



# 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

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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。

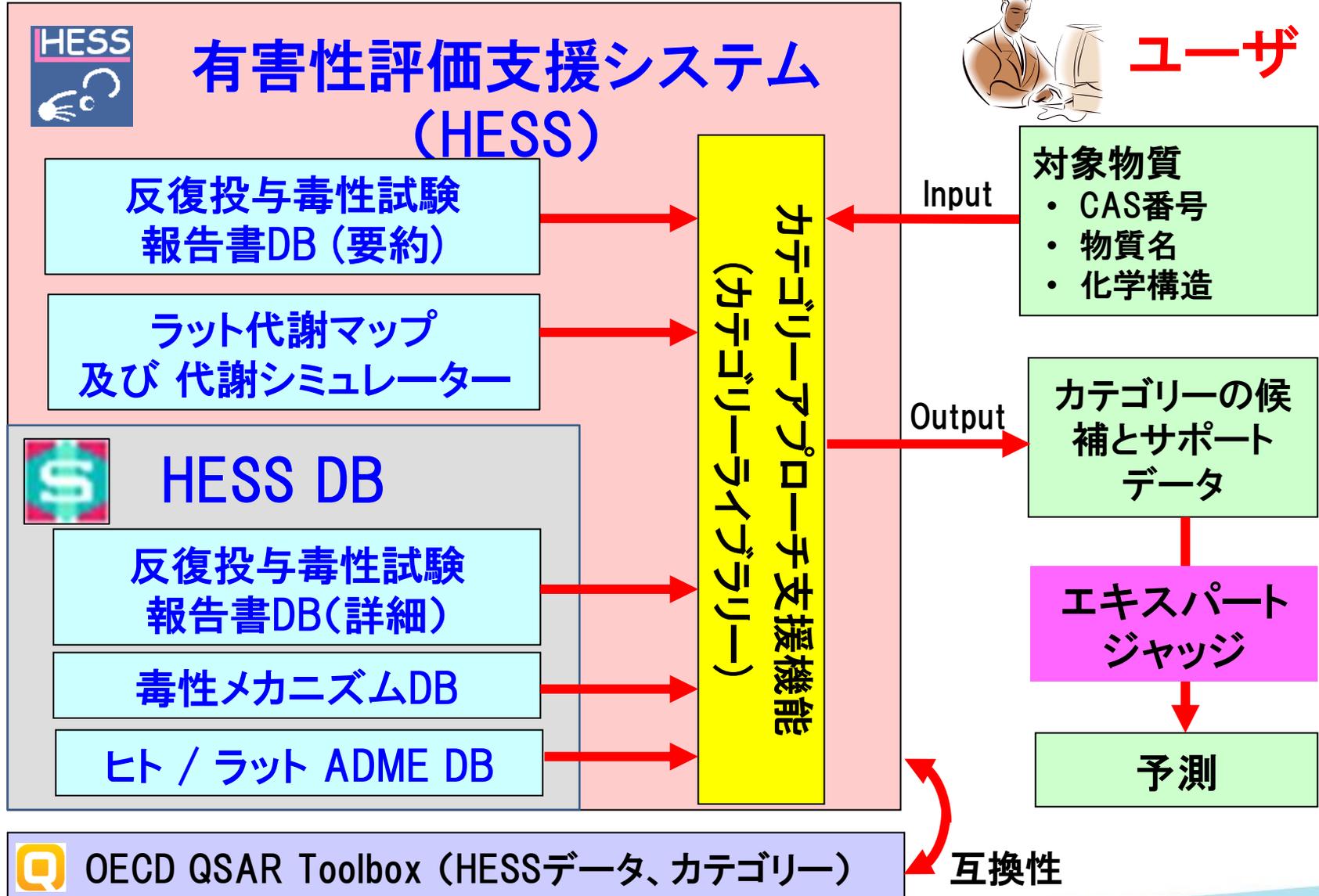
開発方針：

- ・ 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

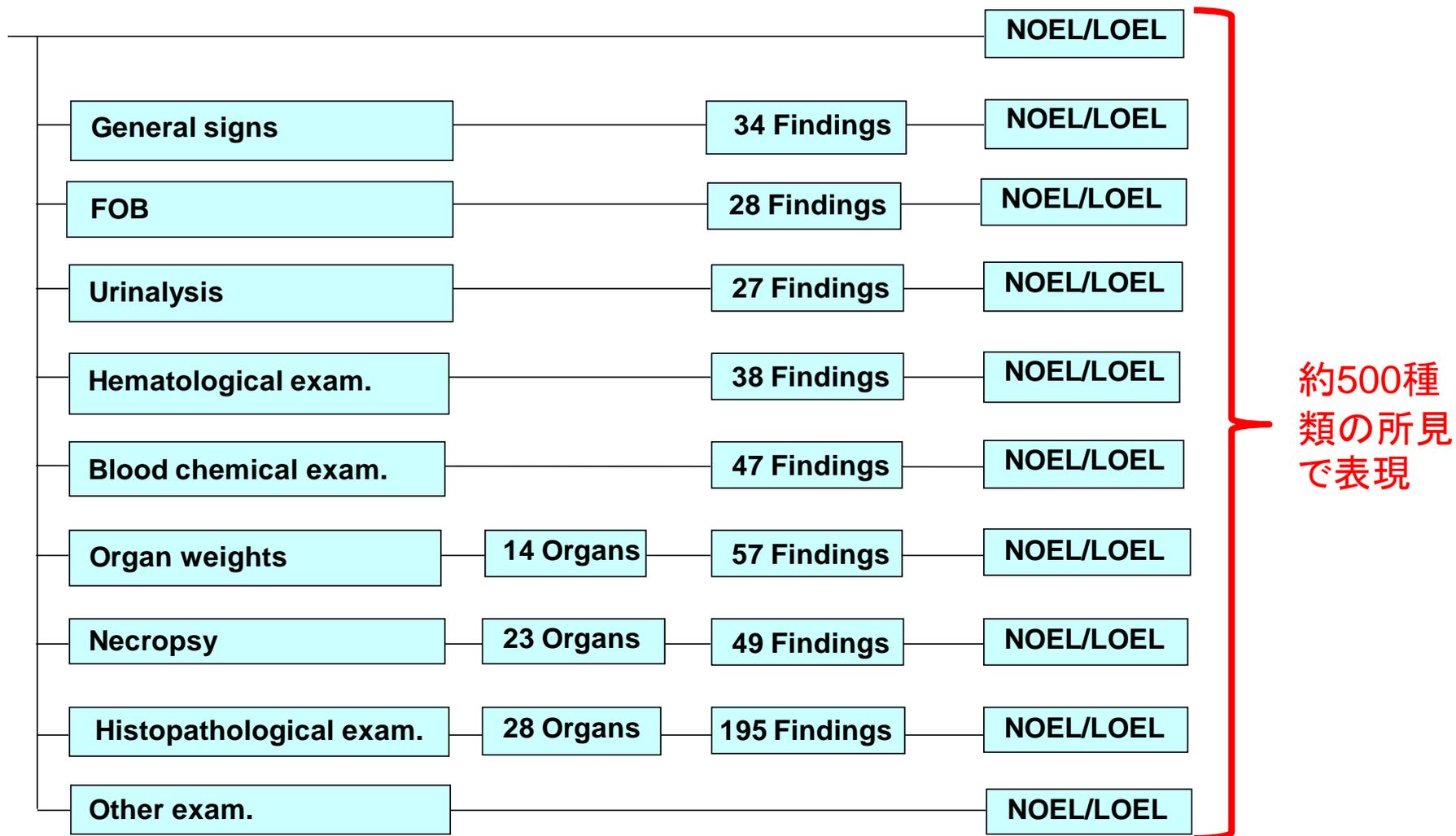
# HESSに収載されているSub database

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
<b>HESS Repeated Dose Toxicity</b>	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)(C1CCC(O)CC1)CC(C)(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)CC1
- 15. c1(CC(=O)O)C2C(CCCC2)CC1
- 16. c1(CC(=O)O)C2C(CCCC2)CC1
- 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)(O)C2CCCC2)OC2CCCC2)C(C)CCCC1
- 24. c12c(ccc1)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=C2CCCC2)C2C(CC(S(=O)=O)O[Na])CC
- 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 illustrates the HESS (Hazard Evaluation Support System) interface. The main window shows the input section for 3,4-dimethylaniline (3,4-xylydine) with its chemical structure and SMILES string. The 'Profile' section is expanded to show 'Chemical No. (Link to HESS DB)' with a value of 1. A red box highlights this link, and a red arrow points to the 'Main [ HessDB\_Search ]' window. This window displays search results for '1' and a table with columns for 'Chem...', 'Chemical Data', 'Structure', 'Study Lin...', 'Adme...', and 'Mech...'. A red box highlights the 'Study Lin...' column value '<28>', with a red arrow pointing to the 'Study [ HessDB\_Search ]' window. This window shows detailed test results for the chemical, including a table of 'Test Result' data and a 'Descriptive Data' section.

