

nite



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

渡邊美智子

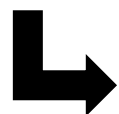
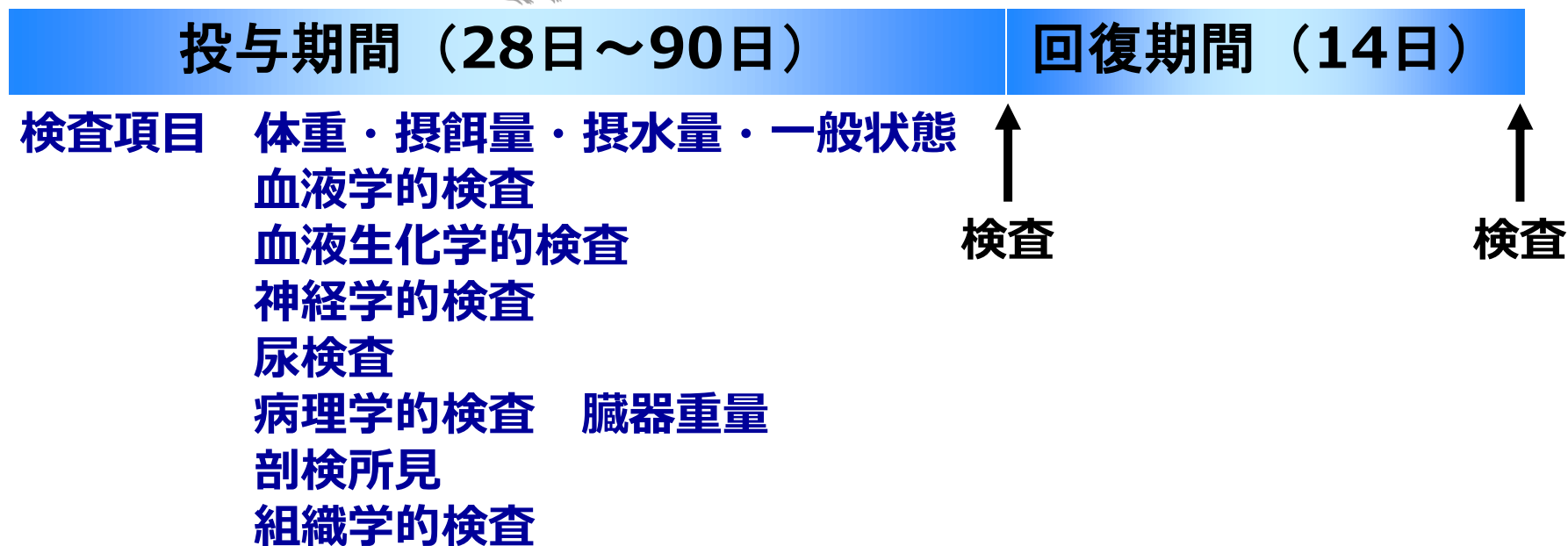
HESS及びHESS DBとは

- 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の要約及び毒性発現のメカニズムに関する情報などを収載
- HESSからHESSDBへ直接リンクが可能
- 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)



