

創薬研究におけるバイオデータベース講習会(第四回データベース講習会@つくば)

化学物質の有害性を*in silico*で予測する ツール -HESS-

2014年2月13日

(独)製品評価技術基盤機構

化学物質管理センター

山田隆志

内容

- はじめに
- Hazard Evaluation Support System (HESS)の開発
- HESSの操作法(デモ)
- HESSの運用状況

～はじめに～

反復投与毒性とカテゴリーアプローチ

■ 反復投与毒性

- 化学物質の有害性評価の重要なエンドポイントのひとつ
- 市場に流通する多くの化学物質についてデータが必要
- 試験には多額の費用を要する

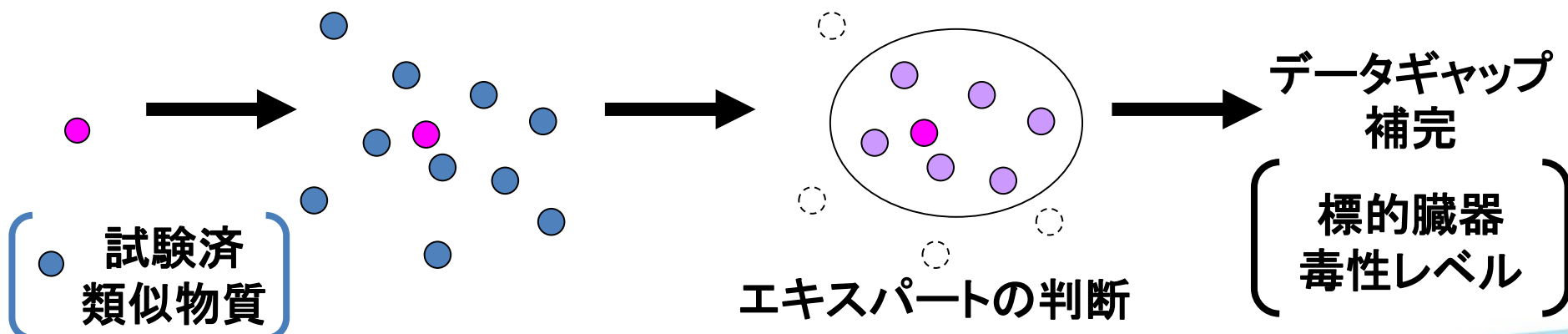
■ カテゴリーアプローチ

未試験
物質

試験済の類似物質
を収集

カテゴリー化

毒性予測



HESS:反復投与毒性のカテゴリーアプローチを支援するツール

Hazard Evaluation Support System [Reset] [Options]

Input Profiling

Chemical name: **2-methylaniline**
 CAS No: **95-53-4**
 SMILES: **c1(N)c(C)cccc1**

未試験物質 ← カテゴリーメンバー →

Categories

Read-across
 Trend analysis
 (Q)SAR models

Report Metabolism

Target Endpoint
 Repeated Dose Toxicity NOEL
 Hematological Examination

試験で観察された所見

Filter endpoint tree...	1 (Target)	2	3	4	5	6
Structure						
Substance Identity						
Repeated Dose Toxicity						
LOEL (7/320)		M: 30 mg/kg/day, 3...	M: 12 mg/kg/day, 1...	M: 40 mg/kg/day, 4...	M: 50 mg/kg/day, 2...	M: 10 mg/kg/day, 1...
NOEL						
Blood Chemical Examination (7/466)		M: 30 mg/kg/day, 3...	M: 60 mg/kg/day, 6...	M: 20 mg/kg/day, 5...	M: 10 mg/kg/day, 5...	M: 10 mg/kg/day, 1...
FOB (2/84)				M: 50 mg/kg/day, 5...		M: 10 mg/kg/day, 1...
General Signs (7/426)		M: 30 mg/kg/day, 3...	M: 60 mg/kg/day, 6...	M: 10 mg/kg/day, 1...	M: 250 mg/kg/day, ...	M: 10 mg/kg/day, 1...
Hematological Examination (7/392)		M: 30 mg/kg/day, 3...	M: 12 mg/kg/day, 1...	M: 20 mg/kg/day, 4...	M: 50 mg/kg/day, 5...	M: 10 mg/kg/day, 1...
Histopathological Findings (7/1747)		M: 30 mg/kg/day, 3...	M: 100 mg/kg/day, 6...	M: 50 mg/kg/day, 5...	M: 50 mg/kg/day, 1...	M: 10 mg/kg/day, 1...
Necropsy (7/437)		M: 100 mg/kg/day, ...	M: 100 mg/kg/day, 6...	M: 50 mg/kg/day, 2...	M: 50 mg/kg/day, 1...	M: 10 mg/kg/day, 1...
NOEL/LOEL (7/113)		M: <30 mg/kg/day	M: 12 mg/kg/day, 1...	M: 10 mg/kg/day, 2...	M: 50 mg/kg/day, 5...	M: <2 mg/kg/day
Organ Weights (7/443)		M: 100 mg/kg/day, ...	M: 12 mg/kg/day, 1...	M: 50 mg/kg/day, 5...	M: 50 mg/kg/day, 5...	M: 10 mg/kg/day, 1...
Urinalysis (5/221)			M: 60 mg/kg/day, 6...	M: 10 mg/kg/day, 5...	M: 50 mg/kg/day, 5...	M: 50 mg/kg/day, 1...
Profile						
Study No. (Link to SSRDT)	201	48		196	157	
Chemical No. (Link to HESS DB)	196	47		168	1	157
Rat Liver Metabolism Database	Root of map No. 251 Metabolite in map ...	Root of map No. 356	N/A	Root of map No. 320 Metabolite in map ...	Root of map No. 1	Root of map No. 1
Repeated dose (HESS)	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...

データギャップ (NOEL/LOEL)

反復投与毒性のデータ (NOEL/LOEL)

HESS DBへリンク

システムが示唆するカテゴリー候補

～HESSの開発～

NEDO/経済産業省委託事業

「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際し、安全性試験データがない化学物質に対し、類似化学物質の反復投与毒性試験データやその他の既知見を用いて、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)。

開発システムの構成

③ 有害性評価支援システム 統合プラットフォーム (HESS)

① 毒性知識情報DB

試験報告書DB

毒性作用機序DB

② 代謝知識情報DB

ラット代謝マップDB
(ラット代謝シミュレータ)

ADME DB
(ヒトP450代謝予測)

ベイジアンネット毒性推定
システム (ToxBay)

カテゴリーアプローチ支援機能
(カテゴリーライブラリー等)

ユーザー

入力
反復投与毒性を
評価したい化学物質
の化学構造、物質名
CAS番号など

出力
評価対象物質や
その類縁物質の
反復投与試験情報、
作用機序情報、
カテゴリー情報、
推定される毒性等

判断材料

エキスパート
ジャッジ

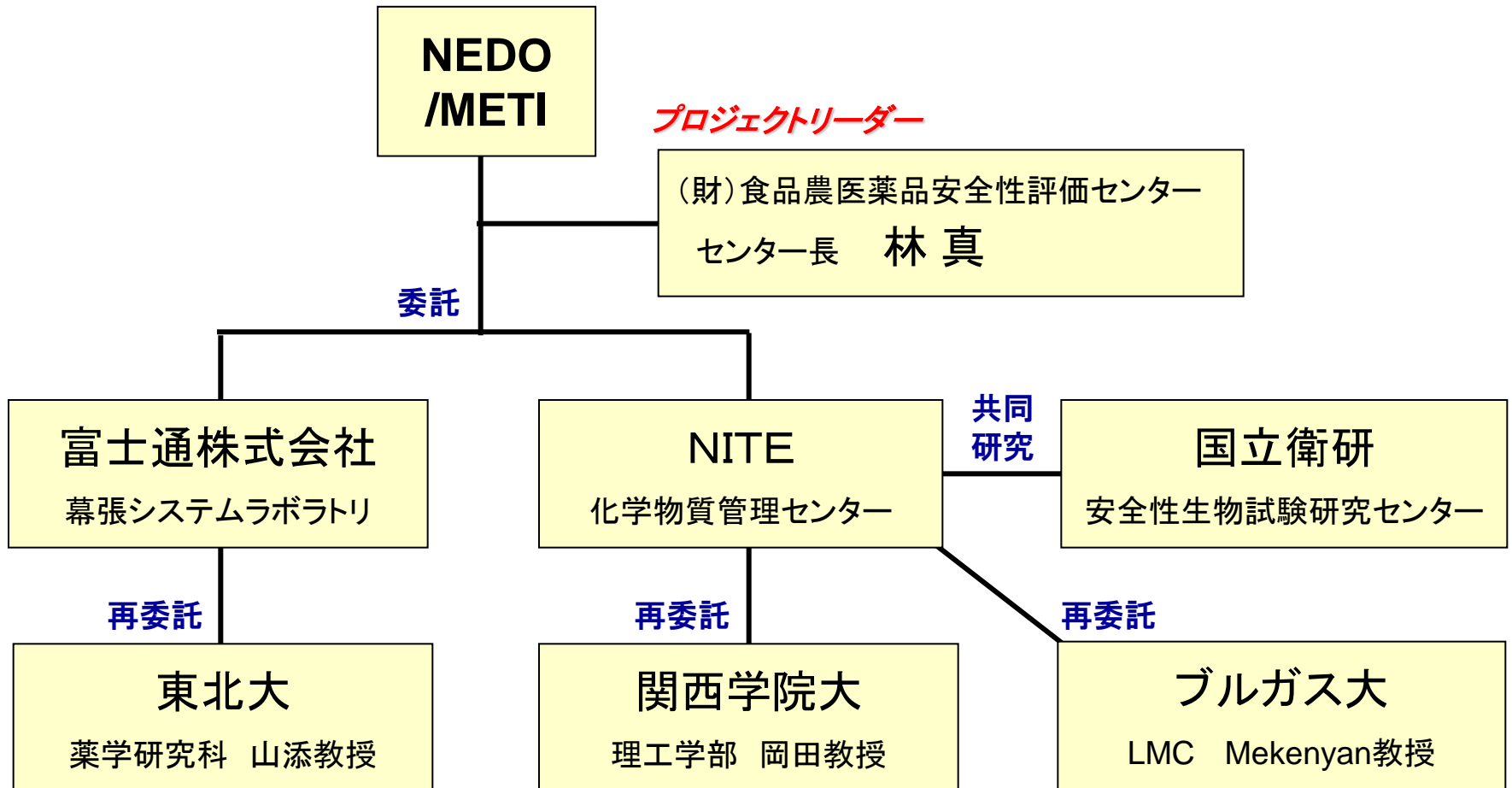
未試験物質の
反復投与毒性

互換性

OECD QSAR Toolbox

EMSD DB

実施体制



開発の流れ

反復投与毒性試験データ（一般化学物質500物質）

毒性専門家とQSAR専門家
によるデータ解析

カテゴリーライブラリー

搭載

Hazard Evaluation Support System (HESS)

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ことを目的とする。

齧歯類(原則ラット)

投与期間 (28日～90日)

回復期間 (14日)

体重・摂餌量・摂水量・一般状態

↑
検査

↑
検査

検査項目: 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

無影響量(NOEL)

No Observed Effect Level

無毒性量(NOAEL)

No Observed Adverse Effect Level

試験報告書の例

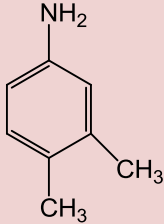
(血液学)

Table 1 Hematology of rats treated orally with 4-aminophenol in 28-day repeat dose toxicity test

Sex	Period	28 Day				
	Dose level (mg/kg)	0	4	20	100	500
Male						
	Number of animals	6	6	6	6	5
	RBC($\times 10^4/\mu l$)	720 \pm 23.6	729 \pm 15.1	752 \pm 15.0	730 \pm 29.6	644 \pm 41.7**
	Hematocrit(%)	43.5 \pm 1.16	44.2 \pm 0.78	45.1 \pm 0.57	43.6 \pm 1.85	41.1 \pm 1.58
	Hemoglobin (g/dl)	14.7 \pm 0.15	15.0 \pm 0.20	15.2 \pm 0.25	14.8 \pm 0.74	14.0 \pm 0.48
	Reticulocyte (%)	31 \pm 2.5	33 \pm 3.1	31 \pm 4.0	34 \pm 5.9	33 \pm 16.1
	MCV (μm^3)	60.4 \pm 0.67	60.7 \pm 1.93	60.1 \pm 0.89	59.8 \pm 0.78	64.0 \pm 3.19
	MCH (pg)	20.4 \pm 0.55	20.5 \pm 0.60	20.2 \pm 0.29	20.3 \pm 0.46	21.8 \pm 0.96*
	MCHC (%)	33.8 \pm 0.77	33.9 \pm 0.40	33.7 \pm 0.37	34.0 \pm 0.50	34.0 \pm 0.38
	Platelet ($\times 10^4/\mu l$)	105.4 \pm 6.03	109.8 \pm 9.58	108.2 \pm 5.96	106.7 \pm 11.76	108.0 \pm 11.92
	PT (sec)	12.8 \pm 0.50	12.8 \pm 0.44	13.0 \pm 0.29	12.5 \pm 0.29	12.9 \pm 0.30
	APTT (sec)	16.9 \pm 0.47	16.8 \pm 1.15	17.1 \pm 0.60	16.6 \pm 0.80	16.0 \pm 1.30
	WBC ($\times 10^2/mm^3$)	139 \pm 30.5	136 \pm 33.6	135 \pm 32.0	141 \pm 29.8	140 \pm 46.3
	Differential leukocyte counts (%)					
	Lymphocytes	86 \pm 9.1	87 \pm 5.0	90 \pm 7.1	90 \pm 3.6	87 \pm 5.6
	Neutrophils					
	segmented	10 \pm 7.4	7 \pm 3.5	4 \pm 2.4	7 \pm 1.2	8 \pm 4.9
	band	0 \pm 0.0	0 \pm 0.4	1 \pm 0.8	0 \pm 0.0	0 \pm 0.9
	Eosinophils	1 \pm 0.9	1 \pm 0.5	0 \pm 0.4	1 \pm 1.2	0 \pm 0.5
	Basophils	0 \pm 0.0	0 \pm 0.0	0 \pm 0.0	0 \pm 0.0	0 \pm 0.0
	Monocytes	4 \pm 3.5	5 \pm 2.0	5 \pm 4.2	3 \pm 1.8	3 \pm 1.7