**Chemical Input:**  
Chemical name: 3,4-dimethylaniline; 3,4-xylydine  
CAS No: 95-64-7  
SMILES: c1(C)(C)cc(N)cc1

**Profile:**  
Chemical No. (Link to HESS DB): 1

**Main [ HessDB\_Search ] Search Results:**

Chem...	Chemical Data	Structure	Study Lin...	Adme...	Mech...
[Cas_No.] 95-64-7	[Name] 3,4-Xylydine	<chem>Cc1ccc(N)cc1C</chem>	<28>	1171	1131

**Study [ HessDB\_Search ] Test Result:**

Test Result	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 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)	-	-

**Descriptive Data:**

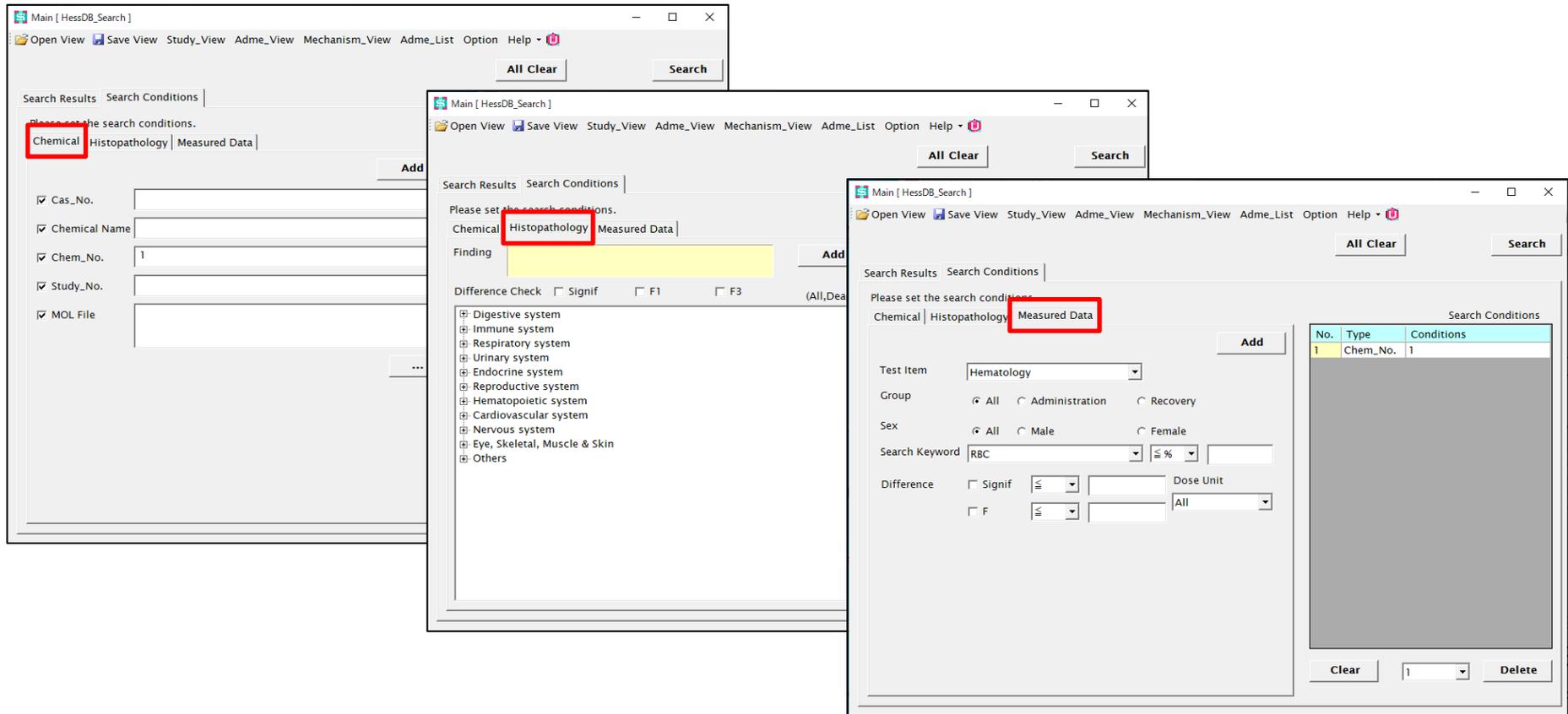
Clinical sign		FOB	
Male: N/A	Female: N/A	Male: -	Female: -