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」

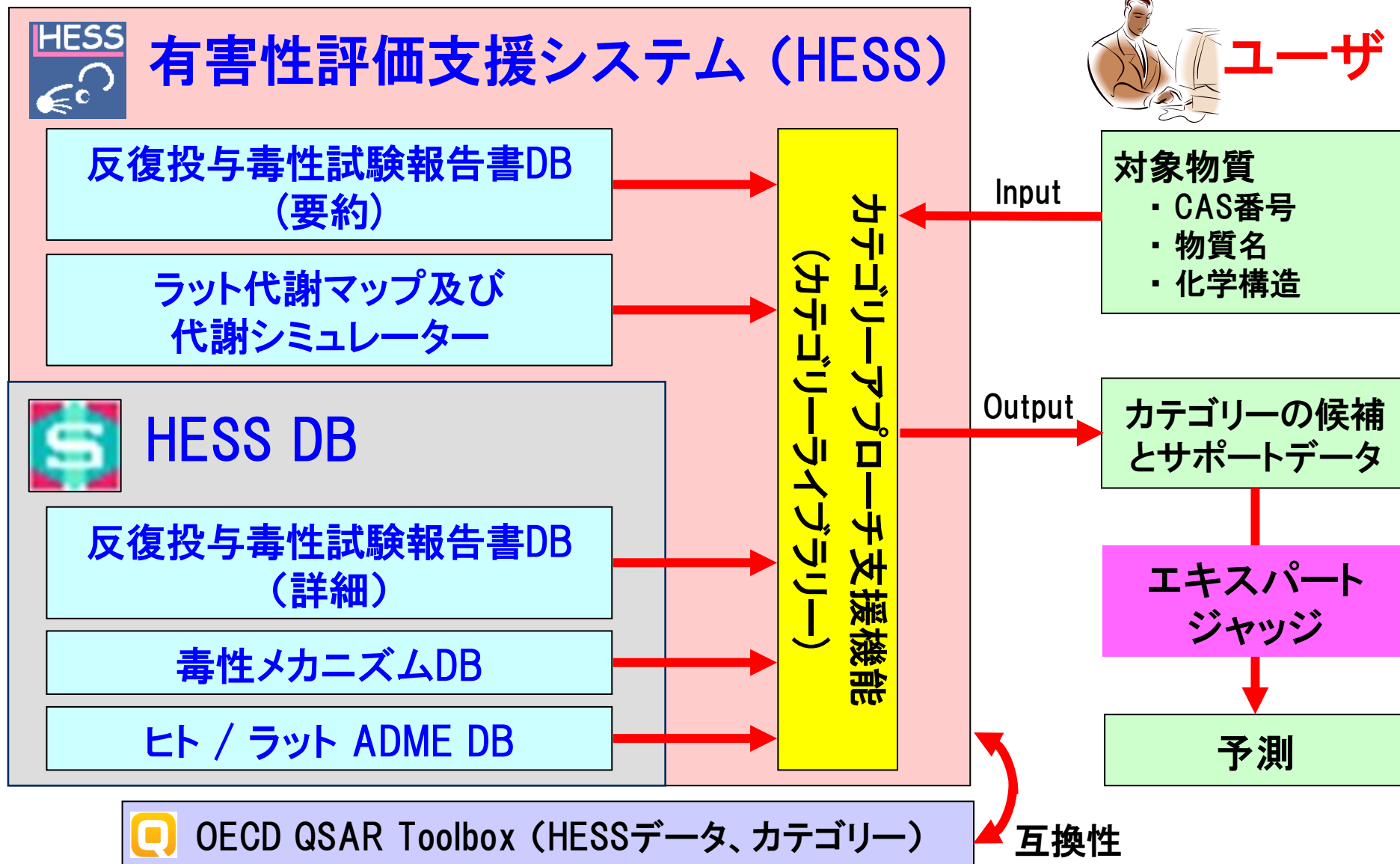
実施期間：平成19年度～平成23年度

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



HESSに収載されている情報

HESSに収載されているSub database

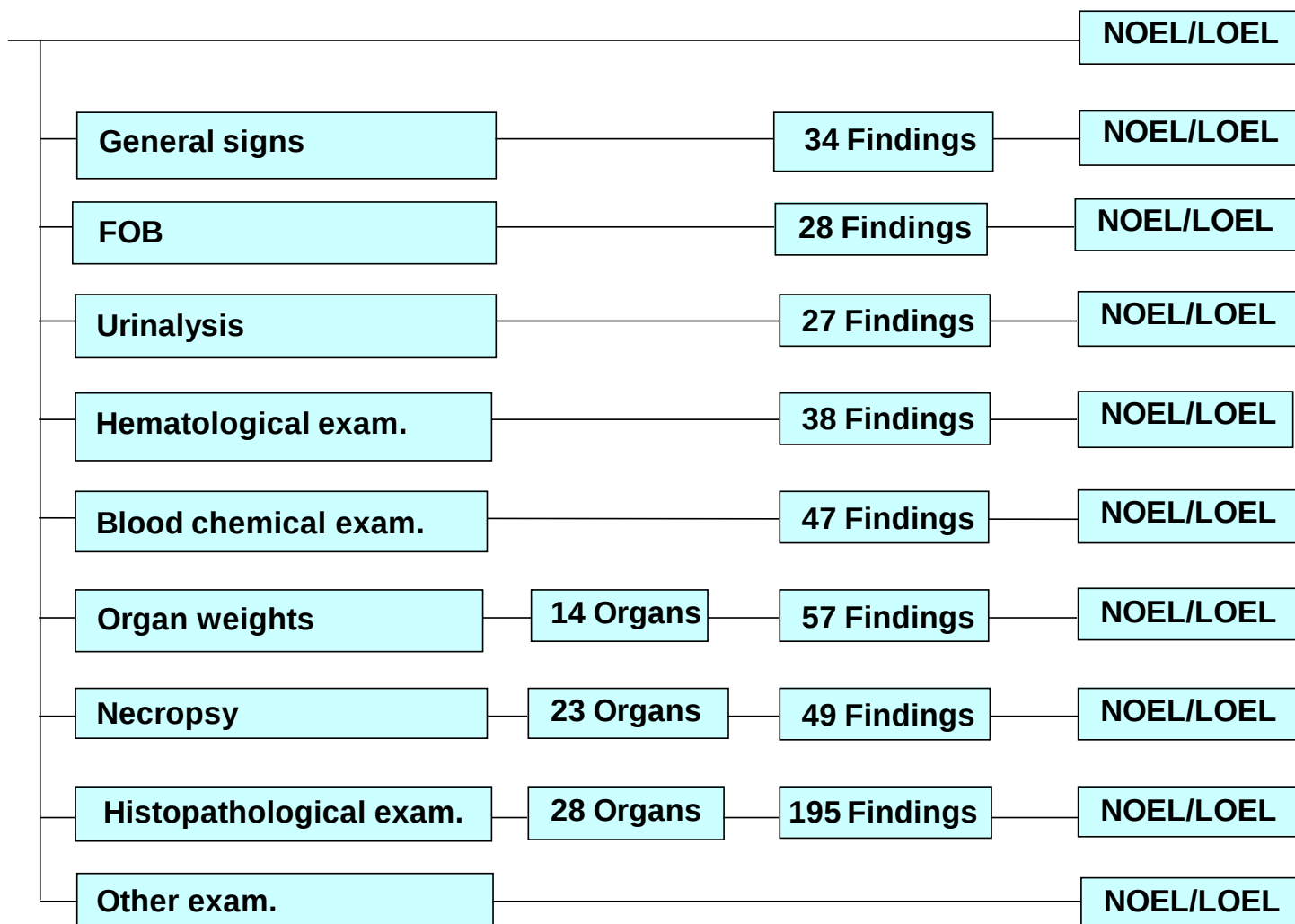
Ver.4.5(2024年)

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
<u>HESS Repeated Dose Toxicity</u>	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)	449	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	3061		

