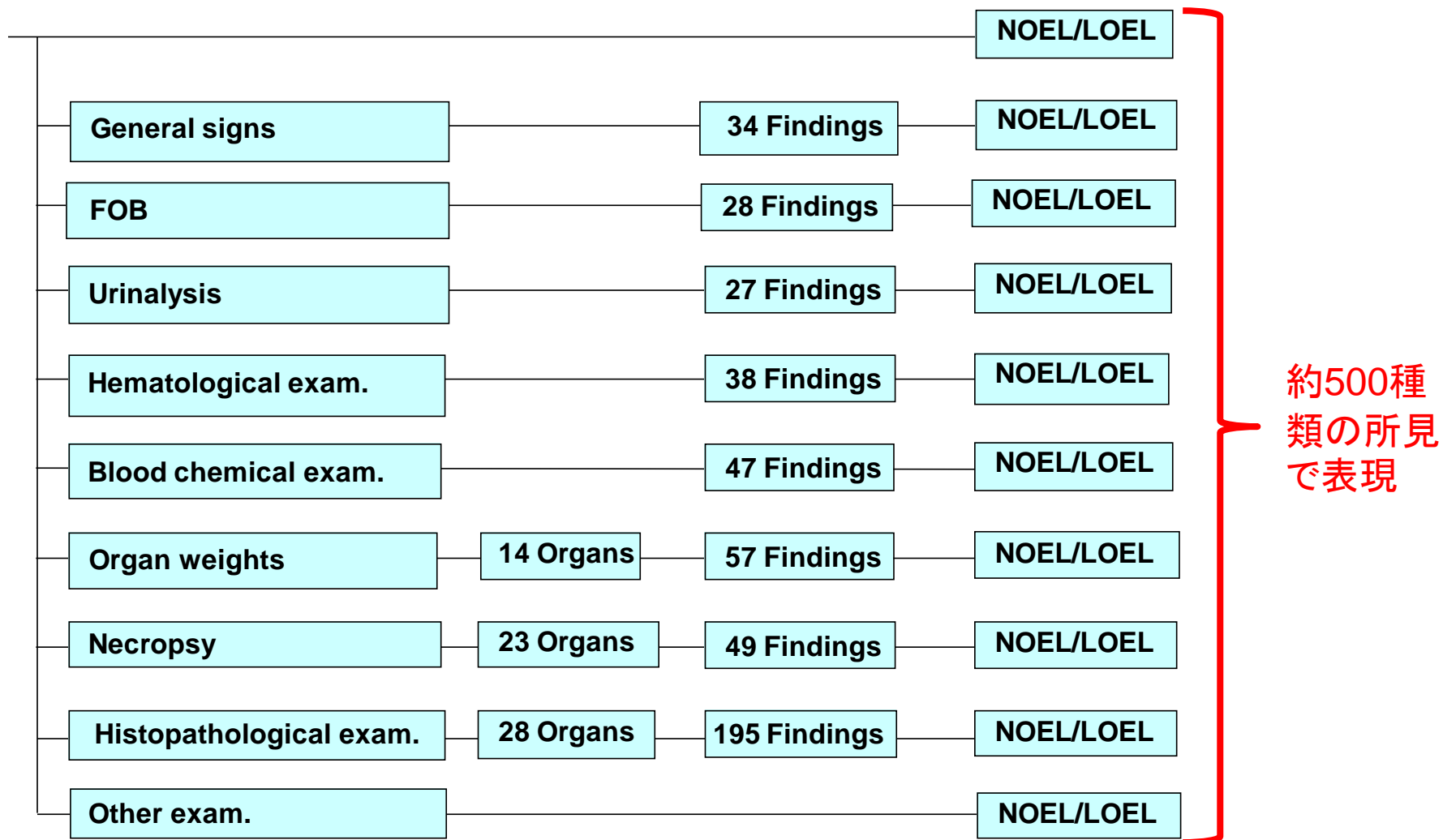
HESSに収載されているSub database

Ver.4.4(2023年)

Sub database名	物質数	物質群	備考
Biomarker	150	化学物質	バイオマーカー情報
COSMOS	852	化粧品	欧州化粧品データ
<u>Drug Repeated Dose Toxicity</u>	50	医薬品	国内医薬品データ
HESS RDT DB(HPV)	130	化学物質	
HESS RDT DB(Inhalation)	33	化学物質	吸収試験データ
HESS Repeated Dose Toxicity	765	化学物質	化審法既存点検データ、NTP短期、NTP長期等
HESS Repeated Dose Toxicity (CSCL New chemical)	383	化学物質	化審法新規化学物質データ
TGP Repeated Dose Toxicity	124	医薬品	国内医薬品データ
<u>Tox-Omics RDT DB</u>	31	化学物質	経産省委託
ToxRef DB	477	農薬	米国の農薬データ
合計			反復投与試験毒性試験物質:約3000物質、 バイオマーカー物質:150物質

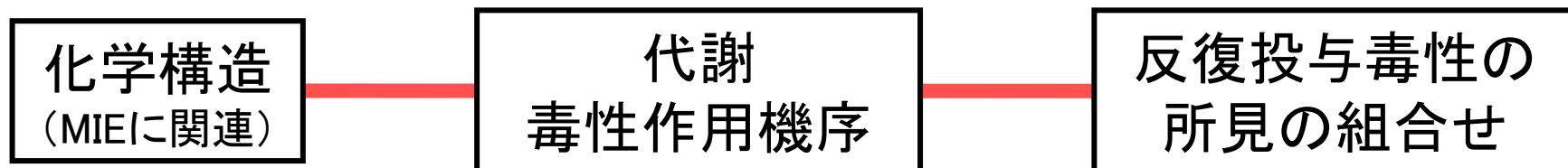
下線がついたデータベースは、詳細な試験報告書(HESS DB)があるもの。
黄色マーカーがついたデータベースは、QSAR Toolboxにも収載されているもの。

HESSにおける反復投与毒性試験データの データ構造



HESSにおける 反復投与毒性のカテゴリー

反復投与毒性における Adverse Outcome Pathway (AOP)



- ① 化学構造上の特徴
- ② 毒性のメカニズム
- ③ 反復投与毒性試験における毒性発現の傾向(毒性強度等)

↓ 類似する物質群

「Repeated dose(HESS)」カテゴリー、260分類(カテゴリー;69、アラート;191)
現在も、追加検討中。

ラット代謝マップDB:代謝マップ

Metabolism profiling...