**Toxicological index:**

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

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	mean	SD	s... F1 F3
BUN	mq/dL	12	1	15 2	12 1	20 2	** Δ
CRN	mq/dL	0.6	0.1	0.6 0.1	0.6 0.0	0.6 0.0	
T-CHO	mq/dL	44	3	39 6	40 7	59 11	* Δ
TG	mq/dL	51	9	37 10	44 14	33 23	
PL							
T-BIL	mq/dL	0.11	0.03	0.14 0.02	0.12 0.02	0.16 0.06	
GLUC	mq/dL	133	16	140 21	125 16	132 24	
TP	q/dL	5.2	0.2	5.1 0.1	5.2 0.2	5.3 0.3	フラグ
BA							
ALB	q/dL	3.3	0.1	3.1 0.1	3.1 0.1	3.1 0.2	
A/G		1.67	0.15	1.58 0.08	1.54 0.17	1.38 0.08	**
Protein %	ALB						

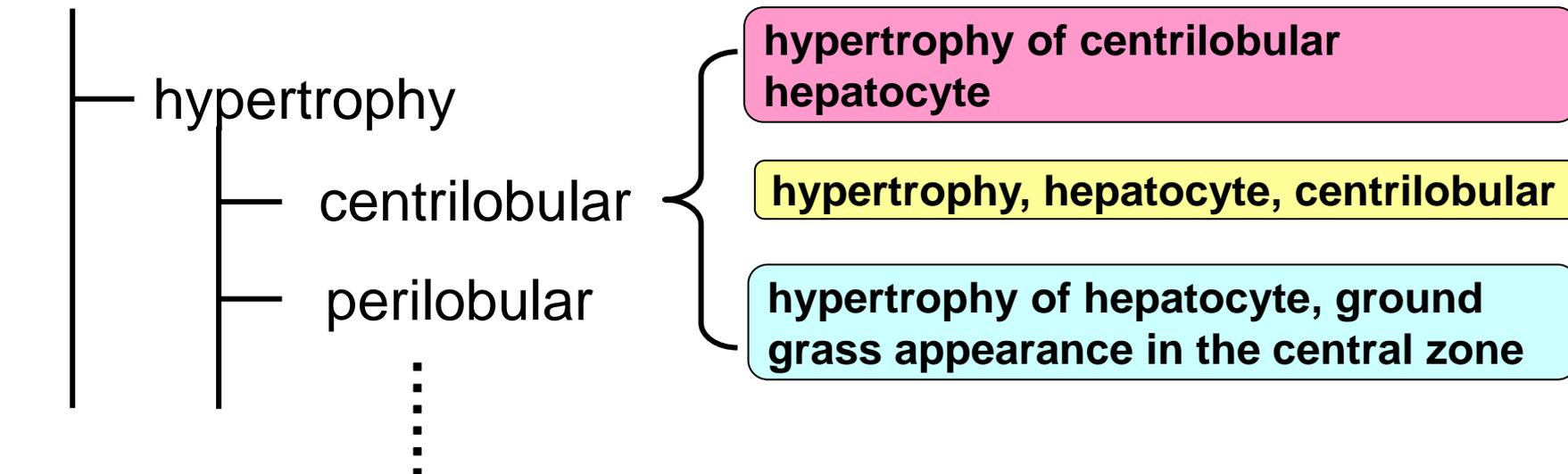
報告書に記載されている毒性所見の有意差マークのほか、本プロジェクトの毒性・病理専門家の意見や既存点検時の化学物質審議会判定に基づく、有意差マーク(フラグ)を付与するなどして、毒性学的な注意喚起を図った。

# 病理所見シソーラス

HESS DB

オリジナル試験報告書

Liver



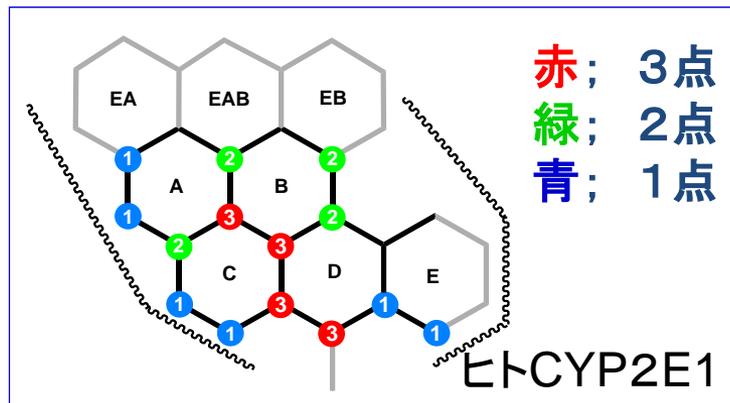
データの検索を正確に行えるよう、データベースに入力する病理所見について、専門家が同義語を分類し関連付けることによって、用語の統一を行い、シソーラスを作成(全83臓器・11302所見)