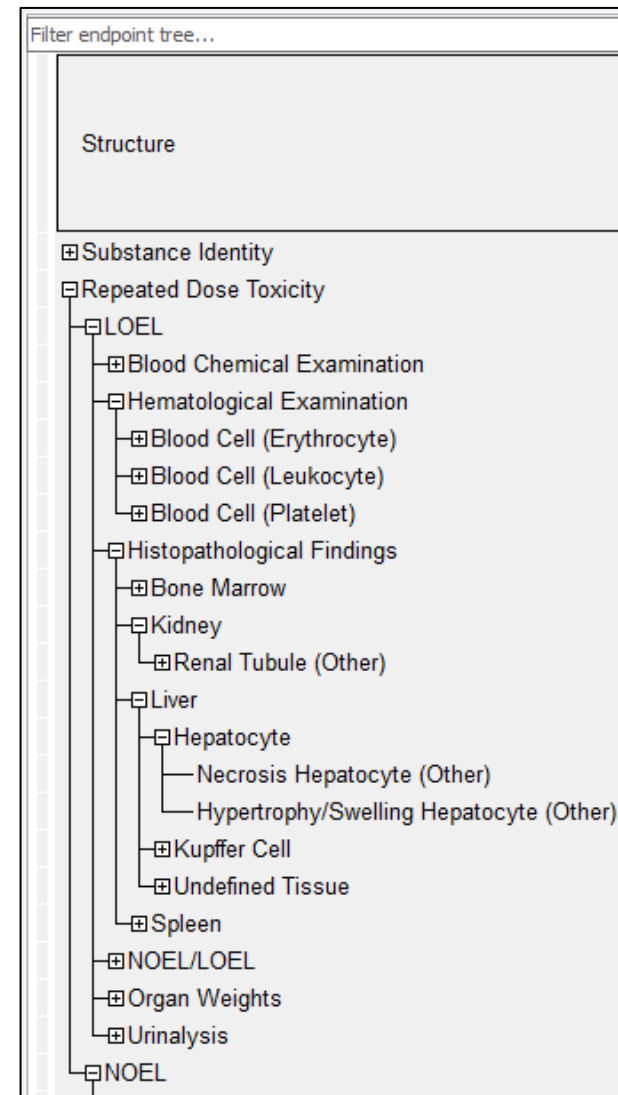
下線がついたデータベースは、詳細な試験報告書（HESS DB）があるもの。
 黄色マーカーがついたデータベースは、QSAR Toolboxにも収載されているもの。

HESSにおける反復投与毒性試験データのデータ構造

HESS画面表示例

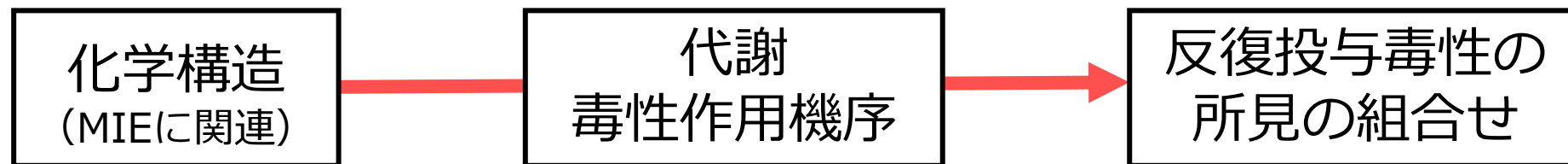


約500種類の
所見で表現



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)