Add as a list Map Info Close

what to add
 sub-tree
 whole map(w/o parent)

METABOLISM DATABASE

- 1. c1(C)C(C)CC(N)CC1
- 2. c1(NC)CCCC1
- 3. c1(NC)CCCC1
- 4. c1(N(C)CC)CCCC1
- 5. C(=O)(CCCC(=O)O)CC(CCCC)CC(O)CC(CCCC)CC
- 6. c1(N)CC(N(=O)=O)CC1
- 7. c1(OCC)CCC(N)CC1
- 8. c1(N)C(C)CC(Cl)CC1
- 9. C(C)(C)(C1CC(O)CC1)CC(C)(C)
- 10. C(=O)N(C1CCCC1)NCCCCCCCCC
- 11. C(C)CCCCCCCCCCCCC
- 12. C(C)CCCCCCCCCCCCC
- 13. C(C)(O)(C)CC(C)(O)CC(C)(C)(C)
- 14. c1(N)c2c(cccc2)ccc1
- 15. c1(CC(=O)O)c2c(cccc2)ccc1
- 16. c1(CC(=O)O)c2c(cccc2)ccc1
- 17. c1(C(C)CC)CCC(O)CC1
- 18. c1(Br)CCC(Br)CC1
- 19. c1(S(=O)(=O)O)CC(N)CC1
- 20. C(=O)C(C(Cl)O){-}.[Na]{+}
- 21. C(CCC)OP(=O)(O)CCCCOCCCC
- 22. C(=C)(C)C
- 23. c1(OP(=O)(Oc2cccc2)Oc2cccc2)c(CC)CCCC1
- 24. c12c(cccc1)N=C(S)N2
- 25. C(#N)c1ccc(O)cc1
- 26. c1(CC(C)N)CCCC1
- 27. c1(CN{+}(C)(C)(C).Cl{-})CCCC1
- 28. c1(O)c(N=Nc2cccc2)c2c(cc(5(=O)O[Na]))cc1
- 29. c1(N)c(O)c2c(cccc2)cc1
- 30. c1(Cl)C(Cl)C(Cl)C(Cl)C(Cl)C=1
- 31. c1(N)CCC(C)CC1
- 32. c1(N)CCC(C)CC1

Search target search parents only
 search as fragment

extended search... Flexible search...
Trans flex search...

Reference: Boyland, E., P. Sims, Biochem. J., 73(2), (1959). (in vivo), pp. 377 - 380

ラット
*in vivo, in vitro*代謝試験
の文献をDB化
800物質、1000マップ
代謝シミュレータも装備

**HESSに付属する詳細なデータベース：
HESS DBに収載されている情報**

収載されている試験報告書

一般化学物質に対するラットの反復経口投与毒性試験報告書。(GLP準拠の類似した試験条件下で行われ、詳細なデータが公表されているものを選定)。現在(2020年4月)、約830物質の試験報告書を収載。

投与経路は強制経口、混餌、飲水。

投与期間は28日～17週。

	報告書群
1	厚労省/国衛研 化審法試験
2	厚労省 安衛法長期試験(予備試験)
3	経産省/CERI試験(Tox-Omics)
4	経産省/NITE試験
5	米国NTP短期試験
6	米国NTP長期試験(予備試験)
7	医薬品データ(企業から提供)
8	Journal Paper

HESSからHESS DBへのリンク

The screenshot displays the Hazard Evaluation Support System (HESS) interface. The main window shows the chemical name "3,4-dimethylaniline; 3,4-xylydine" and its CAS No. "95-64-7". The chemical structure is shown as a benzene ring with methyl groups at the 3 and 4 positions and an amino group at the 1 position. The interface includes a sidebar with various categories like Profiling, RDT Data, and Metabolism. A search window titled "Main [HessDB_Search]" shows search results for "3,4-Xylydine" with a link to "1<28>". A detailed view window titled "Study [HessDB_Search]" shows the test results for "3,4-Xylydine" (Chem. No. 1) under the study link "1<28>". The detailed view includes a table of test results for Hematology, Blood Chemistry, Relative organ weight, Necropsy, Histopathology, and Toxicological index.

Chem...	Chemical Data	Structure	Study Lin...	Adme...	Mech...	No.	Type	Conditions
[Cas_No.] 95-64-7	[Name] 3,4-Xylydine	<chem>Cc1ccc(N)cc1C</chem>	1<28>	1171	1131	1	Chem_No.	1

Study Link ID	Test Result	Flag Summary	Test Method	Measured Data
1<28>				

	Male	Female
Hematology	HCT: 250 HGB: 250 RBC: 250 PT: 250 RET: 250 WBC: 250	HCT: 250 HGB: 250 RBC: 250 PT: 250 RET: 250
Blood Chemistry	T-CHO: 250	T-CHO: 250
Absolute organ weight	Liver: 250 Spleen: 250	N/A
Relative organ weight	Liver: 250 Spleen: 250 Testis: 250	Liver: 250 Spleen: 250 Adrenal: 250
Necropsy (Survival)	N/A	N/A
Necropsy (Dead)	-	-
Histopathology (Survival)	Kidney-Hyaline droplet: 250 Bone marrow-Hematopoiesis, increased: 250 Spleen-Congestion: 250 Spleen-Pigmentation: 250 Spleen-Hematopoiesis, increased: 250 Liver-Deposit of pigment: 250 Liver-Single cell necrosis: 250 Liver-Swelling of liver cell: 250 Liver-Hematopoiesis: 250	Bone marrow-Hematopoiesis, increased: 250 Spleen-Congestion: 250 Spleen-Pigmentation: 250 Spleen-Hematopoiesis, increased: 250 Liver-Deposit of pigment: 250 Liver-Single cell necrosis: 250 Liver-Swelling of liver cell: 250 Liver-Hematopoiesis: 250
Histopathology (Dead)	-	-

	Clinical sign		FOB	
Male: N/A			Male:-	
Female: N/A			Female:-	

	Urinalysis		Body weight	
Male: Volume: 250			Male: N/A	
Female: Volume: 250			Female: N/A	
pH: 250				
Specific gravity: 250				