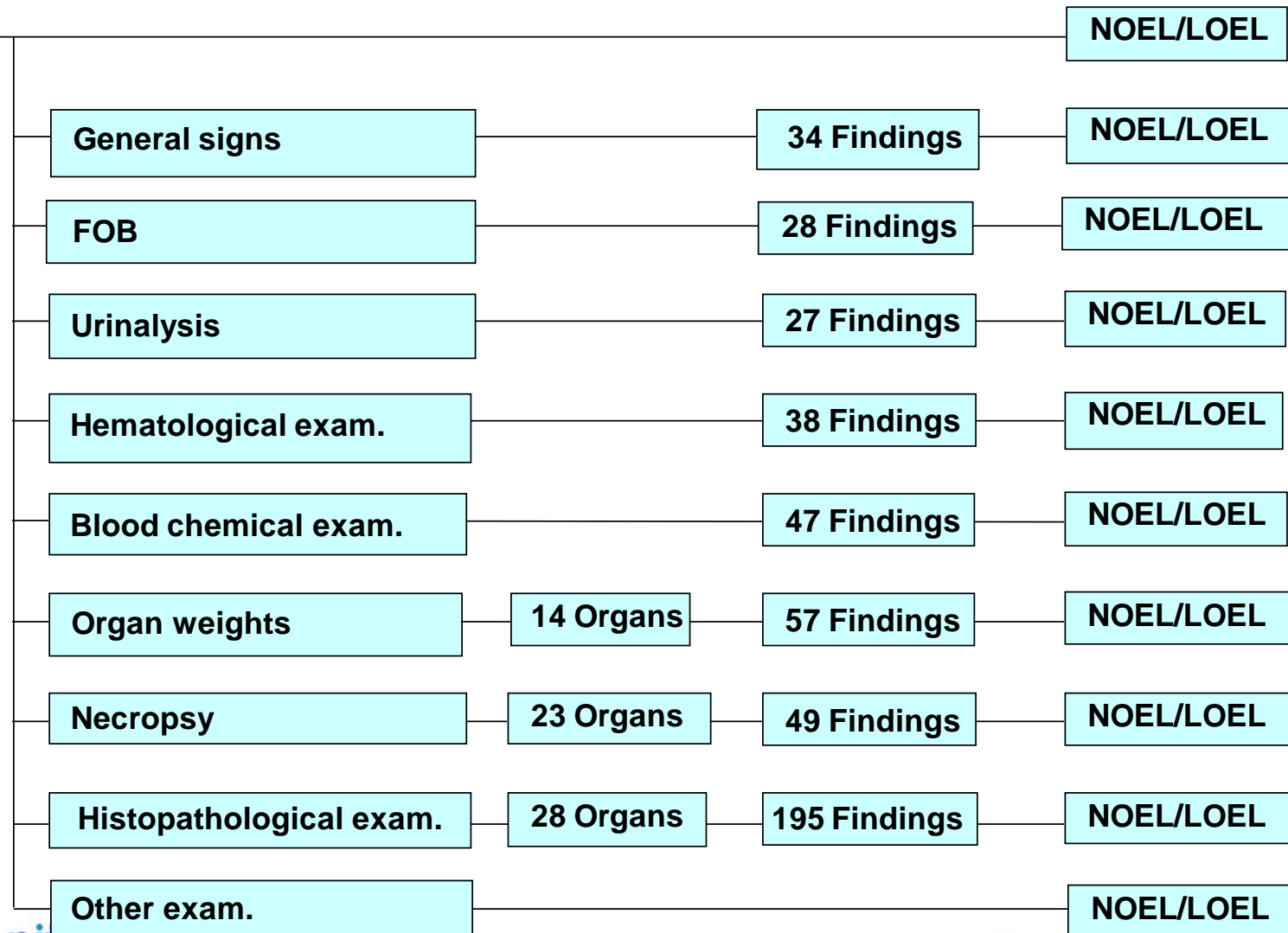
→HESS DB

試験結果の要約の例

S001		CAS No.	95-64-7
名称	3, 4-ジメチルアニリン		
			
28日間	投与方法	強制経口投与 溶媒：コーン油	
	純度	>99.8%	
	用量	3群 (10, 50, 250 mg/kg/day)	
	死亡	-	
	NOEL	反復投与毒性：10 mg/kg/day 生殖発生毒性：mg/kg/day	
	推定根拠	血液生化学的検査(Cho↑：>50♀・250♂) 組織学的所見(腎-硝子滴：>50♂)	
	他の毒性	血液学的検査(Hct↓・Hgb↓・RBC↓・Plt↑・Ret↑：250♂♀、WBC↑：250♂) 尿検査(尿量↑・尿pH↓：250♂♀、尿比重↓：250♀) 絶対重量(肝↑・脾↑：250♂) 相対重量(肝↑・脾↑：250♂♀、副腎↓：250♀、精巢↑：250♂) 組織学的所見(骨髓-造血亢進：250♂♀、 脾-うつ血・色素沈着・造血亢進：250♂♀、 肝-色素沈着・単細胞壊死・肝細胞腫大・髓外造血：250♂♀)	

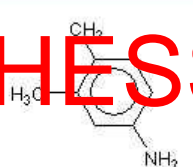
→HESS

HESSにおける反復投与毒性試験データの データ構造



約500種類
の所見
で表現

Input
Profiling



Chemical name: 3,4-dimethylaniline
 CAS No: 55-64-7
 SMILES: CC1=CC=C(N)C=C1C
 to data matrix -> metabolism mode...

HESSにおける反復投与毒性試験データ

RDT Data

Categories

Gap Filling

Report

Metabolism

Gather

Databases

- Biomarker DB
- HESS Repeated Dose Toxicity
- HESS Repeated Dose Toxicity (CSCL New Chemicals)

所見と
NOEL/LOEL

Filter endpoint tree...

Structure

1 (Target)



Endpoint	Results
Repeated Dose Toxicity	
LOEL	
Blood Chemical Examination	
Blood Serum (Lipid)	
Undefined Tissue	
T. Cholesterol↓	(1/2) M: 50 mg/kg/day, 250 mg/kg/day
Hematological Examination	
Blood Cell (Erythrocyte)	
Undefined Tissue	
RBC↓	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
HGB↓	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
Reticulocyte↑	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
HCT↓	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
Blood Cell (Leukocyte)	
Undefined Tissue	(1/1) M: 250 mg/kg/day
Blood Cell (Platelet)	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
Histopathological Findings	
Bone Marrow	
Undefined Tissue	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
Kidney	
Renal Tubule (Other)	(1/1) M: 50 mg/kg/day
Liver	
Hepatocyte	(1/4) M: 250 mg/kg/day, 250 mg/kg/day, ...
Kupffer Cell	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
Undefined Tissue	(1/2) M: 250 mg/kg/day, 250 mg/kg/day
Spleen	
Undefined Tissue	(1/6) M: 250 mg/kg/day, 250 mg/kg/day, ...

収載した試験報告書

一般化学物質(500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)。

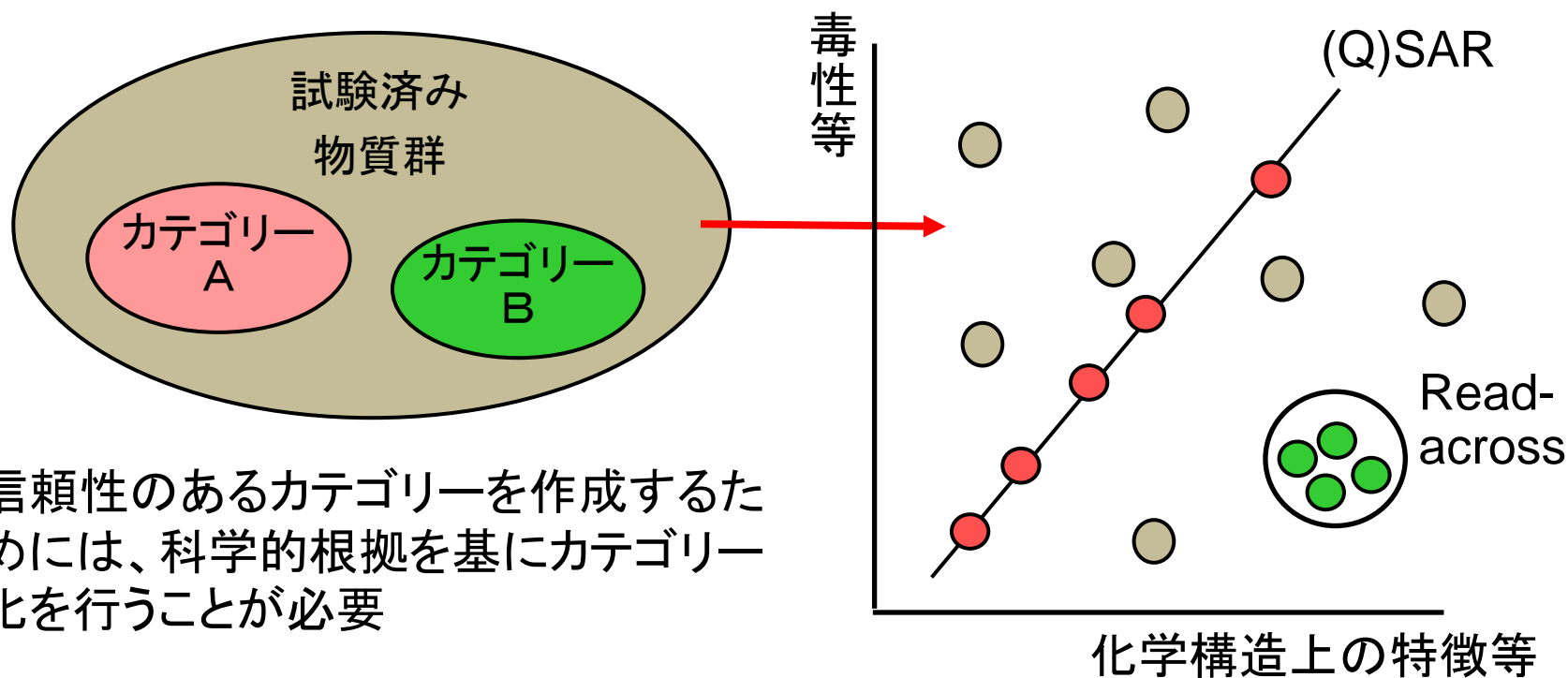
(試験数)

報告書群	投与経路			投与期間			合計
	強制経口	混餌	飲水	28-30日	約42日 [※]	12-17週	
厚労省 / 国衛研 化審法試験	268	0	0	144	122	2	268
経産省 / NITE 試験	50	0	0	27	23	0	50
米国NTP短期試験	20	22	15	4	0	53	57
米国NTP長期試験(予備試験)	66	49	9	2	0	122	124
Journal Paper	19	12	0	18	3	10	31
合計	423	83	24	195	148	187	530

※ 併合試験。雄ラットの反復投与毒性試験データのみ使用。

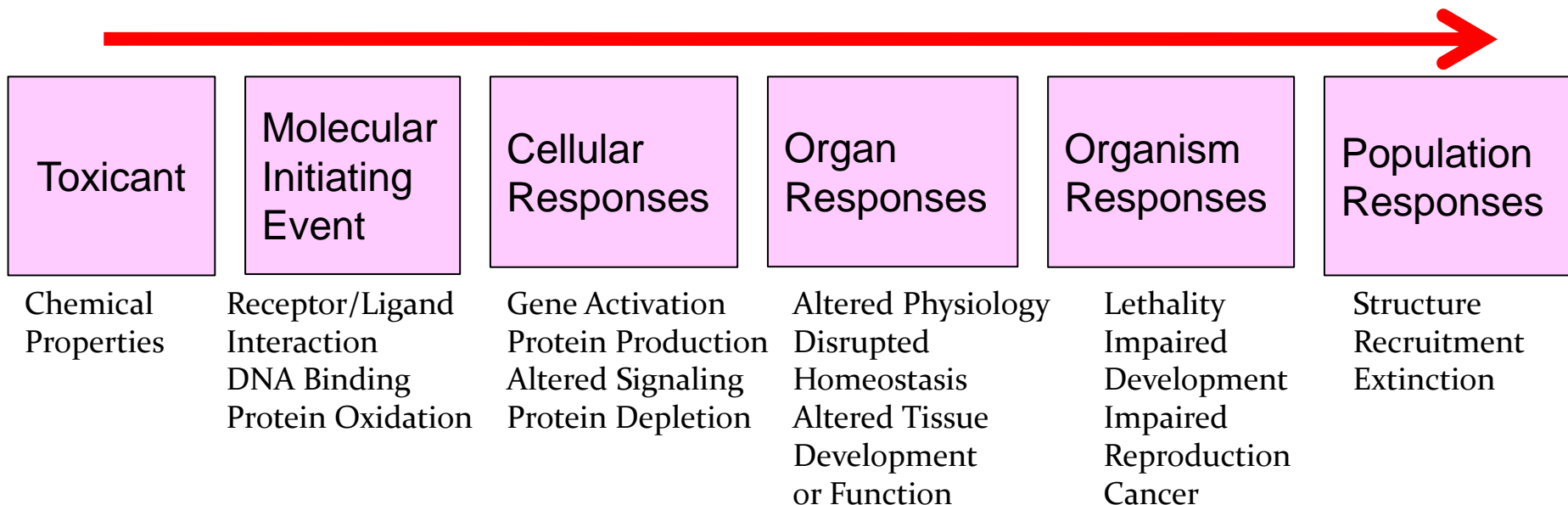
カテゴリーアプローチ

カテゴリーとは、構造類似性により物理化学的及び毒性学的特性が類似又は規則的なパターンを示すと考えられる化学物質のグループ。構造活性相関[(Q)SARや類推(Read-across)によるデータギャップ補完を行う。



透明性の高い評価が可能なことから化学物質管理分野におけるデータギャップ補完手法の主流となっている。

Adverse Outcome Pathway (AOP)