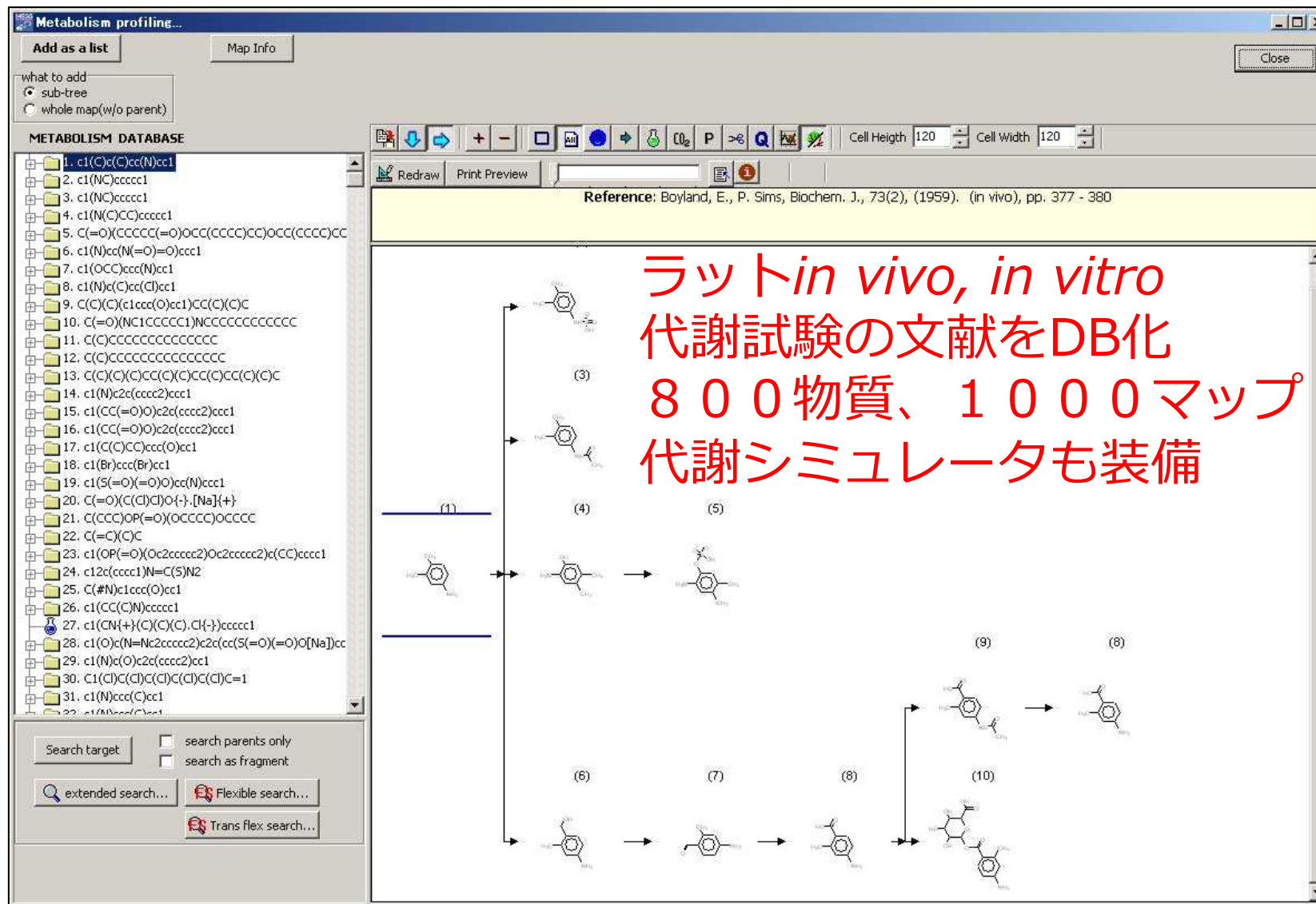


- ① 化学構造上の特徴
- ② 毒性のメカニズム
- ③ 反復投与毒性試験における毒性発現の傾向（毒性強度等）

↓ 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。

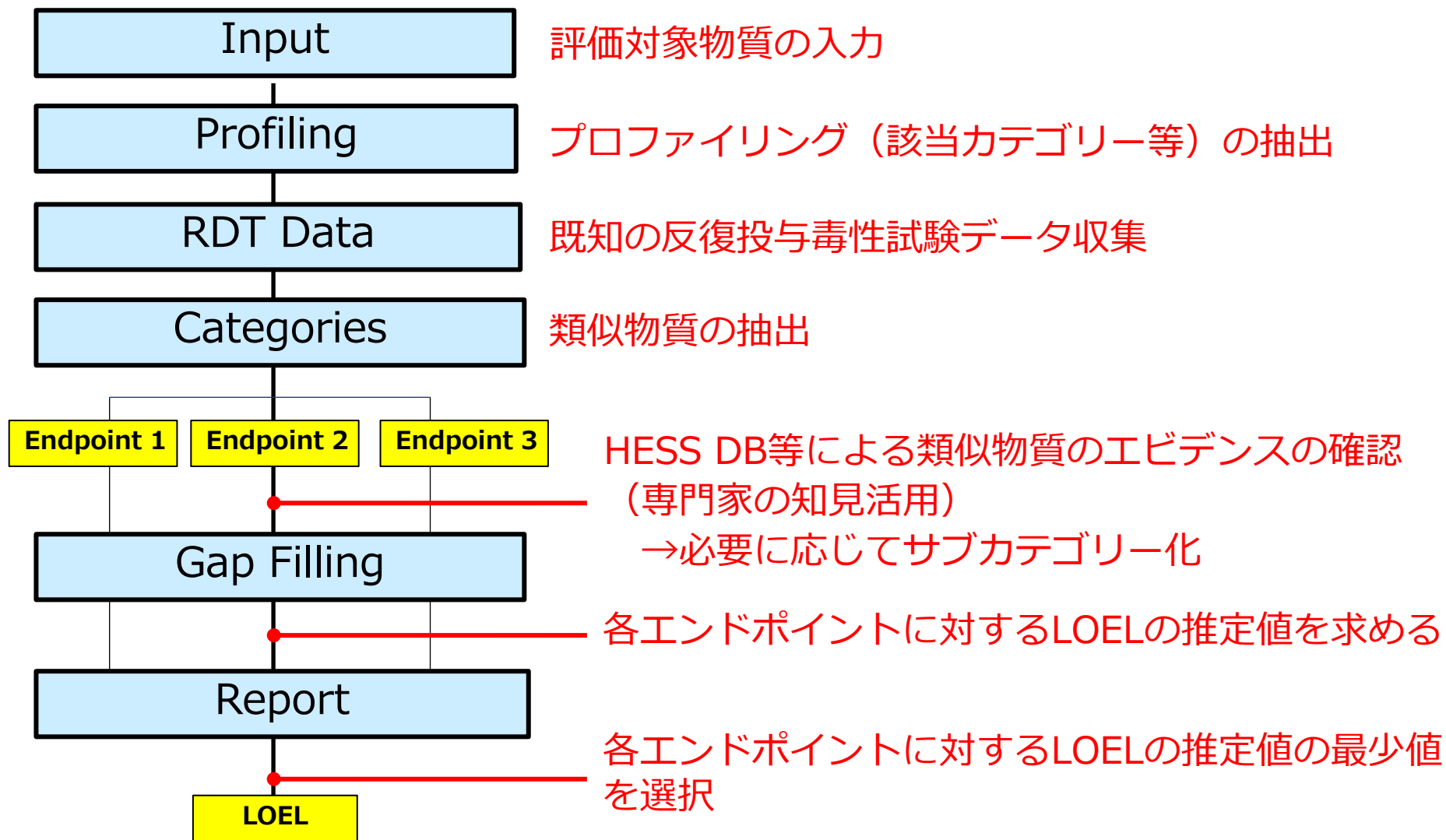
ラット代謝マップDB:代謝マップ



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 4-ethylaniline
(CAS RN: 589-16-2)

Target Chemicalの入力(SMILES)

1

2

3

Hazard Evaluation Support System

Reset Options Help

Input

Profiling

RDT Data

Categories

Gap Filling

Report

Metabolism

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No 589-16-2
SMILES c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

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

Load DB Load Inventory

SMILES/InChI c1(N)ccc(CC)cc1 Draw Mixture Edit names

000000-00-0

Templates Work

1/0/0

Developed by LMC, Bulgaria

STOP

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Target Chemicalの入力(CAS)

Hazard Evaluation Support System

1 **Input**

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No 589-16-2
SMILES c1(N)ccc(CC)cc1

2 **CAS#**

3 Search by CAS #
CAS # 589162

4 **Search**

Selected 1 of 0

Selected	CAS	Smiles	Depiction	Names	CAS/Name	2D/Name	CAS/2D
----------	-----	--------	-----------	-------	----------	---------	--------

drag the mouse with left button pressed to create bond

oasis-lmc.org

1 Single chemical

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Target Chemical のプロファイリング

1 **Profiling**

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

3 **About**

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	3.0
Number of categories	260
Number of help files	260

Close

1 Single chemical

Developed by LMC, Bulgaria

STOP

プロフィールの詳細表示

約260種類の
構造-毒性情報

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/Alcyclic hydrocarbons (Alpha 2u-glob)
- 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
- Clindamycin (Hepatotoxicity) Alert
- Clofibrate (Hepatotoxicity) Alert
- Coumarin (Hepatotoxicity) Alert
- Cuprizone (Hepatotoxicity) Alert
- Cydoheximide (Hepatotoxicity) Alert
- Cydophosphamide (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.