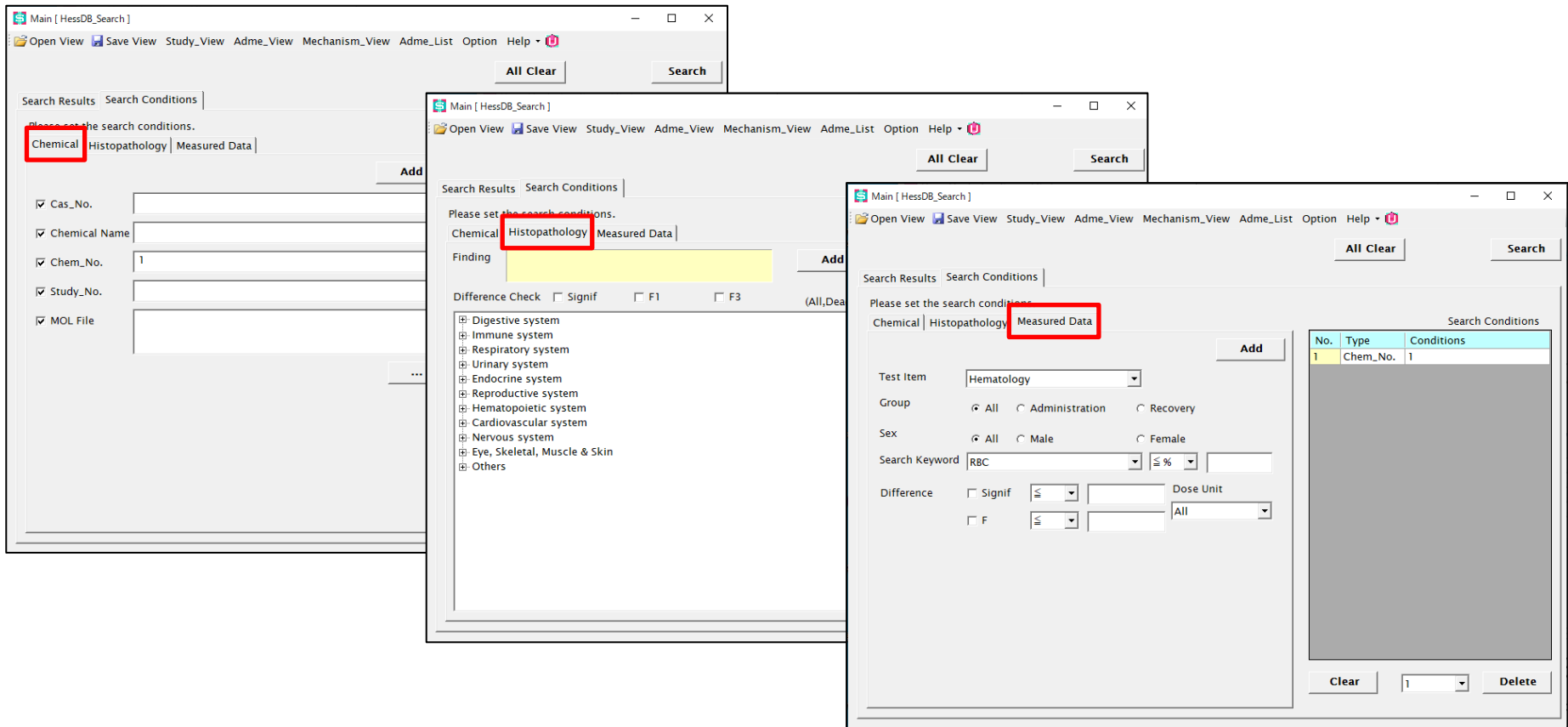
	Food consumption		Water consumption	
Male: N/A			Male:-	
Female: N/A			Female:-	

	NOEL	NOAEL	LOEL	LOAEL
Male	10 mg/kg/day	-	50 mg/kg/day	-
Female	10 mg/kg/day	-	50 mg/kg/day	-

Comment
Evaluated by toxicology experts in the NEDO project

HESSから直接リンクさせることができ、試験データの詳細情報を閲覧できる。

HESS DBの検索画面



化学構造情報のほか、毒性所見に基づいた検索機能を備えており、独立した毒性データベースとして使用することも可能。

試験報告書の用量-反応関係データ

Test Item		Blood Chemistry_Male		Actual		Comment	
*, significantly different from control, P<0.05 **, significantly different from control, P<0.01							
DOSE	mq/kq	Admi...					
		0	20	100	500		
No. of animals		5	5	5	5		
		mean	SD	s...	F1	F3	
BUN	mq/dL	12	1				** Δ
CRN	mq/dL	0.6	0.1				
T-CHO	mq/dL	44	3				* Δ
TG	mq/dL	51	9				
PL							
T-BIL	mq/dL	0.11	0.03				
GLUC	mq/dL	133	16				
TP	q/dL	5.2	0.2				
BA							
ALB	q/dL	3.3	0.1				
A/G		1.67	0.15				**
Protein %	ALB						

フラグ

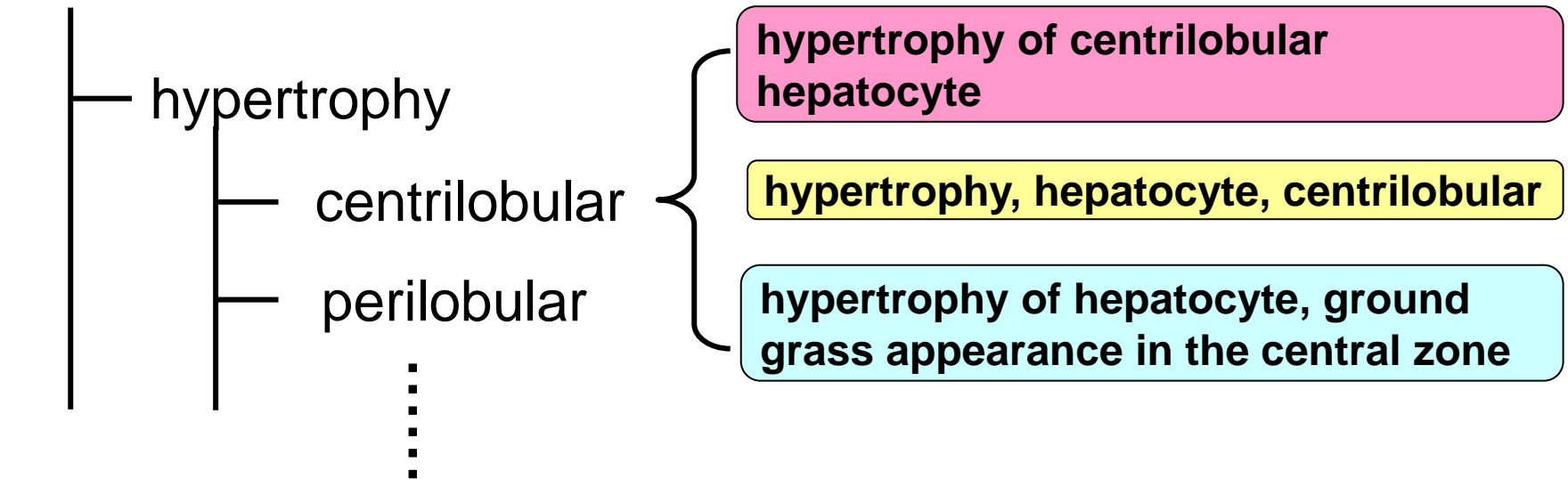
報告書に記載されている毒性所見の有意差マークのほか、本プロジェクトの毒性・病理専門家の意見や既存点検時の化学物質審議会判定に基づく、有意差マーク(フラグ)を付与するなどして、毒性学的な注意喚起を図った。

病理所見シソーラス

HESS DB

オリジナル試験報告書

Liver



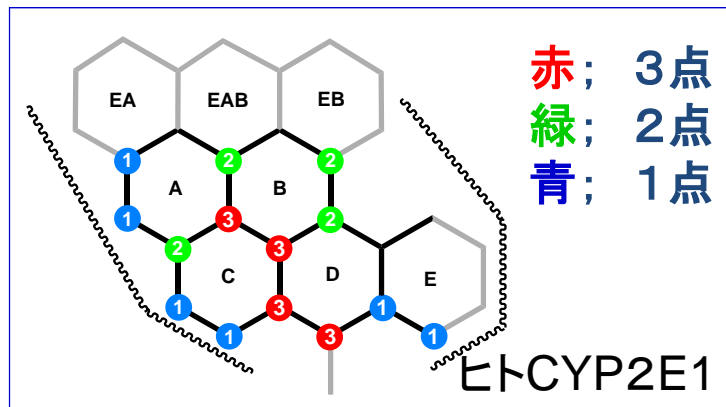
データの検索を正確に行えるよう、データベースに入力する病理所見について、専門家が同義語を分類し関連付けることによって、用語の統一を行い、シソーラスを作成(全83臓器・11302所見)