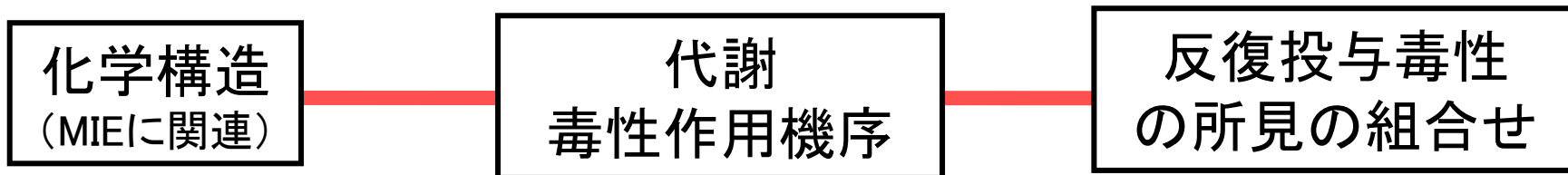


AOPとは、分子レベルのトリガーとなる反応(MIE)から、細胞、臓器、個体レベルの反応を経て、毒性発現に至るまでの経路を示したもの。毒性発現メカニズムが複雑なエンドポイントについては、AOPに基づいてカテゴリー作成するコンセプトがOECDから提案され、最近、精力的に検討がなされている。

HESSの開発プロジェクトでは、反復投与毒性についてAOPに基づくカテゴリーアプローチの方法論を検討し、当該OECD活動に貢献している。

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)

が類似する物質群をカテゴリーとして定義した。

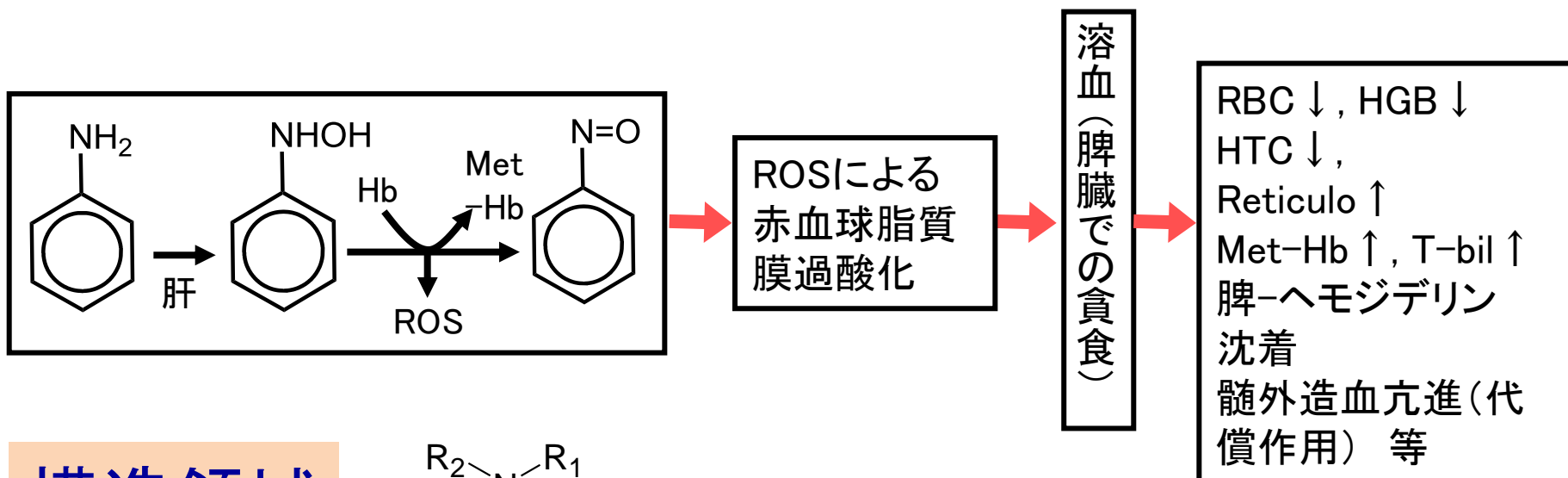
現在、33のカテゴリーをHESSに登録。

(例) アニリン類の溶血性貧血カテゴリー

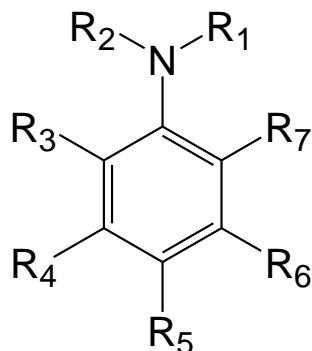
AOP

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



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

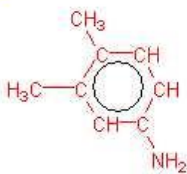
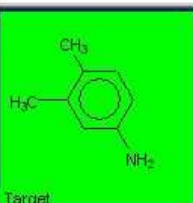
$R_3 \sim R_7 = \text{H, alkyl, halo, alkoxy, NO}_2 \text{ or NH}_2.$

* Sakuratani, Y. Sato, S. Nishikawa, S. Yamada, J. Maekawa, A. and Hayashi, M. 2008. Category analysis of the substituted anilines studied in a 28-day repeat-dose toxicity test conducted on rats: Correlation between toxicity and chemical structure. SAR QSAR Environ. Res. 19:681-696.

Anilines (Hemolytic anemia with methemoglobinemia) Rank A

カテゴリー情報

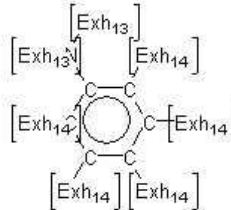
Target

Boundaries Training set Options

Boundary Options Metabolism






Fragment

c(N(*Exh13)*Exh13)c(*Exh14)c(*Exh14)c(*Exh14)c(*Exh14)c1*Exh14


Boundaries Training set Options

CAS	Name
108-44-1	m-Toluidine
87-59-2	2,3-Dimethylaniline
95-68-1	2,4-Dimethylaniline
87-62-7	2,6-Dimethylaniline
95-64-7	3,4-Dimethylaniline
108-69-0	3,5-Dimethylaniline
99-88-7	Aniline, 4-(1-methylethyl-),
95-51-2	o-Chloroanilines
108-42-9	m-Chloroanilines
20265-96-7	p-chloroaniline hydrochloride
536-90-3	3-Methoxybenzenamine
156-43-4	4-Ethoxybenzenamine
100-61-8	N-Methylaniline
103-69-5	n-ethylaniline
121-69-7	n,n-dimethylaniline
99-09-2	3-nitroaniline
97-52-9	4-nitro-o-anisidine
89-63-4	aniline, 4-chloro-2-nitro

Common Fragments

Definition	1	2	3	4	5	6	7	8	9
1	[Exh13]	H							
2	[Exh14]	H		F	Cl	Br	I		

構造領域

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

トレーニングセット

Input



Chemical name: 3,4-dimethylaniline

CAS No 95-64-7

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

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)OCC(CCCC)CC)OCC(CCCC)CC
- 6. c1(N)cc(N(=O)=O)ccc1
- 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(C1CCCCC1)NCCCCCCCCCCCC
- 11. C(C)CCCCCCCCCCCCCCC
- 12. C(C)CCCCCCCCCCCCCCC
- 13. C(C)(C)(C)CC(C)(C)CC(C)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)ccc1
- 20. C(=O)(C(Cl)Cl)O(-)[Na](+)
- 21. C(CCC)OP(=O)(OCCCC)OCCCC
- 22. C(=C)(C)C
- 23. c1(OP(=O)(Oe2ccccc2)Oc2ccccc2)c(CC)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)C(-))cccc1
- 28. c1(O)c(N=Nc2ccccc2)c2c(cc(S(=O)(=O)O[Na])cc
- 29. c1(N)c(O)c2c(cccc2)cc1
- 30. Cl(Cl)C(Cl)C(Cl)C(Cl)C(Cl)C=1
- 31. c1(N)ccc(C)cc1

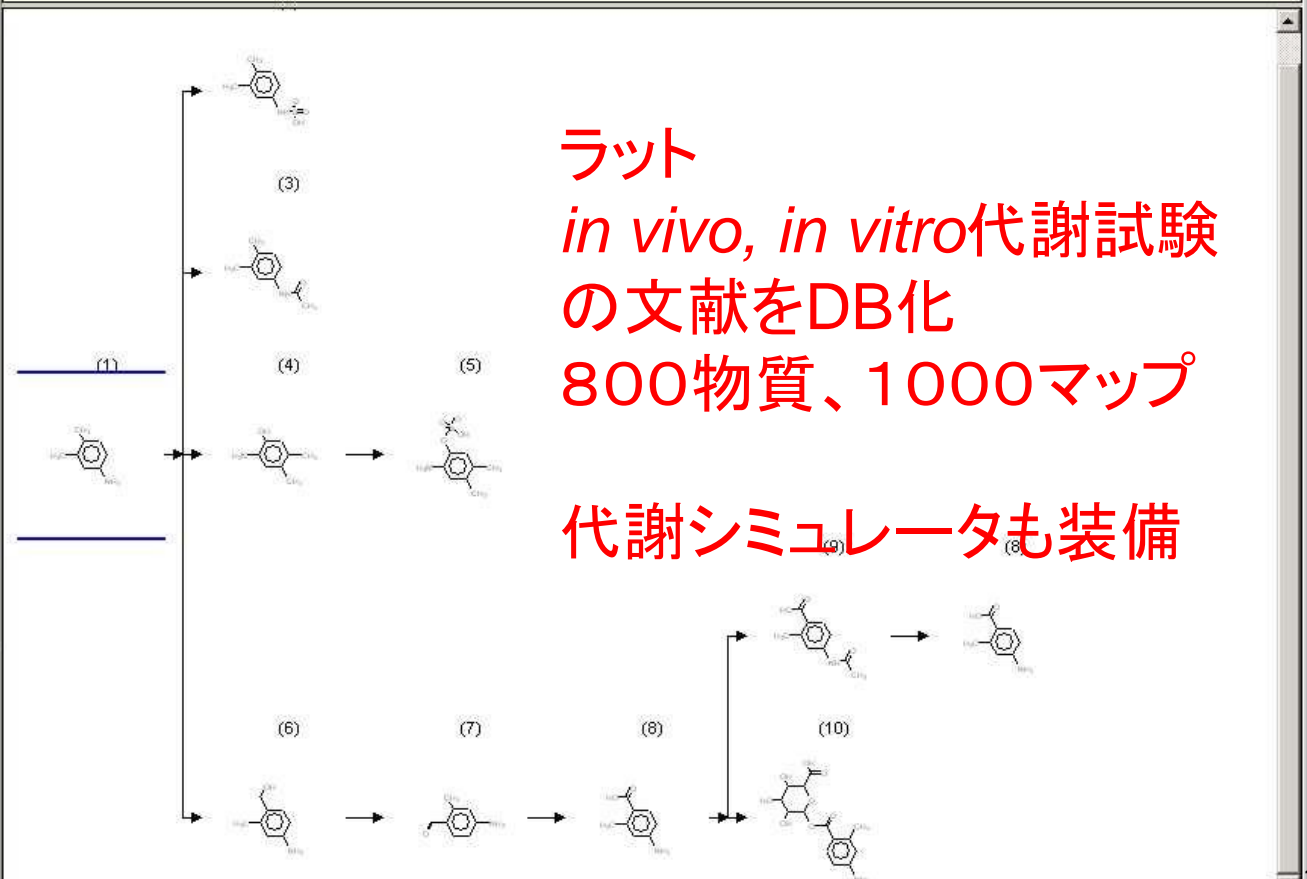
Search target search parents only
 search as fragment

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

Redraw Print Preview

Cell Height 120 Cell Width 120

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の操作法(デモ)～

予測対象物質の入力から
類似物質の抽出まで

Input

Profiling

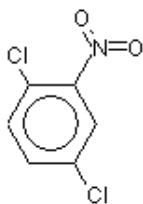
RDT Data

Categories

Gap Filling

Metabolism

Report



Chemical name: 1,4-dichloro-2-nitrobenzene

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

①

評価対象物質の入力
(ケース1: CAS番号による)

Set target

Add to post-targets list

CAS#

Chemical name Drawing RDT tests Database User List

Load DB Load Inventory

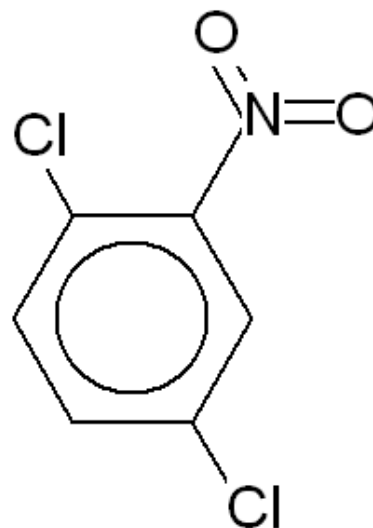
CAS #

89612

Search

89612

Chemical name: 1,4-dichloro-2-nitrobenzene



Input

Profiling

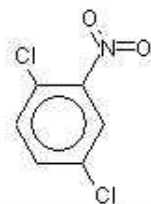
RDT Data

Categories

Gap Filling

Report

Metabolism



Chemical name: 1,4-dichloro-2-nitrobenzene

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

評価対象物質の入力
(ケース2: 化学構造による)

③

①

Set target

Add to post-targets list

CAS#

Chemical name

Drawing

RDT tests

Database

User List

Load DB Load Inventory























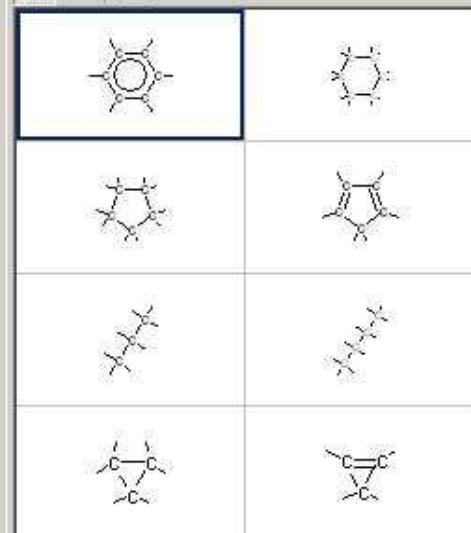
SMILES/InChi c1(Cl)c(N(=O)=O)cc(Cl)cc1

Draw

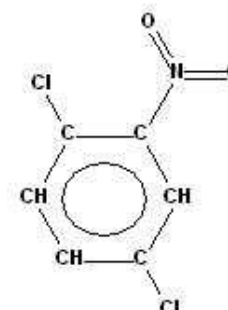
Mixture

Edit names

Templates Work

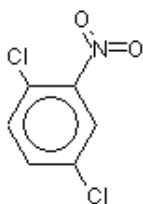


②化学構造描画



Input

Profiling



Chemical name:

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

プロファイリングの抽出

RDT Data

Apply New Scheme

プロファイラー

Gap Filling

Metabolism

Report

①

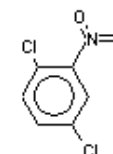
- Filtering methods
- Chemical elements
 - Groups of elements
 - Lipinski Rule Oasis
 - Organic functional groups
 - Organic functional groups (nested)
 - Organic functional groups (US EPA)
 - Organic functional groups, Norbert
 - Study No. (Link to SSRDT)
 - Chemical No. (Link to HESS DB)
 - RDT Report No.
 - Rat Liver Metabolism Database
 - CSCL Class
 - 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

Filter endpoint tree...