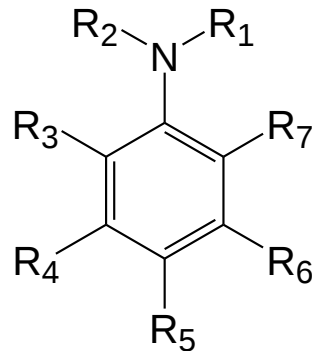
2. Observed Effects in the RDT DB

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

分子→細胞→生体レベルの毒性メカニズム



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

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

プロファイルの詳細には、30物質の単環アニリンの反復投与試験結果がまとめられている。

Target Chemical のプロファイリング

1 **Profiling**

2

3

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No 589-16-2
SMILES c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

Profiling methods

- ☐ Skin irritation/corrosion Exclusion r
- ☐ Skin irritation/corrosion Inclusion n
- 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)
 - ☐ CSCL Class
 - ☒ Rat Liver Metabolism Database
- Toxicological**
 - ☒ Repeated dose (HESS)
- Custom**

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 589-16-2
- Chemical Name 4-ethylaniline
benzenamine, 4-et...
- Structural Formula aniline, p-ethyl-
c1(N)ccc(CC)cc1

Profile

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

N/A

Anilines (Hemolyti...
Anilines (Hepatoto...
Procainamide (Ren...
Primary anilines

ダブルクリック

カテゴリーレポートへ

? Details Close

Target Chemicalの既知の反復投与毒性試験データ収集

1 **RDT Data**

2 **Report Metabolism**

3 **Gather**

4 **OK**

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No 589-16-2
SMILES c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

Filter endpoint tree...

Structure

Substance Identity

CAS Number 589-16-2

Chemical Name

Structural Formula

Profile

Database

☐ 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 (CSCL New Chemicals)

☐ TGP Repeated Dose Toxicity

☐ Tox-Omics RDT DB

☐ ToxRef DB

DELETE Database

Select all

Unselect all

Invert selection

About

Import...

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 765 industrial chemicals (1022 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: 269 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.

URL

Available Data

Number of chemicals	765
Number of data	487201
Number of endpoints	2
Name of endpoints	NOEL, LOEL
Version	
Adopted	Undefined
QA Chemical identity	
QA Data	

OK

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

1 Single chemical

Developed by LMC, Bulgaria

STOP

Target Chemicalの類似物質検索 (1)

Hazard Evaluation Support System

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-
CAS No: 589-16-2
SMILES: c1(N)ccc(CC)cc1

Repeated dose (HESS)

Target(s) profiles

- Anilines (Hemolytic anemia with methemoglobinemia) Rank A
- Anilines (Hepatotoxicity) Rank C
- Procainamide (Renal Toxicity) Alert

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
- ACE inhibitors and angiotensin II receptor blockers (Renal toxicity) R
- Acetamide (Renal Toxicity) Alert
- Acetaminophen (Hepatotoxicity) Alert
- Acetaminophen (Renal toxicity) Alert
- Acetazolamide (Renal Toxicity) Alert
- Acrylamides (Neurotoxicity) Rank C
- Acyclovir (Renal toxicity) Alert

Combine profiles logically with

☒ and ☐ or ☐ Invert result ☐ Strict

OK Cancel

Repeated dose (HESS)

Target(s) profiles

- Anilines (Hemolytic anemia with methemoglobinemia) Rank A

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
- ACE inhibitors and angiotensin II receptor blockers (Renal toxicity) R
- Acetamide (Renal Toxicity) Alert
- Acetaminophen (Hepatotoxicity) Alert
- Acetaminophen (Renal toxicity) Alert
- Acetazolamide (Renal Toxicity) Alert
- Acrylamides (Neurotoxicity) Rank C
- Acyclovir (Renal toxicity) Alert

Combine profiles logically with

☒ and ☐ or ☐ Invert result ☐ Strict

OK Cancel

1 Categories

2 Toxicological

3 Define

4 Filter endpoint tree...

5

6

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

Target Chemicalの類似物質検索 (2)

Hazard Evaluation Support System

Chemical name: 4-ethylaniline; benzenamine
CAS No: 589-16-2
SMILES: c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

Define category name

Category name (28 chemicals): hemoglobinemia Rank A (Repeated dose (HESS))

OK Cancel

Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism

Define
Subcategorize
Combine Categories

Grouping methods

- Organic functional groups
- Organic functional groups (nested)
- 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

Filter endpoint tree...