ADME情報

毒性試験が行われた化合物を対象にADME情報を収集し、DB化。

吸収	吸収率、Cmax、Tmax トランスポータの関与
分布	見かけの分布容積、反復に伴う経時変化 脳→中枢作用、脂肪組織→蓄積 肝臓→酸化抱合代謝、腎臓→尿中排泄 腎臓→タンパク結合 血液よりも高い濃度を示す臓器/器官 トランスポータの関与

代謝	関連酵素と分子情報 細胞内画分、代謝物 種差・系統差
排せつ	排せつ率 トランスポータの関与 種差・系統差
相互作用、酵素阻害、酵素誘導試験の結果	
毒性との関連性	



リガンド構造に基づいた
P450代謝予測モデルによる
代謝予測データも収載

毒性作用機序DBのデータ項目

変性・壊死など重篤な毒性に対する毒性メカニズム情報を収集しDB化

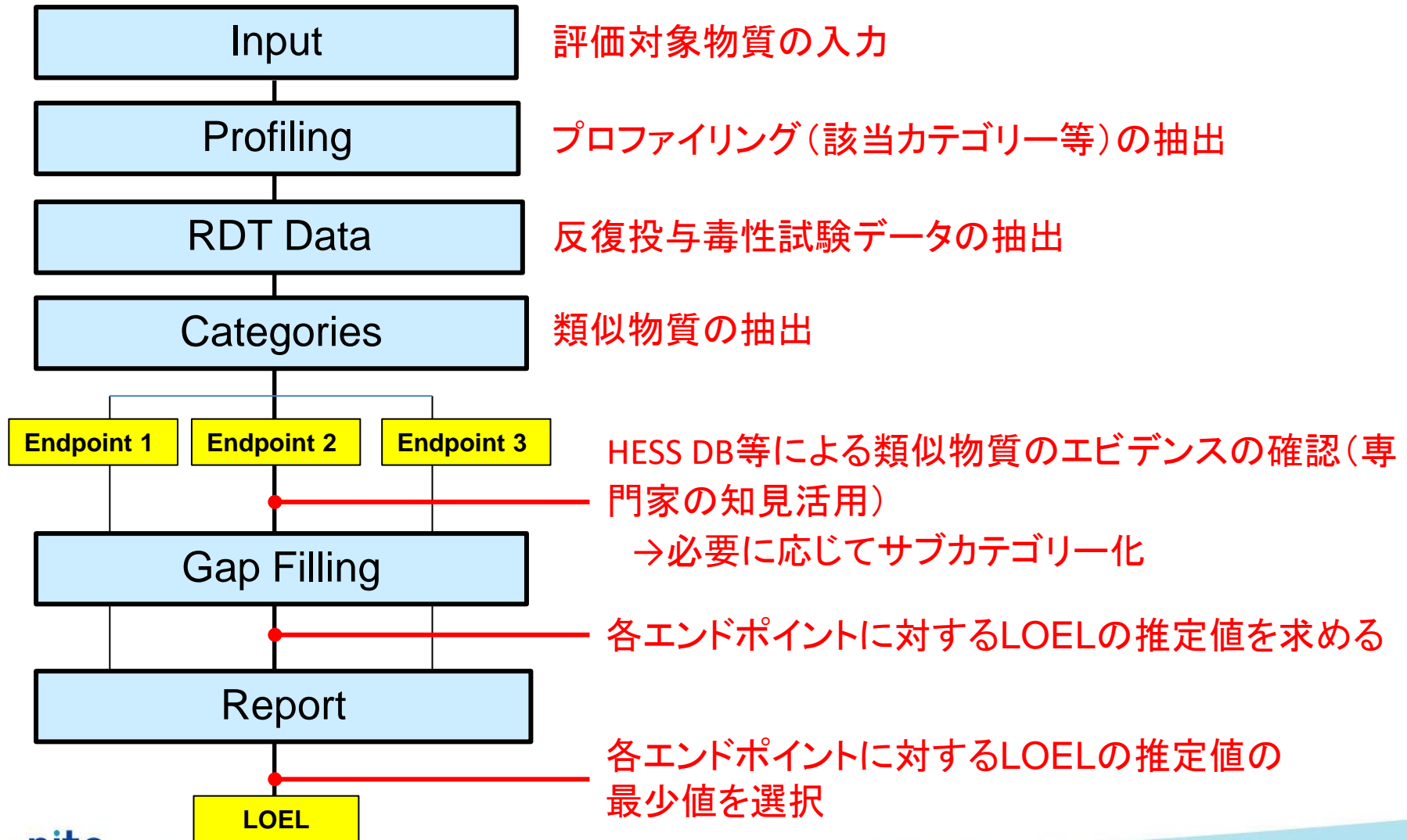
対象毒性: 血液、肝臓、腎臓、精巣、神経、膀胱、甲状腺

収載情報の分類	データ項目
A: 物質情報	CAS. No., 物質名, 構造式
B: 文献情報	レファレンス
C: 試験方法情報	細胞株/動物種、実験デザイン、in vitro/ in vivo/ex vivo、濃度/投与量
D: 作用機序関連情報	キーワード, 要約, 化学反応/代謝, トキシカント, 生体分子との相互作用, エフェクト, 標的細胞/組織/臓器, 有効濃度/投与量
E: その他	関連物質, 追加情報, 著者の機序的考察, 備考, 関連文献

HESS の操作説明

Read-acrossによる反復投与毒性の予測

HESSによる反復投与毒性のデータギャップ補完のワークフロー(OECD Toolboxに準拠)



Case study 1:
Anemia for 2,4-difluoroaniline
(CAS RN: 367-25-9)

Target Chemicalの選択

1

Hazard Evaluation Support System

Hazard Evaluation Support System Reset Options Help

Input

Chemical name: **2,4-difluoroaniline**
CAS No: **367-25-9**
SMILES: **c1(N)c(F)cc(F)cc1**

to data matrix -> metabolism mode...

Profiling

RDT Data

Categories

Gap Filling

Report

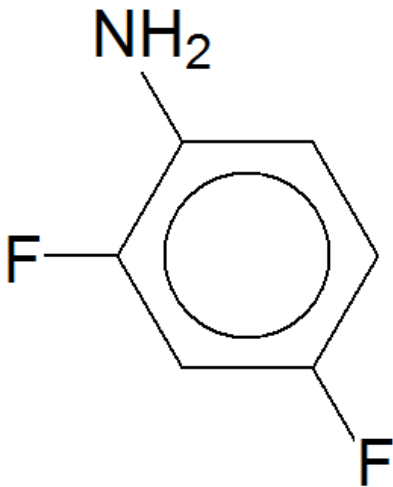
Metabolism

↑ Set target ↑ Add to post-targets list 🔍 CAS# 🏠 Chemical name 📄 Drawing 🧪 RDT tests 📁 Database 👤 User List 📄 Load DB

Load Inventory

CAS # 🔍 Search

Chemical name: 2,4-difluoroaniline



The image shows a screenshot of the Hazard Evaluation Support System interface. The main window displays the chemical name '2,4-difluoroaniline', its CAS number '367-25-9', and its SMILES string 'c1(N)c(F)cc(F)cc1'. A red box highlights the chemical name, CAS No, and SMILES fields. A blue box highlights the 'Set target' button in the 'Categories' section. Another blue box highlights the 'CAS #' search input field in the 'Gap Filling' section. The chemical structure of 2,4-difluoroaniline is shown in the main window, featuring a benzene ring with an amino group (NH₂) at the 1-position and fluorine atoms (F) at the 2 and 4 positions.