1 (Target)

Structure



Substance Identity

Profile

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

N/A

(N/A)

Nitrobenzenes (Hemolytic anemia with methemoglobin...)

Nitrobenzenes (Hepato toxicity) Rank C

該当カテゴリー

ニトロベンゼン(溶血)

ニトロベンゼン(肝毒性)

Input

Profiling

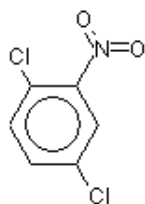
RDT Data

Categories

Gap Filling

Metabolism

Report



Chemical name:

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

プロファイラーの確認

②

Show Boundaries Apply New S

Profilers

Profiling methods

- 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.
- Rat Liver Metabolism Database
- CSCL Class

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

①

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

Advanced

Repeated dose (HESS) - Category definition

- Aliphatic amines (Mucous m...
- Aliphatic nitriles (Hepato to...
- Aliphatic/Alicyclic hydrocarb...
- Anilines (Hemolytic anemia ...)
- Anilines (Hepato toxicity) R...
- Azobenzenes (Hemolytic an...
- Benzene/Naphthalene sulfo...
- Benzenesulfonamides (Toxi...
- Diphenyl Disulphides (Hemol...
- Ethyleneglycol Alkylethers (...)
- Ethyleneglycol Alkylethers (...)
- Halobenzenes (Hepato toxi...
- Halobenzenes (Renal toxicit...
- Halogenated Aliphatic Comp...
- Hydrazines (Hemolytic ane...
- N-Alkyl-N'-phenyl-p-phenyle...
- Nitrobenzenes (Hemolytic a...
- Nitrobenzenes (Hepato toxi...
- Nitrobenzenes (Testicular t...
- Nitrophenols/Harophenols (...)
- o-/p-Aminophenols (Hemoly...
- Organophosphates (Neurot...
- Oximes (Hemolytic anemia ...)
- p-Alkylphenols (Hepatotoxic...
- p-Aminophenols (Renal toxi...
- Phenols (Mucous membrane...
- Phenyl phosphates (Lipodosi...
- Phthalate esters (Testicular...

Profile Description

Nitrobenzenes (Hemolytic Anemia with methemoglobinemia) Rank A

1. Toxicity Information

The mechanism of hemolytic anemia induced by nitrobenzenes is considered to be as the following.

- 1) Nitrobenzenes are metabolized to anilines by intestinal bacterial flora^{1,2}.
- 2) Anilines are metabolized in hepatocytes by oxidases such as P450 to N-hydroxyl anilines.
- 3) N-hydroxyl anilines react with hemoglobin (HGB) in erythrocyte to produce nitrosoaniline and methaemoglobin (Met-HGB)^{1,2}. As a result, increase of the concentration of methaemoglobin (Met-HGB) is observed in hematological examination in RDT test.
- 4) Erythrocytes are degenerated (peroxidation of lipid membrane etc.) by reactive oxygen species (ROS) produced in the above reaction³.
- 5) Phagocytosis of degenerate erythrocytes mainly in the spleen results in hemolysis⁴.
- 6) As a result, decrease of red blood cell (RBC), decrease of hemoglobin (HGB), decrease of hematocrit (HTC) and increase of reticulocyte (Reticulo) are observed in hematological examination in RDT test. In addition, pigmentation

カテゴリーの記述

Advanced

Repeated dose (HESS) - Category definitions

- 4,4'-Methylenedianilines/benzidines (Hepatobiliary ...
- Acrylamides (Neurotoxicity) Rank C
- Aliphatic amines (Mucous membrane irritation) Rank C
- Aliphatic nitriles (Hepatotoxicity) Rank B
- Aliphatic/Alicyclic hydrocarbons (Alpha 2u-globulin ...
- Anilines (Hemolytic anemia with methemoglobinemi...
- Anilines (Hepatotoxicity) Rank C
- Aromatic hydrocarbons (Liver enzyme induction) R...
- Azobenzenes (Hemolytic anemia with methemoglob...
- Benzene/ Naphthalene sulfonic acids (Less suscept...
- Benzenesulfonamides (Toxicity to urinary system) ...
- Diphenyl disulphides (Hemolytic anemia with methe...
- Ethylene glycol alkylethers (Hemolytic anemia) Rank A
- Ethylene glycol alkylethers (Testicular toxicity) Rank B
- Halobenzenes (Hepatotoxicity) Rank A
- Halobenzenes (Renal toxicity) Rank A
- Halogenated aliphatic compounds (Hepatotoxicity) ...
- Hydrazines (Hemolytic anemia with methemoglobin...
- Hydroquinones (Hepatotoxicity) Rank B
- Imidazole-2-thione derivatives (Thyrotoxicity) Rank B
- N-Alkyl-N'-phenyl-p-phenylenediamine (Hemolytic a...
- Nitrobenzenes (Hemolytic anemia with methemoglo...**
- Nitrobenzenes (Hepatotoxicity) Rank C
- Nitrobenzenes (Testicular toxicity) Rank C
- Nitrophenols/ Halophenols (Energy metabolism dys...
- o-/ p-Aminophenols (Hemolytic anemia with methe...
- Organophosphates (Neurotoxicity) Rank A
- Oximes (Hemolytic anemia with methemoglobinemi...
- p-Alkylphenols (Hepatotoxicity) Rank A
- p-Aminophenols (Renal toxicity) Rank B
- Phenols (Mucous membrane irritation) Rank C
- Phenyl phosphates (Lipodosis of adrenocortical) Rank C
- Phthalate esters (Testicular toxicity) Rank C

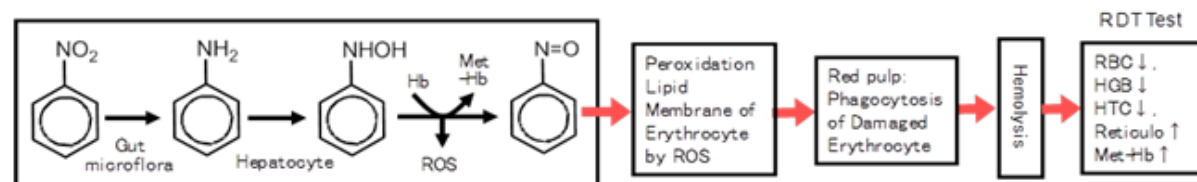
Profile Description

Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A

1. Toxicity Information

The mechanism of hemolytic anemia induced by nitrobenzenes is considered to be the following.

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



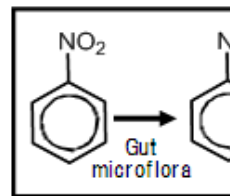
カテゴリーに関連する反復投与毒性所見

Repeated dose (HESS) - Category definition

Profile Description

- 2-Imidazolidinethiones (Thyrot...
- 4,4'-Methylenedianilines/Benzid...
- Acrylamides (Neurotoxicity) Ra...
- Aliphatic amines (Mucous memb...
- Aliphatic nitriles (Hepato toxic...
- Aliphatic/Alicyclic hydrocarbons...
- Anilines (Hemolytic anemia with...
- Anilines (Hepato toxicity) Rank C
- Azobenzenes (Hemolytic anemi...
- Benzene/Naphthalene sulfonic ...
- Benzenesulfonamides (Toxicity ...
- Diphenyl Disulphides (Hemolytic...
- Ethylene glycol Alkylethers (He...
- Ethylene glycol Alkylethers (Tes...
- Halobenzenes (Hepato toxicity...
- Halobenzenes (Renal toxicity) ...
- Halogenated Aliphatic Compou...
- Hydrazines (Hemolytic anemia ...
- N-Alkyl-N'-phenyl-p-phenylene...
- Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A**
- Nitrobenzenes (Hepato toxicity)
- Nitrobenzenes (Testicular toxicity)
- Nitrophenols/Harophenols
- o-/p-Aminophenols (Hemolytic anemia with methemoglobinemia)
- Organophosphates (Neurotoxicity)
- Oximes (Hemolytic anemia with...
- p-Alkylphenols (Hepatotoxicity)...
- p-Aminophenols (Renal toxicity...
- Phenols (Mucous membrane irri...
- Phenyl phosphates (Lipodosis of...
- Phthalate esters (Testicular to...
- Polycyclic Aromatic Hydrocarbo...
- Trinitrophenol (Hemolytic anemi...

- Attach reference
- Supplementary
- Export to File
- Toxicological profiler info**
- Color



Nitrobenzenes (Hemolytic Anemia with methemoglobinemia) Rank A

1. Toxicity Information

- The mechanism of action of nitrobenzenes is not fully understood. However, the following findings are observed in humans and animals:
- 1) Nitrobenzenes are metabolized to nitrophenols and nitroanilines.
 - 2) Anilines are metabolized to nitroanilines.
 - 3) N-hydroxylated nitrobenzenes are metabolized to nitrophenols and nitroanilines.
 - 4) Erythrocytes are damaged, leading to hemolysis and the release of hemoglobin into the plasma.
 - 5) Phagocytosis of hemoglobin by reticuloendothelial cells leads to the formation of methemoglobin.
 - 6) As a result, decreased oxygen-carrying capacity of the blood occurs.

Extended Profile Info

Columns: Rows:

Add column Add row

Delete row

Examination Items	Organ(Tissue)	Tissue	Effect
Hematological examination	Blood cell (Erythrocyte)		RBC↓
Hematological examination	Blood cell (Erythrocyte)		HGB↓
Hematological examination	Blood cell (Erythrocyte)		HTC↓
Hematological examination	Blood cell (Erythrocyte)		Reticulocyte↑
Hematological examination	Blood cell (Erythrocyte)		Methemoglobin↑
Blood chemical examination	Blood serum (Bilirubin)		T. bilirubin↑
Histopathological findings	Liver	Kupffer cell	Pigmentation (Hemosiderin)
Histopathological findings	Liver	Kupffer cell	Pigmentation (Other)
Histopathological findings	Liver		Extramedullary hematopoiesis
Organ weights	Spleen		Absolute organ weight↑
Organ weights	Spleen		Relative organ weight↑
Histopathological findings	Spleen		Pigmentation (Hemosiderin)
Histopathological findings	Spleen		Pigmentation (Other)
Histopathological findings	Spleen		Extramedullary hematopoiesis
Histopathological findings	Spleen		Congestion

2. Observed Effects

There are 25 RDTs related to this category.

In the studies of nitrobenzenes without phenol or benzoic acid structure (Nos. 1-13), the findings related to hemolytic

Clear Table

Apply to Profile

Cancel

Input

Profiling

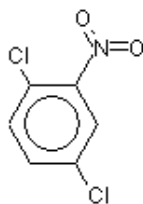
RDT Data

Categories ①

Gap Filling

Metabolism

Report



Chemical name:

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

反復投与毒性試験データの抽出

②

Gather

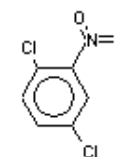
Databases

 Biomarker DB
 Repeated dose toxicity NEDO

Filter endpoint tree...

1 (Target)

Structure



NEDO HESS

No data found.

OK

☑ Substance Identity

☐ Profile

— Study No. (Link to SSRC)

— Chemical No. (Link to HE)

— RDT Report No.

— Rat Liver Metabolism Database

— CSCL Class

— Repeated dose (HESS)

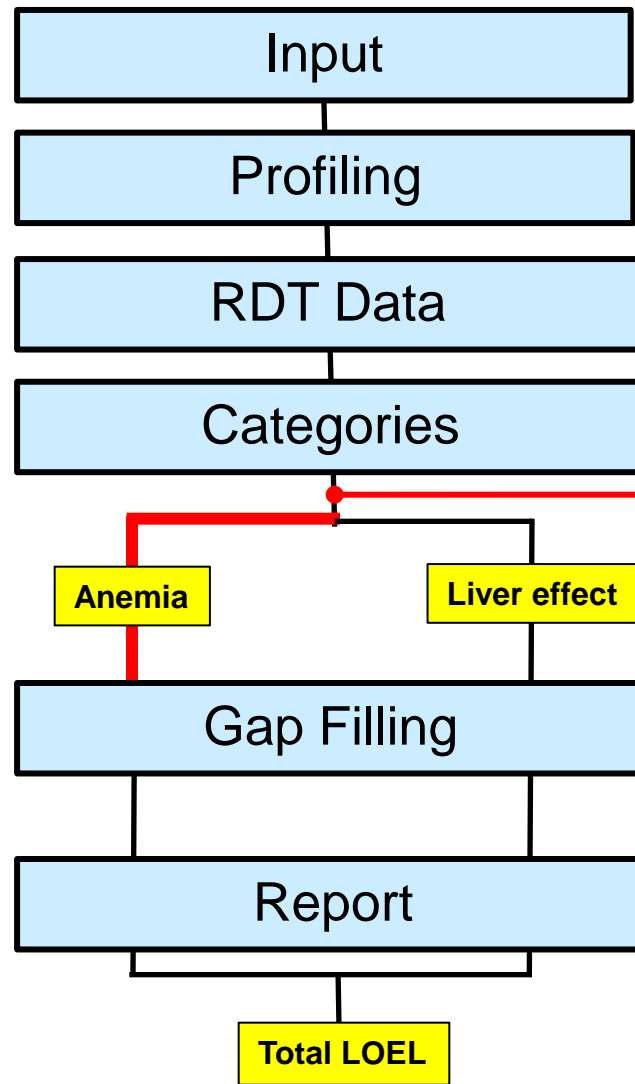
N/A

(N/A)

Nitrobenzenes (Hemolytic anemia with methemoglobin...)