# 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

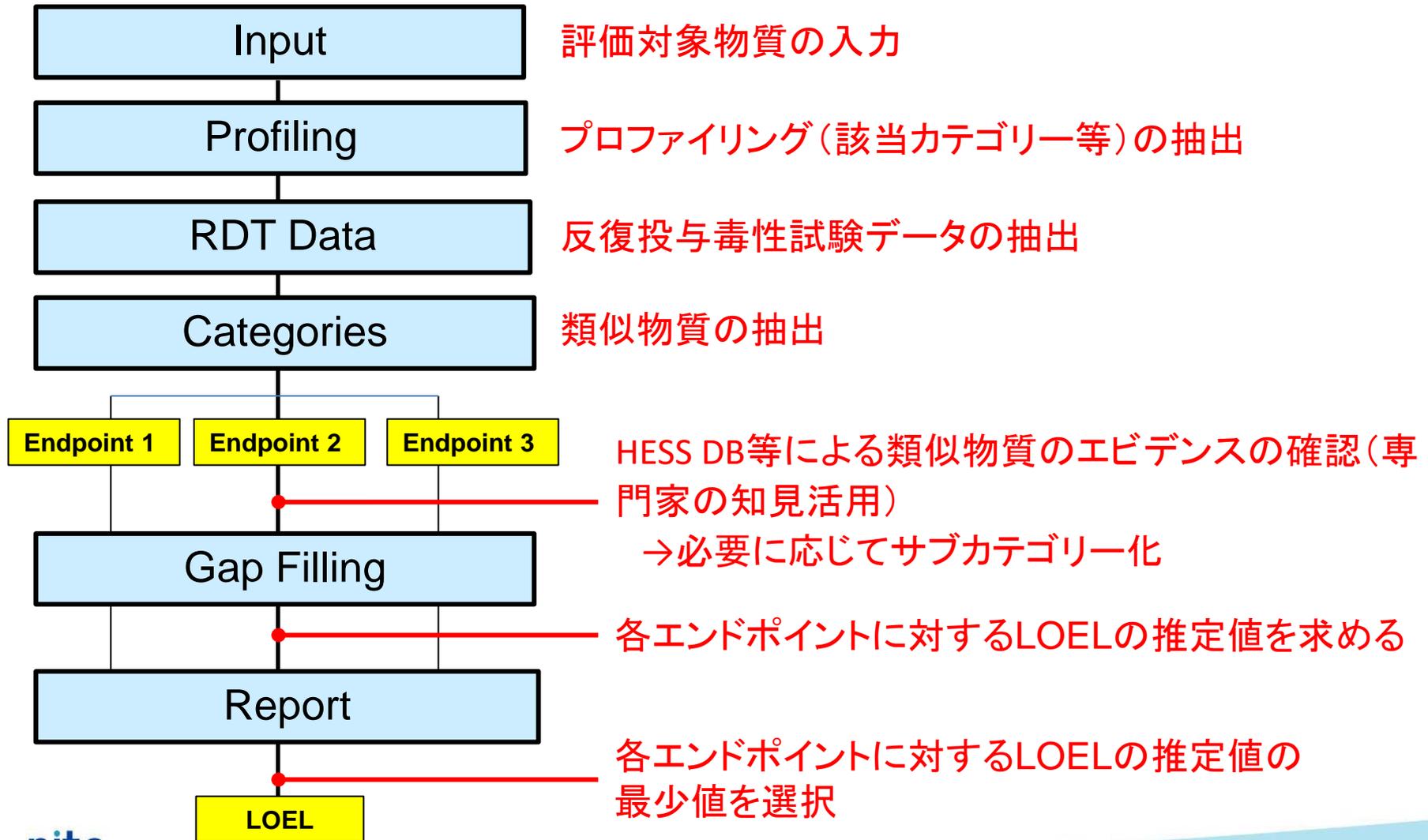
対象毒性：血液、肝臓、腎臓、精巣、神経、膀胱、甲状腺

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**

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**

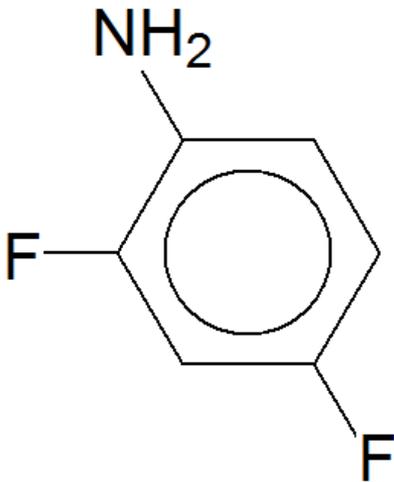
to data matrix -> metabolism mode...