Target Chemical のプロファイリング

Hazard Evaluation Support System

Hazard Evaluation Support System

Input

Profiling

RDT Data

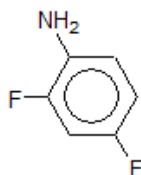
Categories

Gap Filling

Report

Metabolism

2



Chemical name: 2,4-difluoroaniline

CAS No 367-25-9

SMILES c1(N)c(F)cc(F)cc1

to data matrix ->

metabolism/tautomerism mode...

Show Boundaries Apply New Scheme

- Profiling methods
- Bioaccumulation – metabolism half
 - Biodegradation fragments (BioWII)
 - Carcinogenicity (genotox and non
 - Eye irritation/corrosion Exclusion ru
 - Eye irritation/corrosion Inclusion ru
 - in vitro mutagenicity (Ames test)
 - in vivo mutagenicity (Micronucleus
 - Oncologic Primary Classification
 - Skin irritation/corrosion Exclusion r
 - Skin irritation/corrosion Inclusion r
- Empiric
- Chemical elements
 - Groups of elements
 - Lipinski Rule Oasis
 - Organic functional groups
 - Organic functional groups (nested
 - Organic functional groups (US EPA
 - Organic functional groups, Norber
 - Study No. (Link to SSRDT)
 - Chemical No. (Link to HESS DB)
 - RDT Report No.
 - CSCL Class
 - Rat Liver Metabolism Database
- Toxicological
- Repeated dose (HESS)

Filter endpoint tree

About

Name
Repeated dose (HESS)

Short description
The profiler contains category boundaries to be expected to induce similar toxicological effects in repeated dose oral toxicity. These category boundaries were developed based on repeated dose toxicity test data in the database of Hazard Evaluation Support System (HESS). Justification for each category (mechanistic or empirical information) is described.

Disclaimer

Donator(s)
National Institute of Technology and Evaluation (NITE)

Author(s)
The profiler was developed by National Institute of Technology and Evaluation (NITE) in the contract research project "Development of Hazard Assessment Techniques using

Website

Details

Version	2.8
Number of categories	237
Number of help files	237

Close

プロファイラの
選択

Repeated dose (HESS) を選択して右クリック→
 About: プロファイラの概要を表示
 Show Boundaries: プロファイラのカテゴリーを表示
 次のスライドへ

プロフィール表示

Repeated dose (HESS) (Toxicological) - Profiling Scheme Browser

Advanced

Repeated dose (HESS) - Category definitions

- 4,4'-Diethylaminoethoxyhexestrol (Hepatotox
- 4,4'-Methylenedianilines/benzidines (Hepatobi
- 4-Aminopyrazolopyrimidine (Hepatotoxicity) A
- Acetaminophen (Hepatotoxicity) Alert
- Acrylamides (Neurotoxicity) Rank C
- Aflatoxin B1 (Hepatotoxicity) Alert
- Ajmaline (Hepatotoxicity) Alert
- Aliphatic amines (Mucous membrane irritation)
- Aliphatic nitriles (Hepatotoxicity) Rank B
- Aliphatic/Alicyclic hydrocarbons (Alpha 2u-glot
- Allopurinol (Hepatotoxicity) Alert
- Allyl esters (Hepatotoxicity) Rank A
- Alpha olefin (Less susceptible) No Rank
- Alpha-Amanitin (Amatoxin) (Hepatotoxicity) A
- Alpha-Naphthyl-isothiocyanate (Hepatotoxicit
- Amine oxides (Less susceptible) No Rank
- Amineptine (Hepatotoxicity) Alert
- Amiodarone (Hepatotoxicity) Alert
- Anilines (Hemolytic anemia with methemoglobi
- Anilines (Hepatotoxicity) Rank C
- Aromatic hydrocarbons (Liver enzyme inducti
- Azithromycin (Hepatotoxicity) Alert
- Azobenzenes (Hemolytic anemia with methem
- Benzene/ Naphthalene sulfonic acids (Less su
- Benzenesulfonamides (Toxicity to urinary syst
- Beta-Naphthylisothiocyanate (Hepatotoxicity)
- Bosentan (Hepatotoxicity) Alert
- Bromfenac (Hepatotoxicity) Alert
- Carbamazepine (Hepatotoxicity) Alert
- Carbon Disulfide (Hepatotoxicity) Alert
- Carboxylic acids (Hepatotoxicity) No rank
- Chloramphenicol (Hepatotoxicity) Alert
- Chloroquine (Hepatotoxicity) Alert
- Chlorphentermine (Hepatotoxicity) Alert
- Chlorpromazine (Hepatotoxicity) Alert
- Cisplatin (Hepatotoxicity) Alert
- Cindamycin (Hepatotoxicity) Alert
- Clofibrate (Hepatotoxicity) Alert
- Coumarin (Hepatotoxicity) Alert
- Cuprizone (Hepatotoxicity) Alert
- Cycloheximide (Hepatotoxicity) Alert
- Cyclophosphamide (Hepatotoxicity) Alert
- Cydosporin A (Hepatotoxicity) Alert
- Cyproterone Acetate (Hepatotoxicity) Alert
- Danazol (Hepatotoxicity) Alert
- Dantrolene (Hepatotoxicity) Alert

Profile Description

Anilines (Hemolytic anemia with methemoglobinemia) Rank A

1. Toxicity Information

The toxicant of methemoglobinemia induced by anilines is considered to be N-hydroxyl anilines that are metabolites of anilines in the liver^{1,2}. The hemolytic anemia induced by anilines is considered to be related to the oxidation of erythrocytes by N-hydroxyl anilines^{3, 4}.

- 1) Anilines are metabolized in hepatocytes by oxidases such as P450 to N-hydroxyl anilines.
- 2) N-hydroxyl anilines react with hemoglobin (Hgb) in erythrocytes to produce nitrosoaniline and methemoglobin (Met-Hgb). The resulting increase in the concentration of Met-Hgb is observed in hematological examination.
- 3) Erythrocytes are degenerated (peroxidation of lipid membrane etc.) by reactive oxygen species (ROS) produced in the above reaction³.
- 4) Phagocytosis of degenerate erythrocytes, mainly in the spleen, results in hemolysis⁴.
- 5) The result is: decrease in red blood cells (RBC), decrease in Hgb, decreased hematocrit (Hct) and increase in reticulocytes (Ret) observed upon hematological examination in RDT test. In addition, pigmentation of hemosiderin and congestion are observed in the spleen on histopathological examination⁵.
- 6) As a compensatory response to anemia, extramedullary hematopoiesis (mainly in the spleen) is observed on histopathological examination⁴.

The mechanism of this toxicity is common to experimental animals and humans.

2. Observed Effects in the RDT DB

There are 33 RDT studies of monocyclic anilines in the RDT DB as shown in the following table (30 compounds).