Nitrobenzenes (Hepato toxicity) Rank C

この場合、評価対象物質の反復投与毒性試験データは、なかった。そこで、以降の手順において類似物質の試験データを用いてデータギャップ補完を試みる。

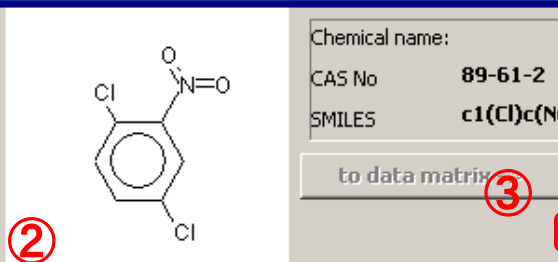


検討するカテゴリー
の選択

類似物質の抽出

Input
Profiling
RDT Data
Categories
Gap Filling
Metabolism

Report



Define

Subcategorize

Combine Categories

Grouping methods

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

Toxicological

- Repeated dose (HESS)

Custom

Defined Categories

- Document_1

Repeated dose (HESS)

Target(s) profiles

- Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
- Nitrobenzenes (Hepato toxicity) Rank C

All Profiles

- (N/A)
- 2-Imidazolidinethiones (Thyrotoxicity) Rank B
- 4,4'-Methylenedianilines/Benzidines (Hepatobiliary toxicity) Rank B
- Acrylamides (Neurotoxicity) Rank C
- Aliphatic amines (Mucous membrane irritation) Rank C
- Aliphatic nitriles (Hepato toxicity) Rank A
- Aliphatic/Alicyclic hydrocarbons (Alpha 2u-globulin nephropathy) Rank C
- Anilines (Hemolytic anemia with methemoglobinemia) Rank A
- Anilines (Hepato toxicity) Rank C
- Azobenzenes (Hemolytic anemia with methemoglobinemia) Rank B
- Benzene/Naphthalene sulfonic acids (Less susceptible) Rank C
- Benzenesulfonamides (Toxicity to Urinary System) Rank B
- Diphenyl Disulphides (Hemolytic anemia with methemoglobinemia) Rank C
- Ethyleneglycol Alkylethers (Hemolytic anemia) Rank A
- Ethyleneglycol Alkylethers (Testicular toxicity) Rank B

Combine profiles logically with

and or

Invert result

Strict

OK

Cancel

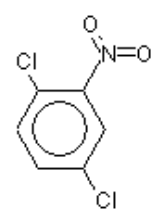
この場合ニトロベンゼンの溶血性貧血カテゴリーに該当する物質を類似物質として抽出

Hazard Evaluation Support System

Reset

Options

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



Chemical name: **1,4-dichloro-2-nitrobenzene**
 CAS No **89-61-2**
 SMILES **c1(Cl)c(N(=O)=O)cc(Cl)cc1**

to data matrix ->

- Define
- Subcategorize
- Combine Categories

- Grouping methods
- 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

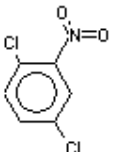
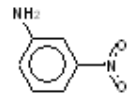
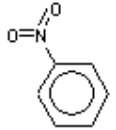
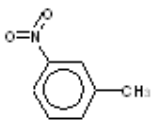
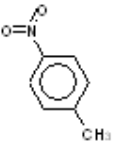
- Defined Categories
- Document 1
 - [13] Nitrobenzenes (Hemolytic anemia with methemog)
- Delete Delete All

Filter endpoint tree...	1 (Target)	2
Structure		
<input checked="" type="checkbox"/> Substance Identity		
<input checked="" type="checkbox"/> Repeated Dose Toxicity (12/7036)		M: 15 mg/kg/day, 1
<input type="checkbox"/> Profile		
Study No. (Link to SSRDT)		
Chemical No. (Link to HESS DB)		
RDT Report No.		
CSCL Class		
Rat Liver Metabolism Database	N/A	
Repeated dose (HESS)	Nitrobenzenes (He... Nitrobenzenes (Hep...	

12物質(評価対象物質を除く)の類似物質が抽出された

類似物質の 毒性試験データの確認

類似物質の反復投与毒性試験データの確認

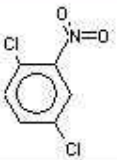
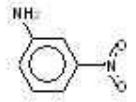
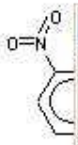
Filter endpoint tree...	1 (Target)	2	3	4	5
Structure					
☑ Substance Identity					
☑ Repeated Dose Toxicity					
☑ LOEL					
☑ Blood Chemical Examination	(9/56)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
☑ General Signs	(6/37)		M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
☑ Hematological Examination					
☑ Blood Cell	(2/3)	M: 15 mg/kg/day, 5...	M: 60 mg/kg/day		
☑ Blood Cell (Coagulation)					
☑ Blood Cell (Erythrocyte)					
☑ Undefined Tissue					
☑ RBC↓	(9/16)	M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
☑ HGB↓	(10/17)	M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
☑ HTC↓	(10/17)	M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	
☑ MCV↑	(4/7)	M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
☑ MCH↑	(3/5)	M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
☑ MCHC↓	(4/6)	M: 170 mg/kg/day, ...		M: 769 mg/kg/day, ...	
☑ Reticulocyte↑	(10/14)	M: 50 mg/kg/day, 5...	M: 60 mg/kg/day	M: 385 mg/kg/day, ...	
☑ Methemoglobin↑	(5/9)		M: 20 mg/kg/day	M: 192 mg/kg/day, ...	M: 769 mg/kg/day, ...
☑ Blood Cell (Leukocyte)	(5/12)	M: 170 mg/kg/day	M: 25 mg/kg/day, 1...		
☑ Blood Cell (Platelet)	(3/4)	M: 170 mg/kg/day			
☑ Histopathological Findings	(12/134)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
☑ Necropsy	(3/10)	M: 15 mg/kg/day, 1...			
☑ NOEL/LOEL	(12/20)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
☑ Organ Weights	(12/71)	M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
☑ Other Examinations	(3/5)			M: 769 mg/kg/day, ...	M: 769 mg/kg/day
☑ Urinalysis	(1/5)				
☑ NOEL	(12/6585)	M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
☑ Profile					

(物質数/試験数)

類似物質

各所見に対するLOELを物質間で横並びに比較

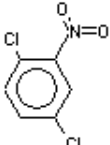
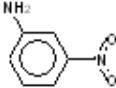
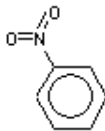
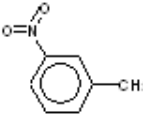
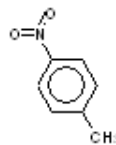
類似物質の反復投与毒性試験データの確認（試験条件の確認）

Filter endpoint tree...	1 (Target)	2	3	4	5
Structure					
☑ Substance Identity					
☐ Repeated Dose Toxicity					
☐ LOEL					
☑ Blood Chemical Examination (9/56)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/		
☑ General Signs (6/37)			M: 100 mg/k		
☐ Hematological Examination					
☑ Blood Cell (2/3)		M: 15 mg/kg/day, 5...	M: 60 mg/kg		
☑ Blood Cell (Coagulation) (1/3)					
☐ Blood Cell (Erythrocyte)					
☐ Undefined Tissue					
RBC↓ (9/16)		M: 15 mg/kg/day, 1...	M: 20 mg/kg		
HGB↓ (10/17)		M: 15 mg/kg/day, 1...	M: 20 mg/kg		
HTC↓ (10/17)		M: 15 mg/kg/day, 1...	M: 20 mg/kg		
MCV↑ (4/7)		M: 50 mg/kg/day, 1...			
MCH↑ (3/5)		M: 50 mg/kg/day, 1...			
MCHC↓ (4/6)		M: 170 mg/kg/day, ...			
Reticulocyte↑ (10/14)		M: 50 mg/kg/day, 5...	M: 60 mg/kg		
Methemoglobin↑ (5/9)			M: 20 mg/kg		
☑ Blood Cell (Leukocyte) (5/12)		M: 170 mg/kg/day	M: 25 mg/kg		
☑ Blood Cell (Platelet) (3/4)		M: 170 mg/kg/day			
☑ Histopathological Findings (12/134)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/		
☑ Necropsy (3/10)		M: 15 mg/kg/day, 1...			
☑ NOEL/LOEL (12/20)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/		
☑ Organ Weights (12/71)		M: 15 mg/kg/day, 5...	M: 5 mg/kg/		
Other Examinations (3/5)					
☑ Urinalysis (1/5)					
☐ NOEL (12/6585)		M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
☑ Profile					

Data points		
#	1	2
Test organisms (species)	Rat	Rat
Administration period (day)	28	28
QA (CAS-2D)	N/A	N/A
Assigned SMILES	NO	NO
Database name	HESS Repeated Dose Toxicity	HESS Repeated Dose Toxicity
Purity	99.8	99.8
Recovery period (day)	0	0
Publication	National Institute of Health Sciences, Japan	National Institute of Health Sciences, Japan
Gender	Male	Female
Organ (Tissue)	Blood cell (Erythrocyte)	Blood cell (Erythrocyte)

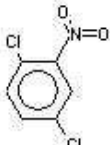
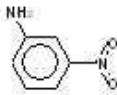
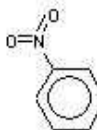
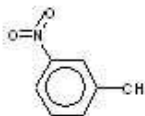
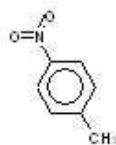
Transpose

類似物質の反復投与毒性試験データの確認（最小値の表示）

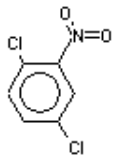
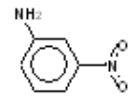
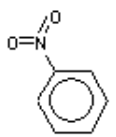
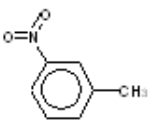
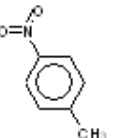
Filter endpoint tree...	1 (Target)	2	3	4	5
Structure					
Substance Identity					
Repeated Dose Toxicity					
LOEL					
Blood Chemical Examination		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
General Signs			M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
Hematological Examination					
Blood Cell		M: 15 mg/kg/day, 5...	M: 60 mg/kg/day		
Blood Cell (Coagulation)					
Blood Cell (Erythrocyte)					
Undefined Tissue					
RBC↓					
HGB↓					
HTC↓					
MCV↑					
MCH↑					
MCHC↓					
Reticulocyte↑					
Methemoglobin↑					
Blood Cell (Leukocyte)					
Blood Cell (Platelet)					
Histopathological Findings		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
Necropsy		M: 15 mg/kg/day, 1...			
NOEL/LOEL		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
Organ Weights		M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
Other Examinations				M: 769 mg/kg/day, ...	M: 769 mg/kg/day
Urinalysis					
NOEL		M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
Profile					

- Hide
- Show hidden
- Collapse all
- Sort (targets priority) ▶
- Sort ▶
- Function...
 - ✓ All
 - Average
 - Min
 - Max
- Filter effects ▶
- Set tree hierarchy...
- Export CAS list
- Export
- Copy path

類似物質の反復投与毒性試験データの確認（最小値の表示）

Filter endpoint tree...	1 (Target)	2	3	4	5
Structure					
各影響のLOELの最小値（すなわち全身のLOEL）					
<input checked="" type="checkbox"/> Substance Identity					
<input checked="" type="checkbox"/> Repeated Dose Toxicity					
<input checked="" type="checkbox"/> LOEL	Min	M: 15 mg/kg/day	M: 5 mg/kg/day	M: 48.1 mg/kg/day	M: 48.1 mg/kg/day
<input checked="" type="checkbox"/> Blood Chemical Examination (9/56)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
<input checked="" type="checkbox"/> General Signs (6/37)			M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
<input checked="" type="checkbox"/> Hematological Examination					
<input checked="" type="checkbox"/> Blood Cell (2/3)		M: 15 mg/kg/day, 5...	M: 60 mg/kg/day		
<input checked="" type="checkbox"/> Blood Cell (Coagulation) (1/3)					
<input checked="" type="checkbox"/> Blood Cell (Erythrocyte)					
<input checked="" type="checkbox"/> Undefined Tissue					
RBC↓ (9/16)		M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
HGB↓ (10/17)		M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
HTC↓ (10/17)		M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	
MCV↑ (4/7)		M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
MCH↑ (3/5)		M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
MCHC↓ (4/6)		M: 170 mg/kg/day, ...		M: 769 mg/kg/day, ...	
Reticulocyte↑ (10/14)		M: 50 mg/kg/day, 5...	M: 60 mg/kg/day	M: 385 mg/kg/day, ...	
Methemoglobin↑ (5/9)			M: 20 mg/kg/day	M: 192 mg/kg/day, ...	M: 769 mg/kg/day, ...
<input checked="" type="checkbox"/> Blood Cell (Leukocyte) (5/12)		M: 170 mg/kg/day	M: 25 mg/kg/day, 1...		
<input checked="" type="checkbox"/> Blood Cell (Platelet) (3/4)		M: 170 mg/kg/day			
<input checked="" type="checkbox"/> Histopathological Findings (12/134)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
<input checked="" type="checkbox"/> Necropsy (3/10)		M: 15 mg/kg/day, 1...			
<input checked="" type="checkbox"/> NOEL/LOEL (12/20)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
<input checked="" type="checkbox"/> Organ Weights (12/71)		M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
Other Examinations (3/5)				M: 769 mg/kg/day, ...	M: 769 mg/kg/day
<input checked="" type="checkbox"/> Urinalysis (1/5)					
<input checked="" type="checkbox"/> NOEL (12/6585)		M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
<input checked="" type="checkbox"/> Profile					