**Set target** Add to post-targets list CAS# Chemical name Drawing RDT tests Database User List Load DB

Load Inventory

CAS # 367259 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 chemical structure of 2,4-difluoroaniline is shown, consisting of a benzene ring with an amino group (-NH<sub>2</sub>) at the 1-position and two fluorine atoms (-F) at the 2 and 4 positions. The 'Input' tab is selected in the left sidebar, and the 'Set target' button is highlighted. A search bar at the bottom shows the CAS number '367259' and a search button. The chemical structure is also displayed in a larger view at the bottom of the window.

# Target Chemical のプロファイリング

Hazard Evaluation Support System

## Hazard Evaluation Support System

Input

Profiling

RDT Data

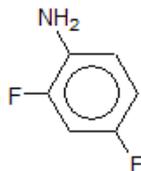
Categories

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

<b>Name</b>	Repeated dose (HESS)	<b>Donator(s)</b>	National Institute of Technology and Evaluation (NITE)
<b>Short description</b>	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.	<b>Author(s)</b>	The profiler was developed by National Institute of Technology and Evaluation (NITE) in the contract research project "Development of Hazard Assessment Techniques using
<b>Disclaimer</b>		<b>Website</b>	
		<b>Details</b>	
		<b>Version</b>	2.8
		<b>Number of categories</b>	237
		<b>Number of help files</b>	237

Close

1

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 sus
- 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<sup>1,2</sup>. The hemolytic anemia induced by anilines is considered to be related to the oxidation of erythrocytes by N-hydroxyl anilines<sup>3, 4</sup>.

- 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 reaction<sup>3</sup>.
- 4) Phagocytosis of degenerate erythrocytes, mainly in the spleen, results in hemolysis<sup>4</sup>.
- 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 examination<sup>5</sup>.
- 6) As a compensatory response to anemia, extramedullary hematopoiesis (mainly in the spleen) is observed on histopathological examination<sup>4</sup>.

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).

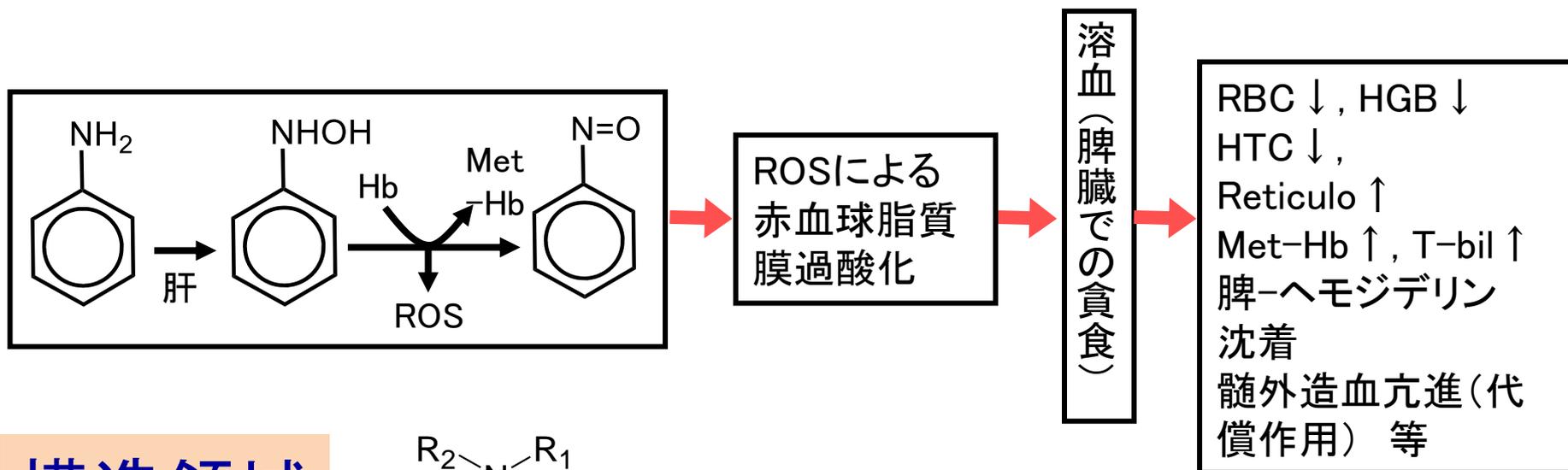
In studies of anilines without hydroxyl or acid groups (Nos. 1-23), the findings related to hemolytic anemia are frequently cited as the primary reason for the setting of a NOEL value.