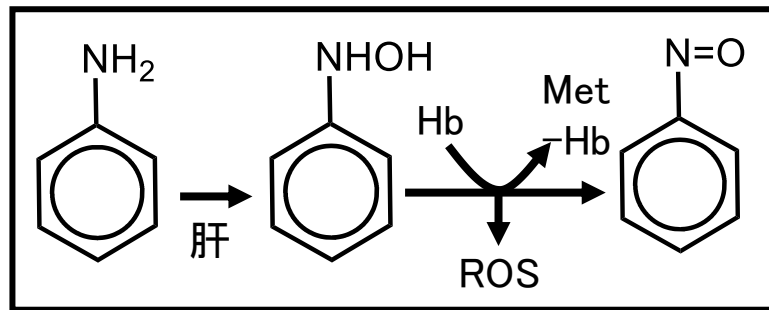
In studies of anilines without hydroxyl or acid groups (Nos. 1-23), the findings related to hemolytic anemia are frequently cited as the primary reason for the setting of a NOEL value.

アニリン類の溶血性貧血カテゴリー

AOP

分子→細胞→生体レベルの毒性メカニズム

関連する
反復投与毒性所見

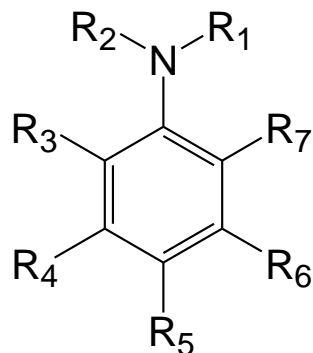


ROSによる
赤血球脂質
膜過酸化

溶血（脾臓での貪食）

RBC ↓, HGB ↓
HTC ↓,
Reticulo ↑
Met-Hb ↑, T-bil ↑
脾-ヘモジデリン
沈着
髄外造血亢進（代
償作用）等

構造領域



$R_1, R_2 = \text{H, methyl or ethyl.}$

$R_3 \sim R_7 = \text{H, alkyl, halo, alkoxy, NO}_2 \text{ or NH}_2.$

Target Chemical のプロファイリング

1 Profiling

Chemical name: 2,4-difluoroaniline
 CAS No: 367-25-9
 SMILES: c1(N)c(F)cc(F)cc1

2 Profiling methods

- Skin irritation/corrosion Inclusion r...
- Empiric**
 - Chemical elements
 - Groups of elements
 - Lipinski Rule Oasis
 - Organic functional groups
 - Organic functional groups (nested)
 - Organic functional groups (US EPA)
 - Organic functional groups, Norbert
 - Study No. (Link to SSRDT)
 - Chemical No. (Link to HESS DB)
 - RDT Report No.
 - CSCL Class
 - Rat Liver Metabolism Database
- Toxicological**
 - Repeated dose (HESS)
- Custom**
 - HESS Chemical Class

3 Apply

4 Anilines (Hemolytic...
Anilines (Hepatotox...)

1) Hemolytic anemia with methemoglobinemia for AnilinesおよびHepatotoxicity for Anilinesに該当

プロファイル
の選択

4 ダブルクリックでカテゴリレポートへリンク

Target Chemical のRDT dataの収集

The screenshot shows the HESS interface with the following details:

- Chemical name:** 2,4-difluoroaniline
- CAS No:** 367-25-9
- SMILES:** c1(N)c(F)cc(F)cc1
- Left Panel (RDT Data):**
 - 1. RDT Data (highlighted)
 - 2. Report (highlighted)
 - 3. Gather (highlighted)
 - 4. Databases list:
 - Biomarker DB
 - COSMOS DB
 - Drug Repeated Dose Toxicity (registered in Japan)
 - HESS RDT DB (HPV chemicals)
 - HESS RDT DB (Inhalation)
 - HESS Repeated Dose Toxicity
 - HESS Repeated Dose Toxicity (IARC New Chemicals)
 - TGP Repeated Dose Toxicity
 - Tox-Omics RDT DB
 - ToxRef DB
- Right Panel (Structure):**
 - Substance Identity
 - CAS Number: 367-25-9
 - Chemical Name: 2,4-difluoroaniline
 - SMILES: c1(N)c(F)cc(F)cc1
 - Root of map No. 901
 - Available Data: Anilines (Hemolytic...), Anilines (Hepatotox...)

データベース
にチェック

データベースの中身を確認するに...
HESS Repeated Dose Toxicityを選択して
右クリック→Aboutを選択

The 'About' dialog box contains the following information:

- Database Name:** HESS Repeated Dose Toxicity
- Short Description:** The HESS (Hazard Evaluation Support System) Repeated Dose Toxicity database contains repeated dose toxicity test data of 745 industrial chemicals (1002 studies) conducted under the following test condition.
 - GLP test
 - Test animal: Rat
 - Administration period: 28 day · 17 week
 - Administration route: Oral (gavage, feed, drinking water)
- Donators:** The database was developed by National Institute of Technology and Evaluation (NITE) in the contract research project "Development of Hazard Assessment Techniques by using Structure-activity Method (FY2007-FY2011)" by New Energy and Industrial Technology Development Organization (NEDO) and Ministry of Economy, Trade and Industry (METI) in Japan (Project Leader: Dr. Makoto Hayashi, Biosafety Research Center, Foods, Drugs and Pesticides, Director General)
- Disclaimer:** Copyrights of the database are to be owned by NITE. Users are requested to comply with international conventions and rules related to copyrights. The commercial use of the database is prohibited. For example, it is prohibited to extract or to copy the contents of database, such as data.

The dialog box titled 'NITE HESS' displays the message 'No data found.' with an 'OK' button.

選択したDB
からはデータ
は見つからな
かった

Target Chemicalの類似物質検索 (1)

HESSカテゴリー(2種類: 溶血性貧血・肝毒性)のポップアップが表示されるため、溶血性貧血のみでカテゴリー化を実施

The screenshot shows the HESS software interface. On the left, a sidebar contains menu items: Input, Profiling, RDT Data, Categories (highlighted with a blue box and labeled '1'), Gap Filling, Report, and Metabolism. The 'Categories' menu is open, showing a list of grouping methods. 'Toxicological' is selected, and 'Repeated dose (HESS)' is highlighted with a blue box and labeled '2'. A red arrow points from this selection to a dialog box titled 'Repeated dose (HESS)'. The dialog box has a 'Target(s) profiles' section with a list of profiles. 'Anilines (Hepatotoxicity) Rank C' is highlighted with a blue box and labeled '4'. A blue box with the text 'Hepatotoxicityを選択して除外する' (Select Hepatotoxicity and exclude) is overlaid on the dialog. A blue box with a downward arrow is labeled '5'. At the bottom of the dialog, the 'Combine profiles logically with' section has 'and' selected, and the 'OK' button is highlighted with a blue box and labeled '6'. The main window shows the chemical structure of Aniline (SMILES: Nc1ccccc1) and its CAS number (367-25-9).