類似物質の反復投与毒性試験データの確認（影響フィルター）

Filter endpoint tree...	1 (Target)	2	3	4	5
<p>Structure</p> <p>カテゴリーと関連のある影響のみを表示する</p> <p>☑ Substance Identity</p> <p>☑ Repeated Dose Toxicity</p> <p>☑ LOEL</p> <ul style="list-style-type: none"> ☑ Blood Chemical Examination ☑ General Signs ☑ Hematological Examination <ul style="list-style-type: none"> ☑ Blood Cell <ul style="list-style-type: none"> ☑ Blood Cell (Coagulation) ☑ Blood Cell (Erythrocyte) <ul style="list-style-type: none"> ☑ Undefined Tissue <ul style="list-style-type: none"> RBC↓ HGB↓ HTC↓ MCV↑ MCH↑ MCHC↓ Reticulocyte↑ Methemoglobin↑ ☑ Blood Cell (Leukocyte) <ul style="list-style-type: none"> (5/12) ☑ Blood Cell (Platelet) <ul style="list-style-type: none"> (3/4) ☑ Histopathological Findings <ul style="list-style-type: none"> (12/134) ☑ Necropsy <ul style="list-style-type: none"> (3/10) ☑ NOEL/LOEL <ul style="list-style-type: none"> (12/20) ☑ Organ Weights <ul style="list-style-type: none"> (12/71) Other Examinations <ul style="list-style-type: none"> (3/5) ☑ Urinalysis <ul style="list-style-type: none"> (1/5) ☑ NOEL <ul style="list-style-type: none"> (12/6585) 					
		M: 15 mg/kg/day	M: 5 mg/kg/day	M: 48.1 mg/kg/day	M: 48.1 mg/kg/day
		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
			M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
		M: 15 mg/kg/day, 5...	M: 60 mg/kg/day		
			1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...
			1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...
		M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
		M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
		M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
		M: 170 mg/kg/day, ...		M: 769 mg/kg/day, ...	
		(10/14)	M: 50 mg/kg/day, 5...	M: 60 mg/kg/day	M: 385 mg/kg/day, ...
		(5/9)		M: 20 mg/kg/day	M: 192 mg/kg/day, ...
			M: 170 mg/kg/day	M: 25 mg/kg/day, 1...	M: 769 mg/kg/day, ...
		(5/12)	M: 170 mg/kg/day		
		(3/4)	M: 170 mg/kg/day		
		(12/134)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...
		(3/10)	M: 15 mg/kg/day, 1...		M: 48.1 mg/kg/day, ...
		(12/20)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...
		(12/71)	M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...
		(3/5)			M: 769 mg/kg/day, ...
		(1/5)			M: 769 mg/kg/day
		(12/6585)	M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...
					M: 48.1 mg/kg/day, ...

Min

- Hide
- Show hidden
- Collapse all
- Sort (targets priority) ▶
- Sort ▶
- Function... ▶
- Filter effects** ▶
 - Edit filters...**
 - Remove filter
- Set tree hierarchy...
- Export CAS list
- Export
- Copy path

類似物質の反復投与毒性試験データの確認（影響フィルター）

Filter endpoint tree...

Structure	1 (Target)	2	3	4	5
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <p>Structure</p> <p>Substance Identity</p> <p>Repeated Dose Toxicity</p> <p>LOEL</p> <ul style="list-style-type: none"> Blood Chemical Examination <ul style="list-style-type: none"> Blood Cell Examination General Signs Hematological Examination <ul style="list-style-type: none"> Blood Cell <ul style="list-style-type: none"> Blood Cell (Coagulation) Blood Cell (Erythrocyte) <ul style="list-style-type: none"> Undefined Tissue <ul style="list-style-type: none"> RBC↓ HGB↓ HTC↓ MCV↑ MCH↑ MCHC↓ Reticulocyte↑ Methemoglobin↑ Blood Cell (Leukocyte) Blood Cell (Platelet) Histopathological Findings Necropsy NOEL/LOEL Organ Weights Other Examinations Urinalysis NOEL </div> <div style="width: 70%;"> <p>1 (Target)</p> <chem>ClC(=O)N=O</chem> <p>2</p> <chem>N</chem> <p>3</p> <chem>O=[N+]([O-])c1ccccc1</chem> <p>4</p> <chem>O=[N+]([O-])c1ccc(C)cc1</chem> <p>5</p> <chem>O=[N+]([O-])c1ccc(C)cc1</chem> </div> </div>					
			M: 5 mg/kg/day	M: 48.1 mg/kg/day	M: 48.1 mg/kg/day
		M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
		M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
		ay, 5...	M: 60 mg/kg/day		
		ay, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
		ay, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
		ay, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	
		ay, 1...		M: 769 mg/kg/day, ...	
		(3/3)	M: 60 mg/kg/day, 1...	M: 769 mg/kg/day, ...	
		(4/6)	M: 170 mg/kg/day, ...	M: 769 mg/kg/day, ...	
		(10/14)	M: 50 mg/kg/day, 5...	M: 60 mg/kg/day	M: 385 mg/kg/day, ...
		(5/9)		M: 20 mg/kg/day	M: 192 mg/kg/day, ...
		(5/12)	M: 170 mg/kg/day	M: 25 mg/kg/day, 1...	
		(3/4)	M: 170 mg/kg/day		
		(12/134)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...
		(3/10)	M: 15 mg/kg/day, 1...		
		(12/20)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...
		(12/71)	M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...
		(3/5)			M: 769 mg/kg/day, ...
		(1/5)			M: 769 mg/kg/day
		(12/6585)	M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...
					M: 48.1 mg/kg/day, ...

Effects...

Profiles...

Filter type

Generic filter... Predefined list...

- Alpha 2u-globulin nephropathy
- Energy metabolism dysfunction
- Hemolytic anemia
- Hemolytic anemia with methemoglobinemia
- Hepatotoxicities/Liver effects
- Less susceptible
- Lipodosis of Adrenocortial
- Liver_enzyme induction
- Mucous membrane irritation
- Neurotoxicity
- Renal Toxicity/Kidney Effects
- Testis
- Thyrotoxicity
- Urinary bladder

Close

類似物質の反復投与毒性試験データの確認（影響フィルター）

Filter endpoint tree...

1 (Target)	2	3	4	5
M: 15 mg/kg/day	M: 5 mg/kg/day	M: 48.1 mg/kg/day	M: 48.1 mg/kg/day	
M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...	
	M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...	
M: 15 mg/kg/day, 5...	M: 60 mg/kg/day			
M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day	
M: 15 mg/kg/day, ...			M: 385 mg/kg/day	
M: 15 mg/kg/day, ...				
M: 50 m				
M: 50 m				
M: 170 mg/kg/day				
M: 50 mg/kg/day				
M: 170 mg/kg/day	M: 25 mg/kg/day, 1...			
M: 170 mg/kg/day				
M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...	
M: 15 mg/kg/day, 1...				
M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...	
M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...	
		M: 769 mg/kg/day, ...	M: 769 mg/kg/day	
M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...	M: 48.1 mg/kg/day, ...	

Effects...

Profiles...

Save current settings to profile... (3)

Delete profile

Predefined list...

- Alpha 2u-globulin nephropathy
- Energy metabolism dysfunction
- Hemolytic anemia
- Hemolytic anemia with methemoglobinemia
- Hepatotoxicities/Liver effects
- Less susceptible
- Lipodosis of Adrenocortial
- Liver_enzyme induction
- Mucous membrane irritation
- Neurotoxicity
- Renal Toxicity/Kidney Effects
- Testis
- Thyrotoxicity
- Urinary bladder

Close (6)

Profile name...

Enter profile name:

Anemia (4)

OK (5) Cancel

MCHC↓ (4/6)

Reticulocyte↑ (10/14)

Methemoglobin↑ (5/9)

Blood Cell (Leukocyte) (5/12)

Blood Cell (Platelet) (3/4)

Histopathological Findings (12/134)

Necropsy (3/10)

NOEL/LOEL (12/20)

Organ Weights (12/71)

Other Examinations (3/5)

Urinalysis (1/5)

NOEL (12/6585)

Profile

類似物質の反復投与毒性試験データの確認 (影響フィルター)

Filter endpoint tree...

Structure

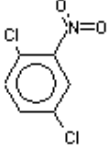
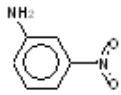
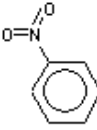
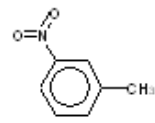
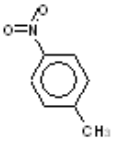
Substance Identity

Repeated Dose Toxicity

LOEL

- [-] Blood Chemical Examination
- [-] General Signs
- [-] Hematological Examination
 - [-] Blood Cell
 - [-] Blood Cell (Coagulation)
 - [-] Blood Cell (Erythrocyte)
 - [-] Undefined Tissue
 - RBC↓
 - HGB↓
 - HTC↓
 - MCV↑
 - MCH↑
 - MCHC↓
 - Reticulocyte↑
 - Methemoglobin↑
 - [-] Blood Cell (Leukocyte)
 - [-] Blood Cell (Platelet)
- [-] Histopathological Findings
- [-] Necropsy
- [-] NOEL/LOEL
- [-] Organ Weights
- [-] Other Examinations
- [-] Urinalysis
- [-] NOEL

Profile

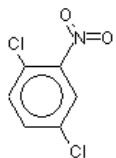
1 (Target)	2	3	4	5
				
	M: 15 mg/kg/day	M: 5 mg/kg/day	M: 48.1 mg/kg/day	M: 48.1 mg/kg/day
	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
		M: 100 mg/kg/day, ...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
	M: 15 mg/kg/day, 5...	M: 60 mg/kg/day		
	/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
	/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	M: 385 mg/kg/day
	M: 15 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	M: 769 mg/kg/day, ...	
	M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
	M: 50 mg/kg/day, 1...		M: 769 mg/kg/day, ...	
(4/6)	M: 170 mg/kg/day, ...		M: 769 mg/kg/day, ...	
(10/14)	M: 50 mg/kg/day, 5...	M: 60 mg/kg/day	M: 385 mg/kg/day, ...	
(5/9)		M: 20 mg/kg/day	M: 192 mg/kg/day, ...	M: 769 mg/kg/day, ...
(5/12)	M: 170 mg/kg/day	M: 25 mg/kg/day, 1...		
(3/4)	M: 170 mg/kg/day			
(12/134)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
(3/10)	M: 15 mg/kg/day, 1...			
(12/20)	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 48.1 mg/kg/day, ...	M: 48.1 mg/kg/day, ...
(12/71)	M: 15 mg/kg/day, 5...	M: 5 mg/kg/day, 20...	M: 385 mg/kg/day, ...	M: 385 mg/kg/day, ...
(3/5)			M: 769 mg/kg/day, ...	M: 769 mg/kg/day
(1/5)				
(12/6585)	M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 0 ...	M: 96.2 mg/kg/day, ...	M: 48.1 mg/kg/day, ...

Context Menu:

- Hide
- Show hidden
- Collapse all
- Sort (targets priority) ▶
- Sort ▶
- Function... ▶
- Filter effects** ▶
 - Edit filters...
 - Remove filter
 - Anemia**
- Set tree hierarchy...
- Export CAS list
- Export
- Copy path

カテゴリーメンバーとしての
エビデンスの確認
(詳細情報へのリンク)

Input
Profiling



Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

類似物質の プロファイリングの抽出

RDT Data

Show Boundary Apply New Scheme

Profilers

Profiling methods

- Biodegradation fragments (BioWIN)
- Eye irritation/corrosion Exclusion rule
- Eye irritation/corrosion Inclusion rule
- Micronucleus alerts by Benigni/Boss
- Mutagenicity/Carcinogenicity alerts
- Oncologic Primary Classification
- Skin irritation/corrosion Exclusion rule
- Skin irritation/corrosion Inclusion rule

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)

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)	2	3	4	5
Structure					
Substance Identity					
Repeated Dose Toxicity					
LOEL (11/84)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 192 mg/kg/day, ...	M: ...
NOEL (12/649)		M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 5 ...	M: 96.2 mg/kg/day, ...	M: ...
Profile					
Study No. (Link to SSRDT)		5	499	296	2
Chemical No. (Link to HESS DB)		5	473	286	2
RDT Report No.		5	477	289	2
CSCL Class			535		
Rat Liver Metabolism Database	N/A	Root of map No. 6 Metabolite in map ...	Root of map No. 593 Root of map No. 594	Root of map No. 228 Root of map No. 229	F F F
Repeated dose (HESS)	Nitrobenzenes (Hem...	Anilines (Hemolytic...	Nitrobenzenes (He...	Nitrobenzenes (He...	M M M

種々の情報にリンクしてカテゴリーメンバーとしてのエビデンスを確認する

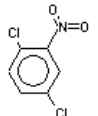

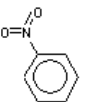
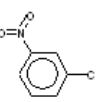
S005.docx [互換モード] - Microsoft Word

試験結果の要約

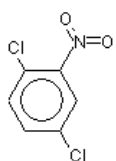
S005	R005	C005
Cas No.	99-09-2	
Study type	TG407/OECD: Repeated Dose 28-day Oral Toxicity Study in Rodents	
Species	Rat (F344)	
Route	Gavage	
Solvent	Olive oil	
Dose level	3 doses (15, 50, 170 mg/kg/day)	
Death	None	
NOEL	<15 mg/kg/day	

Hematology	Hgb↓: >15♂♀
	Hct↓: >15♂♀
	RBC↓: >15♂♀
	WBC↓: 170♀
	E-Blast↑: >15♂, >50♀
	Ret↑: >50♂♀
	MCV↑: >50♀, 170♂
	MCH↑: >50♀, 170♂
	MCHC↓: 170♂♀
	Pit↓: 170♀
Blood chemistry	BUN↑: >15♀
	Cho↑: >50♂, >15♀
	TP↑: >50♂, >15♀
	Alb↑: >50♂, >15♀
	A/G↑: >50♂, 170♀
Absolute organ weight	Liver↑: >50♂♀
	Spleen↑: >50♂♀
	Kidney↑: 170♀
	Testis↓: 170♂
Relative organ weight	Spleen↑: >15♂, >50♀
	Liver↑: >50♂, >150♀
	Kidney↑: 170♂♀
	Testis↓: 170♂
Histopathology	Spleen-hemosiderosis: >15
	Spleen/extramedullary-hematopoiesis: >15
	Spleen-hyperemia and congestion: >15
	Bone marrow-hematopoiesis: >15
	Bone marrow-erythroid hyperplasia: >50
	Liver-swelling of hepatocyte: >50
	Liver-hemosiderosis: 170
	Liver/extramedullary-hematopoiesis: 170
	Kidneys-lipofuscin deposition: >50
	Testis-derangement of spermatogenesis: >50
Testis-multinucleated giant cell formation: 170	
Testis-increase in interstitial cell: 170	
Epididymis-lack of sperm: >50	

類似物質の エビデンスの確認

get)	2	3	4	5
				
	M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 192 mg/kg/day, ...	M
	M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 5 ...	M: 96.2 mg/kg/day, ...	M
	5	499 642	296	2
	5	473	286	2
	5	477 535	289	2
	Designated (Type II...	Designated (Type II...		
	Root of map No. 6 Metabolite in map ...	Root of map No. 593 Root of map No. 594	Root of map No. 228 Root of map No. 229	F F F
benzenes (Hem...	Anilines (Hemolytic...	Nitrobenzenes (He...	Nitrobenzenes (He...	M
benzenes (Hepa...	Anilines (Hepatotox...	Nitrobenzenes (Hep...	Nitrobenzenes (Hep...	M
	Nitrobenzenes (He...	Nitrobenzenes (Tes...	Nitrobenzenes (Tes...	M
	Nitrobenzenes (Hep...			