Structure

- Substance Identity
 - CAS Number
 - Chemical Name
 - Structural Formula
- Repeated Dose Toxicity
 - LOEL (26/1157)
 - NOEL (27/17056)
- Profile
 - Study No. (Link to SSRDT)
 - Chemical No. (Link to HESS DB)
 - RDT Report No.
 - Rat Liver Metabolism Database

Target

1 (Target)	2	3	4	5	6
589-16-2 4-ethylaniline benzenamine, 4-ethyl- aniline, p-ethyl-	95-51-2 2-chloroaniline o-chloroaniline	108-42-9 3-chloroaniline m-chloroaniline	106-47-8 4-chloroaniline p-chloroaniline	99-09-2 3-nitrobenzenamine m-nitroaniline benzenamine, 3-nitro- aniline, m-nitro- c1(N)cc(N(=O)=O)cc1	121-87-9 2-chloro-4-benzenamine aniline, 2-chloro- c1(N)c(Cl)ccc1
<chem>c1(N)ccc(CC)cc1</chem>	<chem>c1(Cl)c(N)cccc1</chem>	<chem>c1(Cl)cc(N)ccc1</chem>	<chem>c1(Cl)ccc(N)cc1</chem>	<chem>c1(N)cc(N(=O)=O)cc1</chem>	<chem>c1(N)c(Cl)ccc1</chem>
	M: 10 mg/kg/day, ... M: 10 mg/kg/day, ...	M: 10 mg/kg/day, ... M: 10 mg/kg/day, ...	M: 5 mg/kg/day, 5 ... M: 5 mg/kg/day, 5 ...	M: 15 mg/kg/day, ... M: 15 mg/kg/day, ...	M: 100 mg/kg/day, ...

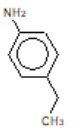
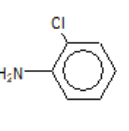
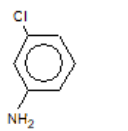
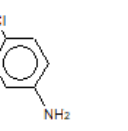
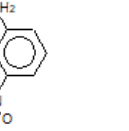
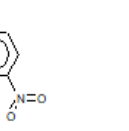
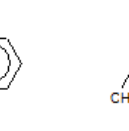
HESSのカテゴリ（溶血性貧血）に該当する27物質の類似物質及び反復投与毒性試験結果が集められた

28 Anilines (Hemolytic anemia with methemoglobinemia) Rank A (Repeated dose (HESS))

Developed by LMC, Bulgaria

類似物質のLOELs/NOELs

類似物質のRDT data

Filter endpoint tree...	1 (Target)	2	3	4	7	8		
Structure								
Substance Identity								
CAS Number	589-16-2	95-51-2	108-42-9	106-47-8	99-09-2	121-87-9	108-44-1	578-54-1
Chemical Name	4-ethylaniline benzenamine, 4-et... aniline, p-ethyl-	2-chloroaniline o-chloroaniline	3-chloroaniline m-chloroaniline	4-chloroaniline p-chloroaniline	3-nitrobenzenamine m-nitroaniline benzenamine, 3-nitro- aniline, m-nitro-	2-chloro-4-nitroaniline benzenamine, 2-ch... aniline, 2-chloro-4-...	3-methylaniline m-toluidine 3-toluidine	2-ethylaniline 2-ethylbenzenamine benzenamine, 2-et... aniline, o-ethyl-
Structural Formula	<chem>c1(N)ccc(CC)cc1</chem>	<chem>c1(Cl)c(N)cccc1</chem>	<chem>c1(Cl)cc(N)ccc1</chem>	<chem>c1(Cl)ccc(N)cc1</chem>	<chem>c1(N)cc(N(=O)=O)cc1</chem>	<chem>c1(N)c(Cl)cc(N(=O)=O)cc1</chem>	<chem>c1(N)cc(C)ccc1</chem>	<chem>c1(N)c(CC)cccc1</chem>
Repeated Dose Toxicity								
LOEL								
Blood Chemical Examination	(22/143)	M: 40 mg/kg/day, ...	M: 10 mg/kg/day, ...		M: 15 mg/kg/day, ...		M: 100 mg/kg/day,...	M: 12.5 mg/kg/day.
FOB	(2/3)							
General Signs	(21/106)	M: 20 mg/kg/day, ...	M: 80 mg/kg/day, ...	M: 80 mg/kg/day			M: 100 mg/kg/day,...	
Hematological Examination								
Blood Cell	(9/17)	M: 80 mg/kg/day, ...	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 15 mg/kg/day, ...			
Blood Cell (Coagulation)	(5/6)							
Blood Cell (Erythrocyte)								
Undefined Tissue								
RBC↓	(23/40)	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 5 mg/kg/day, 5 ...	M: 15 mg/kg/day, ...		M: 100 mg/kg/day	M: 50 mg/kg/day
HGB↓	(22/40)	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...	M: 5 mg/kg/day, 5 ...	M: 15 mg/kg/day, ...		M: 100 mg/kg/day	M: 50 mg/kg/day
MCV↑	(15/26)			M: 5 mg/kg/day, 1...	M: 50 mg/kg/day, ...			M: 50 mg/kg/day
MCV↓	(1/1)							
MCH↑	(13/23)							

(# of chemicals / # of data points)

red blood cells (RBC)の減少に関するLOELs

Data points						
Endpoint	Value	Original value	Route	Strain	Examination Items	Effect

red blood cells (RBC)の減少に関するLOELs

Data points								
	Endpoint	Value	Original value	Route	Strain	Examination items	Effect	Test
1	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

セルをダブルクリックで
試験データ詳細表示

LOELs/NOELsを予測するエンドポイントの選択

青丸あたりをダブルクリック

1

2

表示されている各所見の最小値を表示

メトヘモグロビン血症をとみなう溶血性貧血に関連した所見のみ表示

Chemical Structure	Endpoint	Value
<chem>Nc1ccc(C)cc1</chem>	Min	M: 10 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 10 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 5 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 15 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 30 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 12.5 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 100 mg/kg/day
<chem>Nc1ccc(Cl)cc1</chem>	Min	M: 50 mg/kg/day

エキスパートジャッジのための情報収集(1)

1

Input
Profiling

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No 589-16-2
SMILES c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

2

RDT Data
Categories
Gap Filling
Report
Metabolism

Profiling methods

- ☐ Skin irritation/corrosion Exclusion
- ☐ Skin irritation/corrosion Inclusion
- 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)
- Custom**

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

3

Structure

Filter endpoint tree...