Target Chemicalの類似物質検索 (2)

Hazard Evaluation Support System

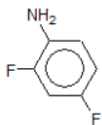
Hazard Evaluation Support System

Reset

Options

Help

Input
Profiling



Chemical name: **2,4-difluoroaniline**
CAS No: **367-25-9**
SMILES: **c1(N)c(F)cc(F)cc1**

to data matrix ->

metabolism/tautomerism mode...

HESSのカテゴリ(溶血性貧血)に該当する27物質の類似物質及び反復投与毒性試験結果が集められた。

RDT Data

Categories

Gap Filling

Report

Metabolism

Define

Subcategorize

Combine Categories

Grouping methods

- Organic functional groups (US EPA)
- Organic functional groups, Norbert H.
- Structure similarity
- Effect similarity
- Study No. (Link to SSRDT)
- Chemical No. (Link to HESS DB)
- RDT Report No.
- CSCL Class
- Rat Liver Metabolism Database

Toxicological

Repeated dose (HESS)

Custom

HESS Chemical Class

Defined Categories

- Document_1
 - [28] Anilines (Hemolytic anemia with methemo...

Delete

Delete All

Filter endpoint tree...

Structure

Substance Identity

Repeated Dose Toxicity

LOEL

Blood Chemical Examination

Hematological Examination

Histopathological Findings

Organ Weights

NOEL

Profile

Study No. (Link to SSRDT)

Chemical No. (Link to HESS DB)

RDT Report No.

Rat Liver Metabolism Database

Repeated dose (HESS)

Min

(12/19)

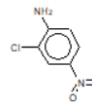
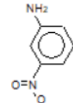
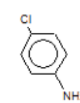
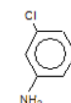
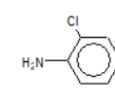
(25/147)

(23/158)

(18/56)

(27/630)

1 (Target)



M: 20 mg/kg/day

M: 10 mg/kg/day

M: 5 mg/kg/day

M: 15 mg/kg/day

M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 5 mg/kg/day, 5 ...	M: 15 mg/kg/day, ...	
M: 80 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 15 mg/kg/day, ...	
M: 40 mg/kg/day, ...	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 15 mg/kg/day, ...	
M: 10 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 15 mg/kg/day, ...	M: 100 mg/kg/d...

312

313

950

5

701

301

302

781

5

564

301

301

806

5

591

Root of map No. 90

Root of map No. 248

Root of map No. 249

Root of map No. 250

Root of map No. 6

N/A

Metabolite in map ...

Metabolite in map ...

Metabolite in map ...

Metabolite in map ...

Metabolite in map ...

Anilines (Hemolyti...
Anilines (Hepatoto...Anilines (Hemolyti...
Anilines (Hepatoto...
Styrene (Renal To...
Toluene (Renal tox...Anilines (Hemolyti...
Anilines (Hepatoto...Anilines (Hemolyti...
Anilines (Hepatoto...
Chlorphentermine (...
Clofibrate (Hepatot...Anilines (Hemolyti...
Anilines (Hepatoto...
Nitrobenzenes (He...
Nitrobenzenes (He...Anilines (Hemoly...
Anilines (Hepatoc...
Nitrobenzenes (I...
Nitrobenzenes (I...

類似物質のLOELs/NOELs

類似物質のRDT data

Filter endpoint tree... 1 (Target)

エンドポイント

- Substance Identity
- Repeated Dose Toxicity
 - LOEL
 - Blood Chemical Examination (16/112)
 - FOB (1/2)
 - General Signs (14/78)
 - Hematological Examination
 - Blood Cell (5/9)
 - Blood Cell (Coagulation) (4/5)
 - Blood Cell (Erythrocyte)
 - Undefined Tissue
 - RBC↓ (15/25)**
 - HGB↓ (14/25)
 - MCV↑ (9/15)
 - MCV↓ (1/1)
 - MCH↑ (7/12)
 - MCH↓ (1/1)

<chem>Nc1ccc(F)c(F)c1</chem>	<chem>Nc1ccc(Cl)cc1</chem>	<chem>Nc1ccc(Cl)cc1</chem>	<chem>Cc1ccc(N)cc1</chem>	<chem>Cc1ccc(N)cc1</chem>	<chem>Cc1ccc(N)cc1</chem>	<chem>Cc1ccc(N)cc1</chem>	<chem>Cc1ccc(N)cc1</chem>	<chem>Cc1ccc(N)cc1</chem>	<chem>Nc1ccc(Cl)cc1</chem>
	M: 40 mg/kg/day, 1...	M: 160 mg/kg/day, ...	M: 100 mg/kg/day, ...	M: 12.5 mg/kg/day, ...	M: 60 mg/kg/day, 3...	M: 40 mg/kg/day, 1...	M: 50 mg/kg/day, 2...	M: 50 mg/kg	
	M: 20 mg/kg/day, 4...	M: 80 mg/kg/day, 8...	M: 100 mg/kg/day, ...		M: 300 mg/kg/day, ...	M: 50 mg/kg/day, 5...			M: 10 mg/kg
	M: 20 mg/kg/day, 8...	M: 20 mg/kg/day, 1...	M: 100 mg/kg/day	M: 50 mg/kg/day	M: 60 mg/kg/day	M: 250 mg/kg/day, ...	M: 250 mg/kg/day, ...		
	M: 20 mg/kg/day, 4...	M: 10 mg/kg/day, 1...	M: 100 mg/kg/day	M: 50 mg/kg/day	M: 60 mg/kg/day	M: 100 mg/kg/day, ...	M: 250 mg/kg/day, ...	M: 50 mg/kg	
				M: 50 mg/kg/day		M: 250 mg/kg/day		M: 50 mg/kg	

red blood cells (RBC)の減少に関するLOELs

(# of chemicals / # of data points)

セルをダブルクリックで
試験データ詳細表示



Data points

	Endpoint	Value	Original value	Route	Strain	Examination items	Effect	Test
	LOEL	20 mg/kg/day	20 mg/kg/day	Oral (Gavage)	F344	Hematological examination	RBC↓	NT
2	LOEL	80 mg/kg/day	80 mg/kg/day	Oral (Gavage)	F344	Hematological	RBC↓	NT

Transpose

LOELs/NOELsを予測するエンドポイントの選択

メトヘモグロビン血症をともなう溶血性貧血のLOELs

メトヘモグロビン血症をともなう溶血性貧血に関連した所見のみを表示

Min (9/14)	M: 20 mg/kg/day	M: 10 mg/kg/day	M: 30 mg/kg/day
			M: 100 mg/kg/day
(15/25)	M: 20 mg/kg/day, 8...	M: 20 mg/kg/day, 1...	M: 100 mg/kg/day
(14/25)	M: 20 mg/kg/day, 4...	M: 10 mg/kg/day, 1...	M: 100 mg/kg/day
	M: 20 mg/kg/day, 4...	M: 10 mg/kg/day, 1...	
	M: 80 mg/kg/day, 8...	M: 20 mg/kg/day, 1...	M: 100 mg/kg/day
	M: 80 mg/kg/day, 8...	M: 20 mg/kg/day, 4...	M: 30 mg/kg/day, 3...
	M: 40 mg/kg/day, 4...	M: 20 mg/kg/day, 2...	
	M: 160 mg/kg/day, ...	M: 160 mg/kg/day, ...	M: 30 mg/kg/day

メトヘモグロビン血症をともなう溶血性貧血に関連した所見のみを表示

メトヘモグロビン血症をともなう溶血性貧血のLOELs

溶血性貧血のLOELを表示
青丸あたりで右クリック
Function -> minimum

Hide
Show hidden
Collapse all
Sort (target priority)
Sort
Function...
Filter effects
Set tree hierarchy...
Export CAS list
Export
Copy path

All
Average
Min
Max

Hazard Evaluation Support System

Chemical name: 2,4-difluoroaniline
 CAS No: 367-25-9
 SMILES: c1(N)c(F)cc(F)cc1

to data matrix ->

Input
 Profiling
 RDT Data
 Categories
 Gap Filling
 Report
 Metabolism

2

Show Boundaries Apply New Scheme

1

Profilers

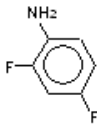
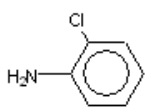
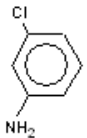
Filter endpoint tree...