Input
Profiling



Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No. 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

類似物質の
エビデンスの確認

RDT Data

Show Boundaries Apply New Scheme

Categories

Profilers
Profiling methods
Biodegradation fragments (BioWIN)

Filter endpoint tree...

1 (Target)

Main [HessDB_Search]

Open View Save View Study_View Adme_View Mechanism_View List Help

Search

Search Results Search Conditions

Select All

Cancel All

Add to Study_View

Delete from Study_View

Results : 1

Chem...	Chemical Data	Structure	Study Lin...	Adme...	Mech...
<input type="checkbox"/> 5	[Cas_No.] 99-09-2 [Name] 3-Nitroaniline		5<28*>	5f11	5f2l

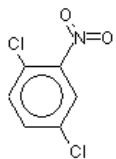
HESS DBへのリンク(詳細情報の参照)

No.	Type	Conditions
1	Chem_No.	5

Searched Conditions

1 (Target)	2	3	4
M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 192 mg/kg/day, ...	M: 192 mg/kg/day, ...
M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 5 ...	M: 96.2 mg/kg/day, ...	M: 96.2 mg/kg/day, ...
5	499 642	296	
5	473	286	
5	477 535	289	
Designated (Type II...	Designated (Type II...		
Root of map No. 6 Metabolite in map ...	Root of map No. 593 Root of map No. 594	Root of map No. 228 Root of map No. 229	
Am... Anilines (Hemolytic...	Nitrobenzenes (He...	Nitrobenzenes (He...	
pa... Anilines (Hepatotox...	Nitrobenzenes (Hep...	Nitrobenzenes (Hep...	
Nitrobenzenes (He...	Nitrobenzenes (Tes...	Nitrobenzenes (Tes...	
Nitrobenzenes (Hep...			

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



Chemical name: 1,4-dichloro-2-nitrobenzene
 CAS No 89-61-2
 SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

類似物質の エビデンスの確認

Show Boundaries Apply New Scheme

- Profilers
- Profiling methods
- Biodegradation fragments (BioWIN)
 - Eye irritation/corrosion Exclusion ru
 - Eye irritation/corrosion Inclusion ru
 - Micronucleus alerts by Benigni/Boss
 - Mutagenicity/Carcinogenicity alerts
 - Oncologic Primary Classification
 - Skin irritation/corrosion Exclusion ru
 - Skin irritation/corrosion Inclusion ru

Empiric

- Chemic
- Groups
- Lipinski
- Organic
- Organic
- Organic
- Organic
- Study M
- Chemic
- RDT Re
- CSCL Cl
- Rat Live

Toxicological

- Repeat

Documente

- Observ

Simulated

- Dissocia
- Liver M
- NEDO I
- NEDO I
- NEDO I

Profiling results

- [-] Chemical profile
 - [-] Rat Liver Metabolism Database
 - Root of map No. 593
 - Root of map No. 594

Details
Close

Filter endpoint tree...

Structure

Substance Identity

Repeated Dose Toxicity

	1 (Target)	2	3	4
(11/84)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 192 mg/kg/day, ...
(12/649)		M: 15 mg/kg/day, 1...	M: 0 mg/kg/day, 5 ...	M: 96.2 mg/kg/day, ...
		5	499	296
		5	642	
		5	473	286
		5	477	289
			335	
		Designated (Type II...	Designated (Type II...	
N/A	Root of map No. 6	Root of map No. 593	Root of map No. 594	Root of map No. 228
	Metabolite in map ...	Root of map No. 229	Root of map No. 229	
	Nitrobenzenes (Hem...	Anilines (Hemolytic...	Nitrobenzenes (He...	Nitrobenzenes (He...
	Nitrobenzenes (Hepa...	Anilines (Hepatotox...	Nitrobenzenes (Hep...	Nitrobenzenes (Hep...
		Nitrobenzenes (He...	Nitrobenzenes (Tes...	Nitrobenzenes (Tes...
		Nitrobenzenes (Hep...		

Add as a list

Map Info

Close

代謝マップDB

what to add

 sub-tree whole map(w/o parent)

METABOLISM DATABASE

- 567. c1(Cl)c(Cl)cc(N(=O)=O)cc1
- 568. C(=O)(O)c1cc(N(=O)=O)ccc1
- 569. c1(C)c(O)cc(C)cc1
- 570. c1(C)c2c(cc(O)c1)CCC{P-}(C)(
- 571. C(#N)c1ccc(N(=O)=O)cc1
- 572. C(#N)c1cc(I)c(O)c(N(=O)=O)c
- 573. c12c(cccc1)N(CC)N=N2
- 574. c12c(cccc1)N(C)N=N2
- 575. C(C)(C)(C)c1c(O)c(C(C)(C)C)cc
- 576. c1(F)c(Cl)cc(N)cc1
- 577. c1(N)c(C)cc(O)cc1
- 578. C(CCCC)N(C)C
- 579. c1(Cl)c(Cl)cc(NC(=O)N(C)C)cc1
- 580. C(C)(C)(C)c1c(O)c(C)ccc1
- 581. C(C)(N)CNCCCCNCCCN
- 582. C1(c2c(-c3ccc(C)cc3)cccc2)=N
- 583. C(=O)(O)c1c(O)cccc1
- 584. C1(C)(CCCC)OC(CCl)CO1
- 585. C(N)CC
- 586. C(F)(F)(F)COC=C
- 587. C(C)(=O)c1c2c(c(OCCCC)cc1)c
- 588. c1(C(C)C)c(O)c(C(C)C)ccc1
- 589. c1(Cl)ccc(NC)cc1
- 590. c1(N=C=S)cccc1
- 591. c1(C(C)(C)c2ccc(O)cc2)ccc(O)c
- 592. c1(C(C)(C)c2ccc(O)cc2)ccc(O)c
- 593. c1(N(=O)=O)cccc1
- 594. c1(N(=O)=O)cccc1

Search target

 search parents only search as fragment

extended search...

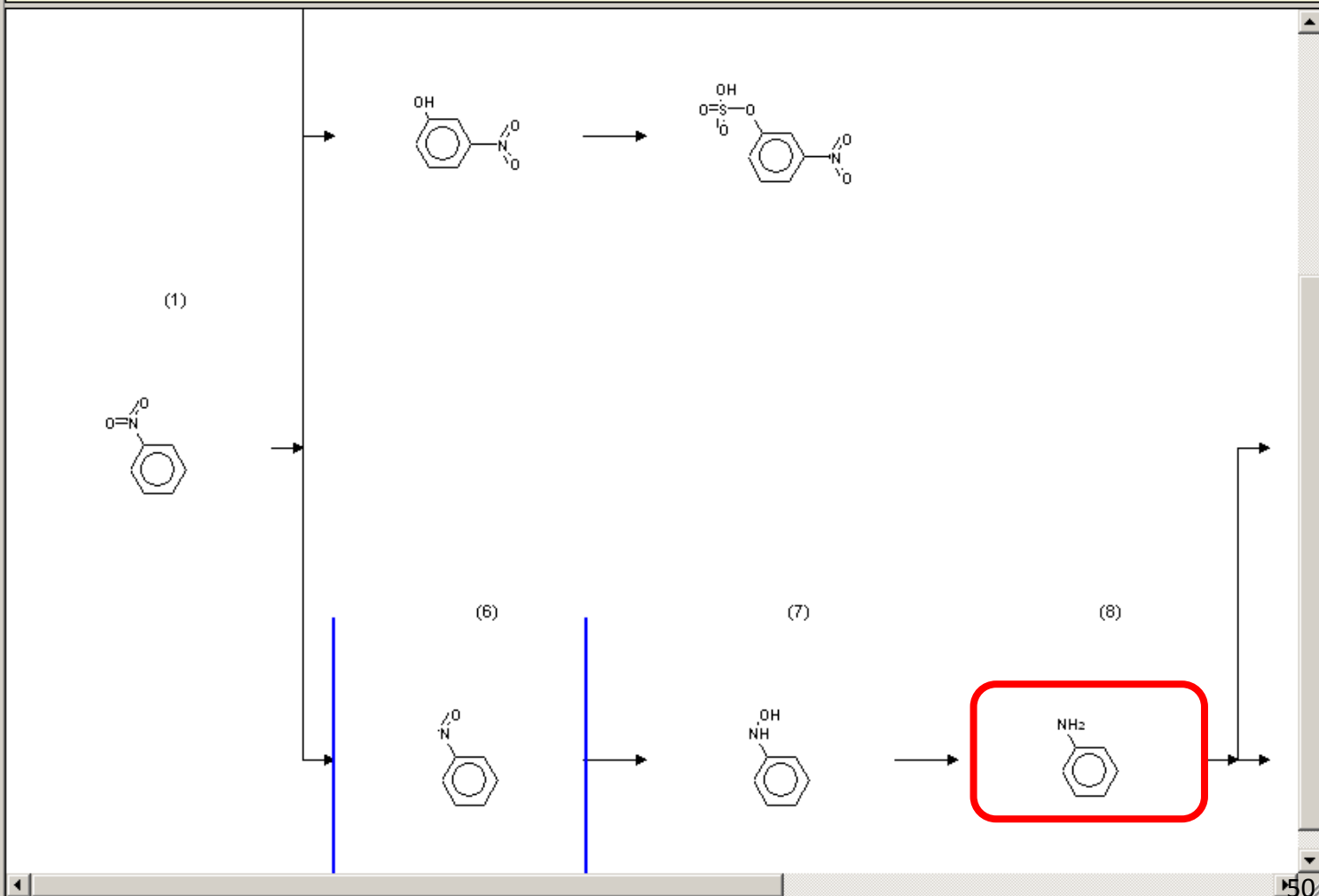
Flex search...

Trans flex search...

Redraw Print Preview

Cell Height 200 Cell Width 200

Reference: Levin, A. A., J. G. Dent, Drug Metab. Dispos., 10(5), (1982). (in vivo/in vitro), pp. 450 - 454



Add as a list

Map Info

Close

what to add

- sub-tree
 whole map(w/o parent)

METABOLISM DATABASE

- 567. c1(Cl)c(Cl)cc(N(=O)=O)cc1
- 568. C(=O)(O)c1cc(N(=O)=O)ccc1
- 569. c1(C)c(O)cc(C)cc1
- 570. c1(C)c2c(cc(O)c1)CCC(P-)(C)(
- 571. C(#N)c1ccc(N(=O)=O)cc1
- 572. C(#N)c1cc(I)c(O)c(N(=O)=O)c
- 573. c12c(ccc1)N(CC)N=N2
- 574. c12c(ccc1)N(C)N=N2
- 575. C(C)(C)(C)c1c(O)c(C(C)(C)C)cc
- 576. c1(F)c(Cl)cc(N)cc1
- 577. c1(N)c(C)cc(O)cc1
- 578. C(CCCC)N(C)C
- 579. c1(Cl)c(Cl)cc(NC(=O)N(C)C)cc1
- 580. C(C)(C)(C)c1c(O)c(C)ccc1
- 581. C(C)(N)CCNCCCNCNCCN
- 582. C1(c2c(-c3ccc(C)cc3)cccc2)=N
- 583. C(=O)(O)c1c(O)cccc1
- 584. C1(C)(CCCC)OC(CCl)CO1
- 585. C(N)CC
- 586. C(F)(F)(F)COC=C
- 587. C(C)(=O)c1c2c(c(OCCCC)cc1)
- 588. c1(C(C)C)c(O)c(C(C)C)ccc1
- 589. c1(Cl)ccc(NC)cc1
- 590. c1(N=C=S)cccc1
- 591. c1(C(C)(C)c2ccc(O)cc2)ccc(O)c
- 592. c1(C(C)(C)c2ccc(O)cc2)ccc(O)c
- 593. c1(N(=O)=O)cccc1
- 594. c1(N(=O)=O)cccc1

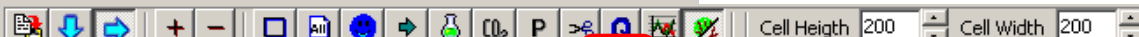
Search target search parents only
 search as fragment

extended search...

Flex search...

Trans flex search...

代謝マップDB



Redraw Print Preview

試験条件の確認

Reference: Levin, A. A., J. G. Dent, Drug Metab. Dispos., 10(5), (1982). (in vivo/in vitro), pp. 450 - 454

NEDO HESS - map information

Map info Chemical info

Literature references

References:

- Levin, A. A., J. G. Dent, Drug Metab. Dispos., 10(5), (1982). (in vivo/in vitro), pp. 450 - 454

Entered by: Maria Velikova

Other text

Studies info:

Rat, male, in vitro, Microsome
 Rat, male, in vitro, Microsome
 Rat, male, in vitro, Microsome
 Rat, male, in vitro, S9 fraction
 Rat, male, in vitro, S9 fraction
 Rat, male, in vitro, S9 fraction
 Rat, male, in vitro, Microsome
 Rat, male, in vitro, Feces, int
 Rat, male, in vivo, Whole org
 Rat, male, in vivo, Whole org
 Rat, male, in vivo, Whole org

Study:

Rat, male, in vitro, Microsomes, liver, incubation media, in vitro incubation, 100 uM, single dose (radiolabeled), Fischer 344

Subjects:

- Species - Rat
- Gender - Male (3 subjects)
- Age - Not reported
- Strain - Fischer 344
- Source - Charles River Breeding Laboratories (Kingston, NY)

In vivo / in vitro:

- In vitro
- Phase I enzymes - Detected (looked for and found)
- Phase II enzymes - Not determined (not looked for)
- Experimental system - Microsomes
- Organ / Tissue - Liver
- Exper. descriptors - Not reported

Sampling / analytical:

- Sample matrix - Incubation media
- Sample times (frequency) - Final
- Duration - 1 hours
- Separations - High-performance liquid chromatography (HPLC), Gas chromatography (GC)
- Detections - Electron ionization mass spectrometry (EI-MS), Liquid scintillation counting (LSC), Ultraviolet spectroscopy (UV)
- Extraction methods - Derivatization (bis(trimethylsilyl)trifluoroacetamide (BSTFA)), Solid phase (Lichrosorb RP-18, SE-30), Solvent (ethyl acetate)
- Conj. analysis methods - Not reported

Dose administration:

(8)

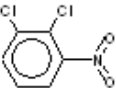
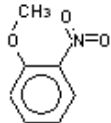
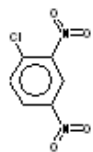


カテゴリーとして不適切と思われる物質を除外する方法

Filter endpoint tree...