# アニリン類の溶血性貧血カテゴリー

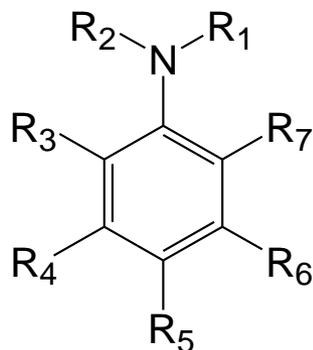
## AOP

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



## 構造領域



$\text{R}_1, \text{R}_2 = \text{H}, \text{methyl or ethyl}.$

$\text{R}_3 \sim \text{R}_7 = \text{H}, \text{alkyl}, \text{halo}, \text{alkoxy}, \text{NO}_2 \text{ or } \text{NH}_2.$

# Target Chemical のプロファイリング

Hazard Evaluation Support System

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

1 **Profiling**

2 **Report**

3 **Apply**

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

4 **ダブルクリックでカテゴリレポートへリンク**

プロファイルの選択

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

Metabolism

- Documented**
  - Observed Rat Liver metabolism
- Simulated**
  - Dissociation simulation
  - Liver Metabolism Simulator
  - NEDO In Vitro Rat Cellular Metabolism
  - NEDO In Vitro Rat Microsomal Metabolism
  - NEDO In Vivo Rat Metabolism Simulator

Filter endpoint tree...

1 (Target)

Structure

Substance Identity

- CAS Number: 367-25-9
- Chemical Name: **2,4-difluoroaniline**
- Structural Formula: c1(N)c(F)cc(F)cc1

Profile

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

Root of map No. 901

- Anilines (Hemolytic...)
- Anilines (Hepatotox...)

# Target Chemical のRDT dataの収集

**1** RDT Data

**2** Metabolism

**3** Gather

**4** NITE HESS

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

Structure: Nc1ccc(F)cc1F

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

- Anilines (Hemolytic...
- Anilines (Hepatotox...

Developed by LMC, Bulgaria

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

Source About

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)

The repeated dose toxicity test data in the database is extracted from the followings published test reports:

- MHLW/NHHS safety examination of existing chemicals under Chemical Substances Control Law in Japan: 282 studies

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.

Available Data

Available Data	
Number of chemicals	745
Number of data	486664
Number of endpoints	2
Name of endpoints	NOEL/LOEL
Version	
Adopted	Undefined
QA Chemical identity	
QA Data	

OK

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

1 Categories

2 HESSのプロファイルを選択

3 Define

4

5

6

Repeated dose (HESS)

Target(s) profiles

- Anilines (Hemolytic anemia with methemoglobinemia) Rank A
- Anilines (Hepatotoxicity) Rank C

Hepatotoxicityを選択して除外する

All Profiles

- 2-Acetylaminofluorene (Hepatotoxicity) Alert
- 2-Amino-4,5-diphenyl thiazole (Renal toxicity) Alert
- 2-Bromoethylamine (Renal Toxicity) Alert
- 3-Methylcholantrene (Hepatotoxicity) Alert
- 4,4'-Diethylaminoethoxyhexestrol (Hepatotoxicity) Alert
- 4,4'-Methylenedianilines/benzidines (Hepatobiliary toxicity) Rank B
- 4-Aminopyrazolopyrimidine (Hepatotoxicity) Alert
- 5-Azacytidine (Renal Toxicity) Alert
- Acetamide (Renal Toxicity) Alert
- Acetaminophen (Hepatotoxicity) Alert
- Acetaminophen (Renal toxicity) Alert
- Acetazolamide (Renal Toxicity) Alert
- Acrylamides (Neurotoxicity) Rank C
- Acydovir (Renal toxicity) Alert
- Aflatoxin B1 (Hepatotoxicity) Alert

Combine profiles logically with

and  or  Invert result  Strict

OK Cancel

17 Anilines (Hemolytic anemia with methemoglot

Developed by LMC, Bulgaria STOP

# Target Chemicalの類似物質検索 (2)

Hazard Evaluation Support System

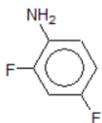
## Hazard Evaluation Support System

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 -&gt;

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)

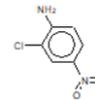
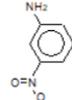
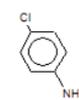
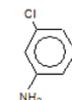
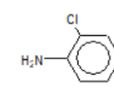
(25/147)

(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...