1 (Target) 2 3

Structure

Methem...
HCT↓
Histopathological Findings (23/158)
Organ Weights (18/56)
NOEL (27/660)
Profile
Study No. (Link to SSRDT)
Chemical No. (Link to HESS DB)
RDT Report No.
Rat Liver Metabolism Database
N/A
Primary anilines
HESS Chemical Class
Metabolism

試験データの要約 (SSRDT) ヘリンク

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

類似物質のプロファイリングの取得
(各類似物質の詳細情報へのリンクの作成)

ラット代謝マップDBヘリンク

Profiling results

Chemical profile

Rat Liver Metabolism Database

Root of map No. 248

Metabolite in map No. 410

Details

Close

emolyti...
epatoto...
anal To...

Anilines (Hemolyti...
Anilines (Hepatoto...

Toluene (Renal tox...

Halobenzenes
Primary anilines

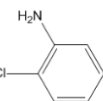
Halobenzenes
Primary anilines

エキスパートジャッジのための情報収集(2)

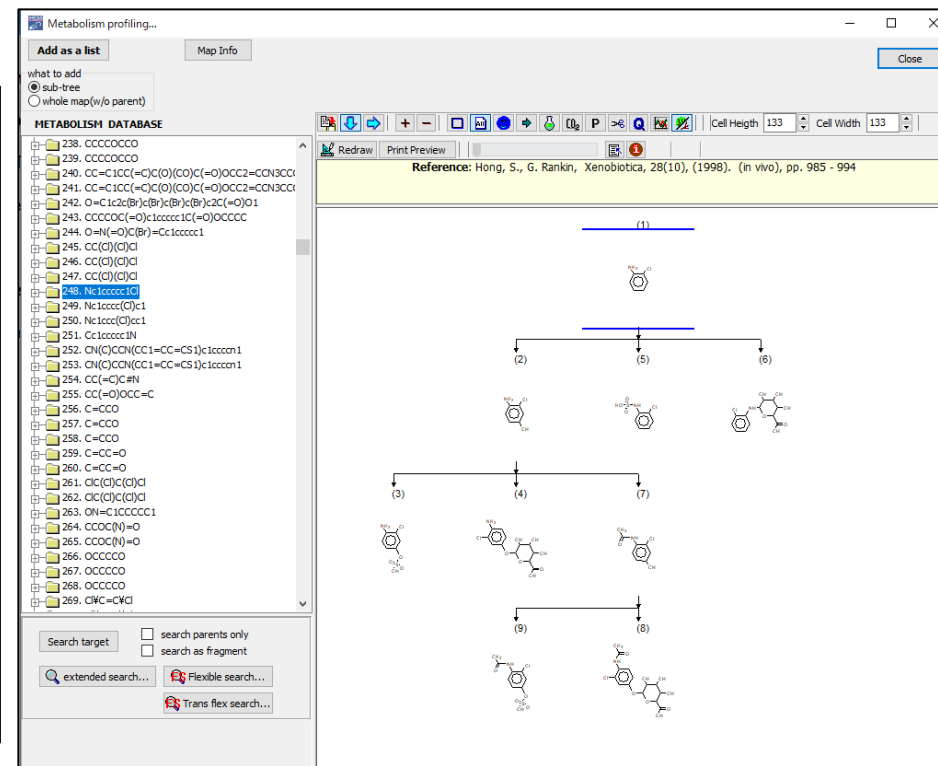
試験データの要約 (SSRDT)

S312-R301-C301	
Cas No.	95-51-2
Study type	Repeated dose oral toxicity study
Species	Rat (F344/N)
Route	Gavage
Solvent	1M hydrochloric acid, sonicating for 20 minutes, and diluting to volume with deionized water
Dose level	5 doses (10, 20, 40, 80, 160 mg/kg/day), 10 animals/group/sex
Death	20 (2: 1/10, 40: 2: 1/10)
NOEL	<10 mg/kg/day
Clinical observation	
Tremors: >80% Wasting: 160% Bleuish discoloration of genital and footpad regions: >80%	
FOB	
Body weight	
Food consumption	
Water consumption	
Urinalysis	
Hematology	
Blood Chemistry	
Absolute organ weight	
Relative organ weight	
Histopathology	

HESS DB→詳細は次の講義にて

Main [HessDB_Search]					
Open View Save View Study_View Adme_View Mechanism_View Adme_List Option Help					
Search Results Search Conditions					
Results : 1					
Chem...	Chemical Data	Structure	Study Lin...	Adme...	Mech...
301	[Cas_No.] 95-51-2 [Name] o-Chloroaniline		312<91*>	301[7]	301[2]

ラット代謝マップDB



Read Acrossによるデータギャップ

Hazard Evaluation Support System

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; anilin
CAS No: 589-16-2
SMILES: c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

1 Categories 2 3 4

Gap Filling

Report Metabolism

Target Endpoint: not defined

Filter endpoint tree...

Structure

Min

1 (Target) 2 3

Similar substances' hemolytic anemia LOEL from, predict the target substance's hemolytic anemia LOEL

Possible data inconsistency

Examination items

Effect

Tissue

Organ (Tissue)

Scale/Unit

☒ mg/kg/day

☐ mg/L

Scaleから“mg/L”のチェックを外す

Selected [395/400] points

OK Cancel

Endpoint	1 (Target)	2	3
LOEL	(12/15)		
Blood Chemical Examination			
Hematological Examination			
Blood Cell (Erythrocyte)			
Undefined Tissue			
RBC↓	(23/40)	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...
HGB↓	(22/40)	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...
Reticulocyte↑	(17/29)	M: 20 mg/kg/day, ...	M: 10 mg/kg/day, ...
Methemoglobin↑	(11/20)	M: 10 mg/kg/day, ...	M: 10 mg/kg/day, ...
HCT↓	(22/38)	M: 80 mg/kg/day, ...	M: 10 mg/kg/day, ...
Histopathological Findings	(23/158)	M: 80 mg/kg/day, ...	M: 10 mg/kg/day, ...
Organ Weights	(18/56)	M: 40 mg/kg/day, ...	M: 20 mg/kg/day, ...
NOEL	(27/660)	M: 10 mg/kg/day, ...	M: 10 mg/kg/day, ...
Profile			
Study No. (Link to SSRDT)	312	313	950
Chemical No. (Link to HESS DB)	301	302	781
RDRT Report No.	301	301	806
Rat Liver Metabolism Database	N/A	Root of map No. 248 Metabolite in map ...	Root of map No. 249 Metabolite in map ...
Repeated dose (HESS)	Anilines (Hemolyti... Anilines (Hepatoto... Procainamide (Ren...)	Anilines (Hemolyti... Anilines (Hepatoto... Styrene (Renal To... Toluene (Renal tox...)	Anilines (Hemolyti... Anilines (Hepatoto... Chlorpheniramine Clobazam (Hepat...
	Primary anilines	Halobenzenes	Halobenzenes