Structure

Substance Identity
 Repeated Dose Toxicity
 Profile

Study No. (Link to SSRDT)
 Chemical No. (Link to HESS DB)
 RDT Report No.
 Rat Liver Metabolism Database
 Repeated dose (HESS)

1 (Target) 2 3

		
	M: 10 mg/kg/day, 1...	M: 10 mg/kg/day, 1...
	312	313
	301	302
	301	301
Root of map No. 901	Root of map No. 248 Metabolite in map ...	Root of map No. 249 Metabolite in map ...
Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...

試験データの要約 (SSRDT) へリンク

HESS DB (試験報告書DB、毒性作用機序DB、ADME DB) へリンク

ラット代謝マップDBへリンク

16 Anilines (Hemolytic anemia with methemoglobine) Developed by LMC, Bulgaria STOP

Read Acrossによるデータギャップ

類似物質の溶血性貧血LOELから、対象物質の溶血性貧血LOELを予測

Read-acrossを選択し、**Apply**

1	2	3	4	5	6	7	8	9
Min 9/14	10 mg/kg/day	M: 10 mg/kg/day	M: 30 mg/kg/day	M: 12.5 mg/kg/day	M: 2.4 mg/kg/day	M: 160 mg/kg/day	M: 250 mg/kg/day	M: 2 mg/kg/day
		M: 100 mg/kg/day	M: 50 mg/kg/day	M: 60 mg/kg/day				M: 50 mg/kg/day

Possible data inconsistency

- Examination items
- Effect
- Tissue
- Organ (Tissue)
- Scale/Unit
 - mg/kg/day
 - mg/L

Scaleから“mg/L”のチェックを外し、OK

Selected [1066/1157] points

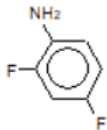
LOELの予測

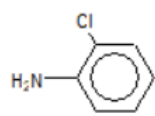
溶血性貧血のLOEL予測値 : 38.0 mg/kg/day


logKowが近い類似物質5つから target chemicalのLOELを予測


1 (Target)
2
3
4
5
7


Structure











LOEL (26/380) Min

M: 20 mg/kg/day

M: 10 mg/l

「Accept the prediction results」で予測を確定し、「return to the data matrix」でもとに戻る。

Descriptors Prediction

Read across prediction of LOEL,
taking the average from the nearest 5 neighbours, based on 5 data points from 5 neighbour chemicals,
Observed target value: N/A, Predicted target value: 38.0 mg/kg/day

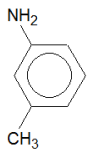
nite - chemical details for 'c1(N)cc(C)ccc1'

Smiles: c1(N)cc(C)ccc1

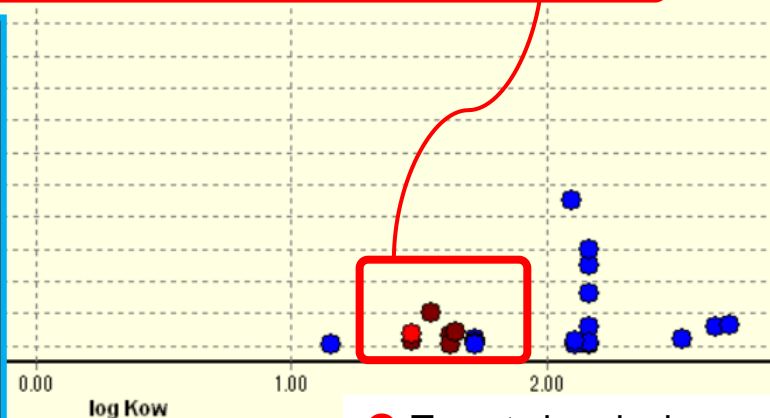
Chem. name(s): 3-methylaniline; m-toluidine; 3-toluidine

CAS No.: 108-44-1

Current subcategorization: N/A



Descriptor	Units	Value	Endpoint reference	Units	Value
log Kow		1.62	Endpoint obs. data (recalculated)	mg/kg/day	30.0
Molar refraction I		36.0			
Molar refraction II		36.0			
Molecular weight	Da	107			
Number of aromatic bonds		6.00			
Number of cyclic bonds		6.00			



●: Target chemical

●: 予測に使用した類似物質

●: 予測に使用していない類似物質

Accept prediction

Return to matrix

- ⊕ Select/filter data
- ⊕ Selection navigation
- ⊕ Gap filling approach
- ⊕ Descriptors/data
- ⊕ Model/(Q)SAR
- ⊕ Calculation options
- ⊕ Visual options
- ⊕ Information
- ⊕ Miscellaneous

データギャップ方法のオプション

類似物質のプロットをダブルクリックすると、データの詳細が表示

nite

詳細予測

専門家の知見や、HESS が提示する様々な関連情報を吟味することにより、HESSが提示したカテゴリーの妥当性を詳細に確認し、必要に応じて、カテゴリーの修正や組み直しを行った上で評価する。

1. 各試験データの毒性の内容の吟味
2. 試験条件の絞り込み
3. 代謝・メカニズムの情報の吟味
4. データギャップ補完に使用する所見の選定、算出方法

Report作成

Hazard Evaluation Support System

Hazard Evaluation Support System Reset Options Help

Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism

Chemical name: **2,4-difluoroaniline**
CAS No: **367-25-9**
SMILES: **c1(N)c(F)cc(F)cc1**

to data matrix -> metabolism mode...

Reports

- Create
- Save as PDF
- Print
- Save as HTML
- Close
- Save as RTF

Repository

Available data to report

- Predictions
 - [1] NITE HESS prediction for LOEL
- (Q)SARs
- Categories

Prediction [1]

Prediction of LOEL for 2,4-difluoroaniline 1 / 25

NITE HESS prediction based on read-across

Prediction of LOEL for 2,4-difluoroaniline

17 Anilines (Hemolytic anemia with methemoglobinemia) Rare Developed by LMC, Bulgaria STOP

HESSの入手方法

NITEのHPからユーザー登録することで、HESS/HESS DBのインストールファイル一式を無料でダウンロードできます。

http://www.nite.go.jp/chem/qsar/hess_01.html

(検索キーワード“NITE”, “HESS”)