Root of map No. 90

Anilines (Hemolyti...  
Anilines (Hepatot...Root of map No. 248  
Metabolite in map ...Anilines (Hemolyti...  
Anilines (Hepatoto...  
Styrene (Renal To...  
Toluene (Renal tox...Root of map No. 249  
Metabolite in map ...  
Metabolite in map ...Anilines (Hemolyti...  
Anilines (Hepatoto...  
Chlorphentermine (...  
Clofibrate (Hepatot...Root of map No. 250  
Metabolite in map ...  
Metabolite in map ...  
Metabolite in map ...Anilines (Hemolyti...  
Anilines (Hepatoto...  
Nitrobenzenes (He...  
Nitrobenzenes (He...Root of map No. 6  
Metabolite in map ...Anilines (Hemolyti...  
Anilines (Hepatoto...  
Nitrobenzenes (He...  
Nitrobenzenes (He...

N/A

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**

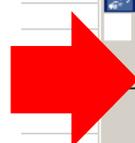
- Substance Identity
- Repeated Dose Toxicity
  - LOEL
    - Blood Chemical Examination (16/112)
    - FOB (1/2)
    - General Signs (14/78)
    - Hematological Examination
      - Blood Cell (5/9)
        - Blood Cell (Coagulation) (4/5)
        - Blood Cell (Erythrocyte)
          - Undefined Tissue
            - 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: 50 mg/kg
									M: 10 mg/kg
	M: 20 mg/kg/day, 3...	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
				M: 50 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**

<b>Min</b>	M: 20 mg/kg/day	M: 10 mg/kg/day	M: 30 mg/kg/day
(9/14)			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

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

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

**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

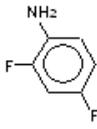
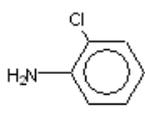
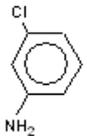
Profilers  
 Filtering methods  
 Empiric  
 Chemical  
 Groups of  
 Lipinski Ru  
 Organic fi  
 Organic fi  
 Organic fi  
 Organic fi  
 Study No  
 Chemical I  
 RDT Repr  
 CSCL Clas  
 Rat Liver  
 Toxicological  
 Repeated  
 Metabolism  
 Documented  
 Observed  
 Simulated  
 Dissociatic  
 Liver Met  
 NEDO In  
 NEDO In

1

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

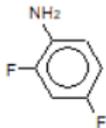
# LOELの予測

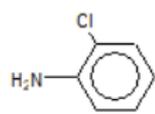
溶血性貧血のLOEL予測値 : 38.0 mg/kg/day

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

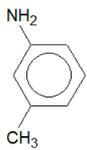
**nite** - chemical details for 'c1(N)cc(C)ccc1'

Smiles: c1(N)cc(C)ccc1

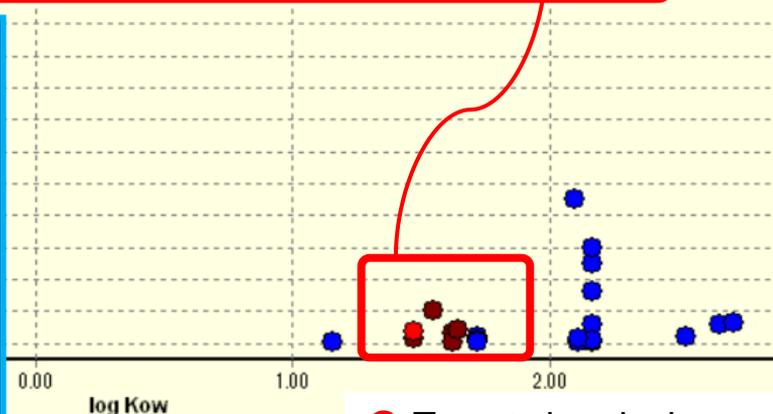
Chem. name(s): 3-methylaniline; m-toluidine; 3-toluidine

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

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

データギャップ方法のオプション

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

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

to data matrix ->      metabolism mode...

Input  
Profiling  
RDT Data  
Categories  
Gap Filling  
**Report**  
Metabolism

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

Register ...    Update ...  
Unregister    Clone ...  
Process History    Design ...

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

(検索キーワード“NITE”, “HESS”)