Read Acrossによるデータギャップ

Hazard Evaluation Support System

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No: 589-16-2
SMILES: c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

Data Gap Filling Method
☒ Read-across
☐ Trend analysis
☐ (Q)SAR models

Target Endpoint
Repeated Dose Toxicity LOEL

Structure

1 (Target) 2 3

Read across prediction of LOEL, taking the average from the nearest 5 neighbours, based on 11 data points from 11 neighbour chemicals. Observed target value: N/A, Predicted target value: 116 mg/kg/day

LOEL (obs.), mg/kg/day

log Kow

Descriptor X: log Kow

溶血性貧血のLOEL予測値 : 116 mg/kg/day
logKowが近い類似物質 5 つから target chemicalのLOELを予測

「Accept the prediction results」 予測確定
「return to the data matrix」 戻る

データギャップ方法のオプション

- Accept prediction
- Return to matrix
- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
- Visual options
- Information
- Miscellaneous

● : 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

Read Acrossによるデータギャップ

Hazard Evaluation Support System

Chemical name: 4-ethylaniline; benzenamine, 4-ethyl-; aniline
CAS No: 589-16-2
SMILES: c1(N)ccc(CC)cc1

to data matrix -> metabolism/tautomerism mode...

Data Gap Filling Method
☒ Read-across
☐ Trend analysis
☐ (Q)SAR models

Target Endpoint
Repeated Dose Toxicity LOEL

Structure

1 (Target)	2	3	4	5	7	8	9	10
(26/400) Min (27/660)	M: 10 mg/kg/day M: 10 mg/kg/day, ...	M: 10 mg/kg/day M: 10 mg/kg/day, ...	M: 5 mg/kg/day M: 5 mg/kg/day, 5 ...	M: 15 mg/kg/day M: 15 mg/kg/day, ...	M: 30 mg/kg/day M: 30 mg/kg/day, ...	M: 12.5 mg/kg/day M: 3 mg/kg/day, 3 ...	M: 2.4 mg/kg/day M: 2.4 mg/kg/day, ...	M: 12 mg/kg/day M: 12 mg/kg/day, ...
Study No. (link to SSRDT)	312	313	950	5	201	922	224	48
	302	781		5	196	754	218	47

Read across prediction of LOEL, based on 11 data points from 11 neighbour chemicals, N/A, Predicted target value: 116 mg/kg/day

範囲選択で拡大等も可能

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

Descriptor X: log Kow

log Kow

Descriptor

Descriptor	Units	Value
log Kow		2.17
Molar refraction I		40.6
Molar refraction II		40.5
Molecular weight	Da	121
Number of aromatic bonds		6.00

Endpoint reference

Endpoint reference	Units	Value
Endpoint obs. data (recalculated)	mg/kg/day	10.0

Details... Differences to target...

Accept prediction
Return to matrix
Select/filter data
Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR
Calculation options

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
(その他の(重篤な) 毒性の影響、死亡や回復期の情報など)
2. 試験条件の絞り込み
(投与量、ラット種など)
3. 代謝・メカニズムの情報の吟味
(代謝活性、プロファイラー情報以外のメカニズム情報の探索など)
4. データギャップ補完に使用する所見の選定、算出方法
(評価したい毒性に関連した所見か、軸の設定や類似物質数の変更など)

Hazard Evaluation Support System

Reset Options Help

Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism

Chemical name: **4-ethylaniline; benzenamine, 4-ethyl-; aniline**
CAS No **589-16-2**
SMILES **c1(N)ccc(CC)cc1**

to data matrix -> metabolism/tautomerism mode...

3

1

2

Prediction [1]

Prediction of LOEL for 4-ethylaniline 1 / 26

NITE HESS prediction based on read-across

Prediction of LOEL for 4-ethylaniline

Available report templates

- Standard (predefined)
 - Category Report (CCRF v.1.0.0)
 - History Report (THRF v.0.0.1)
 - Model Reporting Format (QMRF v.1.0.0)
 - Prediction Report (TPRF v.1.0.2)

28 Anilines (Hemolytic anemia with methemoglobinemia) Rank A

Developed by LMC, Bulgaria STOP

HESSの入手方法と使い方マニュアル

The screenshot shows the NITE website's 'Chemical Substance Management' section. The main heading is '有害性評価支援システム統合プラットフォーム (HESS) 及び HESS DBのユーザー登録'. Below this, there is a section titled 'HESSの使用許諾契約書' (HESS Terms of Use) with a list of 9 conditions. The sidebar on the right contains links to various resources like '動物実験代替法 (QSAR, Read-across, IATA)', '有害性評価支援システム統合プラットフォーム (HESS)', and '分野サイトマップ'.

NITEのHPからユーザー登録

http://www.nite.go.jp/chem/qsar/hess_01.html
(検索キーワード“NITE”, “HESS”)



登録メールアドレスにHESS及びダウンロードURLページが記載されたメールが送付される。



HESS及び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！

以下の動画講習/学習教材サイトにて、常時、動画説明等を見ることができます。
<https://www.nite.go.jp/chem/qsar/ReadAcrossTraining.html>