Structure

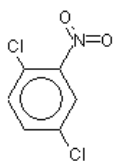
- ☑ Substance Identity
- ☑ Repeated Dose Toxicity
 - ☑ LOEL
 - ☑ Blood Chemical Examination
 - ☑ Blood Serum (Bilirubin)
 - ☑ Undefined Tissue
 - T. Bilirubin↑
 - ☑ Hematological Examination
 - ☑ Blood Cell (Erythrocyte)
 - ☑ Undefined Tissue
 - RBC↓
 - HGB↓
 - HTC↓
 - Reticulocyte↑
 - Methemoglobin↑
 - ☑ Histopathological Findings
 - ☑ Liver
 - ☑ Kupffer Cell
 - Pigmentation (Hemosiderin)
 - Pigmentation (Other)
 - ☑ Undefined Tissue
 - Extramedullary Hematopoiesis
 - ☑ Spleen
 - ☑ Undefined Tissue
 - Pigmentation (Hemosiderin)
 - Pigmentation (Other)

	9	10	11	12	13
					
Min	M: 25 mg/kg/day	M: 15.4 mg/kg/day			
	(3/4)				
	(9/16)	M: 154 mg/kg/day, ...		M: 100 mg/kg/day	
	(10/17) M: 100 mg/kg/day	M: 154 mg/kg/day, ...		M: 100 mg/kg/day	
	(10/17) M: 100 mg/kg/day	M: 154 mg/kg/day, ...		M: 100 mg/kg/day	M: 60 mg/kg/day
	(10/14) M: 100 mg/kg/day	M: 15.4 mg/kg/day, ...		M: 20 mg/kg/day	M: 300 mg/kg/day
	(5/9)	M: 462 mg/kg/day, ...			
	(3/4)	M: 1.38E3 mg/kg/d...		M: 100 mg/kg/day	
	(1/2)				
	(1/3)				
	(7/12) M: 25 mg/kg/day	M: 1.38E3 mg/kg/d...			
	(3/6)				
	(5/9)	M: 462 mg/kg/day		M: 100 mg/kg/day	

- Add as target
- Select all as targets
- Remove all as targets
- Add target
- Add in category
- Delete chemical**
- Delete all except current
- Save to SMI file (DayLight format)
- Save to SMI file
- Print structures
- Export data for targets
- Export CAS list
- Search Ctrl+F

リードアクロスによる データギャップ補完

Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism



Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

データギャップ補完に使用する
所見

②

③

Read-across

Trend analysis

(Q)SAR models

Apply

Target Endpoint

Repeated Dose Toxicity

Possible data inconsistency

- Examination items
- Effect
- Tissue
- Organ (Tissue)

Selected [140/140] points

OK

Cancel

①

Min

(3/4)

(9/16)

(10/17)

(10/17)

(10/14)

(5/9)

(3/4)

(1/2)

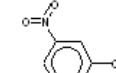
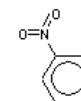
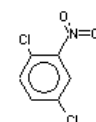
(1/3)

(7/12)

(3/6)

(5/9)

(6/11)



M: 15 mg/kg/day

M: 5 mg/kg/day

M: 48.1 mg/kg/day

M: 20 mg/kg/day

M: 15 mg/kg/day, 1... M: 20 mg/kg/day, 2... M: 769 mg/kg/day, ...

M: 15 mg/kg/day, 1... M: 20 mg/kg/day, 2... M: 769 mg/kg/day, ...

M: 15 mg/kg/day, 1... M: 20 mg/kg/day, 2... M: 769 mg/kg/day, ...

M: 50 mg/kg/day, 5... M: 60 mg/kg/day M: 385 mg/kg/day, ...

M: 20 mg/kg/day M: 192 mg/kg/day, ...

M: 20 mg/kg/day

M: 125 mg/kg/day, ...

M: 20 mg/kg/day, 1...

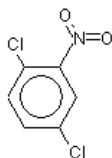
M: 20 mg/kg/day M: 48.1 mg/kg/day, ...

M: 15 mg/kg/day, 1... M: 5 mg/kg/day, 25...

M: 5 mg/kg/day, 25... M: 385 mg/kg/day, ...

M: 15 mg/kg/day, 1... M: 5 mg/kg/day, 5 ...

Input
Profiling



Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

データギャップ補完
の設定の確認①

RDT Data

Categories

Gap Filling

Report

Metabolism

Data Gap Filling Method

- Read-across
 Trend analysis
 (Q)SAR models

Apply

Target Endpoint

Repeated Dose Toxicity LOEL

Filter endpoint tree...

Structure

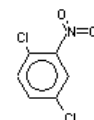
LOEL

(11/140) Min

Descriptors

Prediction

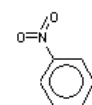
1 (Target)



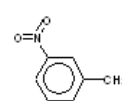
2



3



4



M: 15 mg/kg/day

M: 5 mg/kg/day

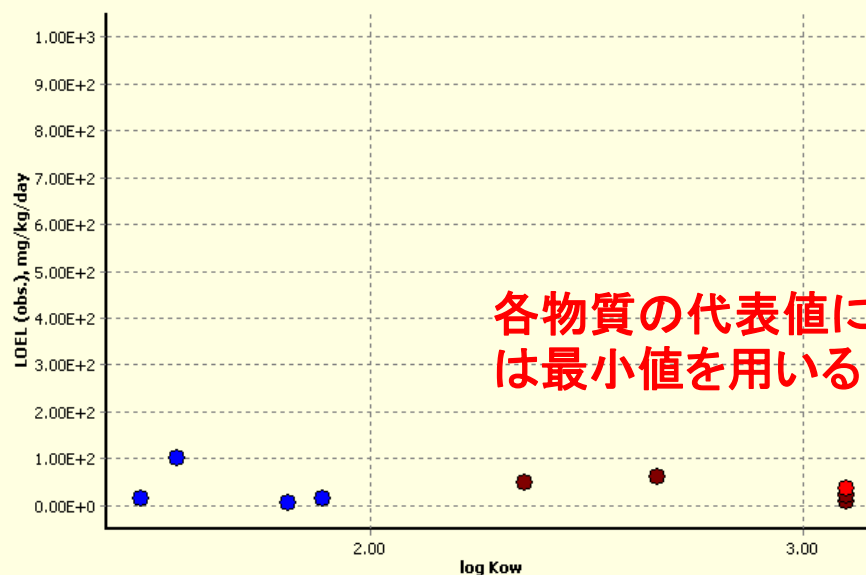
M: 48.1 mg/kg/day

M: 15 mg/kg/day 1

M: 5 mg/kg/day 5

M: 96.2 mg/kg/day

Read across prediction of LOEL,
taking the average from the nearest 5 neighbours, based on 7 data points from 7 neighbour chemicals,
Observed target value: N/A, Predicted target value: 36.7 mg/kg/day



各物質の代表値に
は最小値を用いる

Descriptor X: log Kow

Accept prediction

Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach
- Descriptors/data
- Model/(Q)SAR
- Calculation options
 - Data usage
 - Prediction approach options
 - Set level of significance
- Visual options
- Information

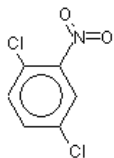
Set usage of data per chemical:

- All
- Minimal
- Maximal
- Average
- Median(s)
- Lower median
- Higher median
- Mode(s)
- Lowest mode
- Highest mode

OK

Cancel

Input
Profiling



Chemical name: 1,4-dichloro-2-nitrobenzene

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

データギャップ補完
の設定の確認②

RDT Data

Data Gap Filling Method

- Read-across
 Trend analysis
 (Q)SAR models

Apply

Target Endpoint

Repeated Dose Toxicity LOEL

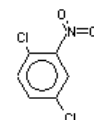
Filter endpoint tree...

Structure

LOEL

(11/140) Min

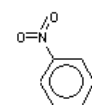
1 (Target)



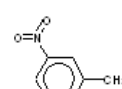
2



3



4



M: 15 mg/kg/day

M: 5 mg/kg/day

M: 48.1 mg/kg/day

M: 15 mg/kg/day 1

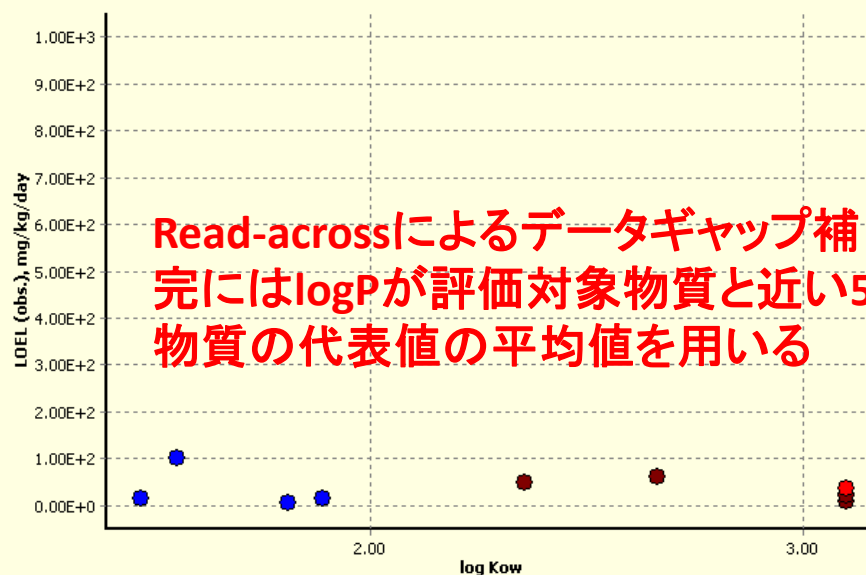
M: 5 mg/kg/day 5

M: 96.2 mg/kg/day

Descriptors

Prediction

Read across prediction of LOEL,
taking the average from the nearest 5 neighbours, based on 7 data points from 7 neighbour chemicals,
Observed target value: N/A, Predicted target value: 36.7 mg/kg/day



Read-acrossによるデータギャップ補完にはlogPが評価対象物質と近い5物質の代表値の平均値を用いる

Descriptor X: log Kow

Accept prediction

Return to matrix

- Select/filter data
- Selection navigation
- Gap filling approach

Read-across

Trend analysis

 Descriptors/data Model/(Q)SAR Calculation options Visual options Information Miscellaneous

Set "Read-across" options:

Approximation type:

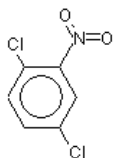
Average

based on 5 neighbours

OK

Cancel

Input
Profiling



Chemical name: 1,4-dichloro-2-nitrobenzene

CAS No 89-61-2

SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1

to data matrix ->

予測結果

RDT Data

Categories

Gap Filling

Report

Metabolism

Data Gap Filling Method

Read-across

Filter endpoint tree...

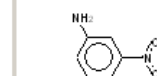
1 (Target)

2

3

4

溶血性貧血に対するLOELの推定値:
36.7 mg/kg/day



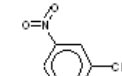
M: 15 mg/kg/day

M: 15 mg/kg/day 1



M: 5 mg/kg/day

M: 5 mg/kg/day 5



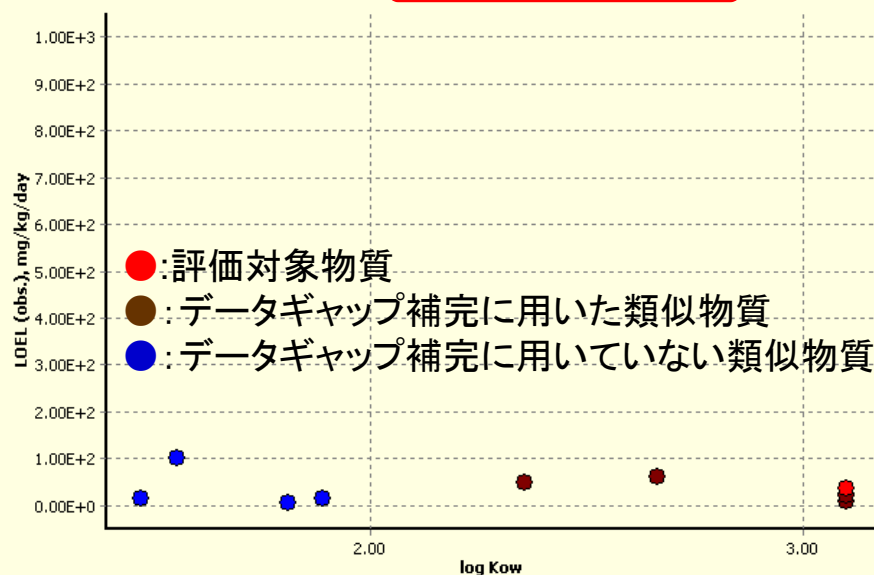
M: 48.1 mg/kg/day

M: 96.2 mg/kg/day

Descriptors

Prediction

Read across prediction of LOEL,
taking the average from the nearest 5 neighbours based on 7 data points from 7 neighbour chemicals,
Observed target value: N/A Predicted target value: 36.7 mg/kg/day



Descriptor X: log Kow

Accept prediction

Return to matrix

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

Set "Read-across" options:

Approximation type:

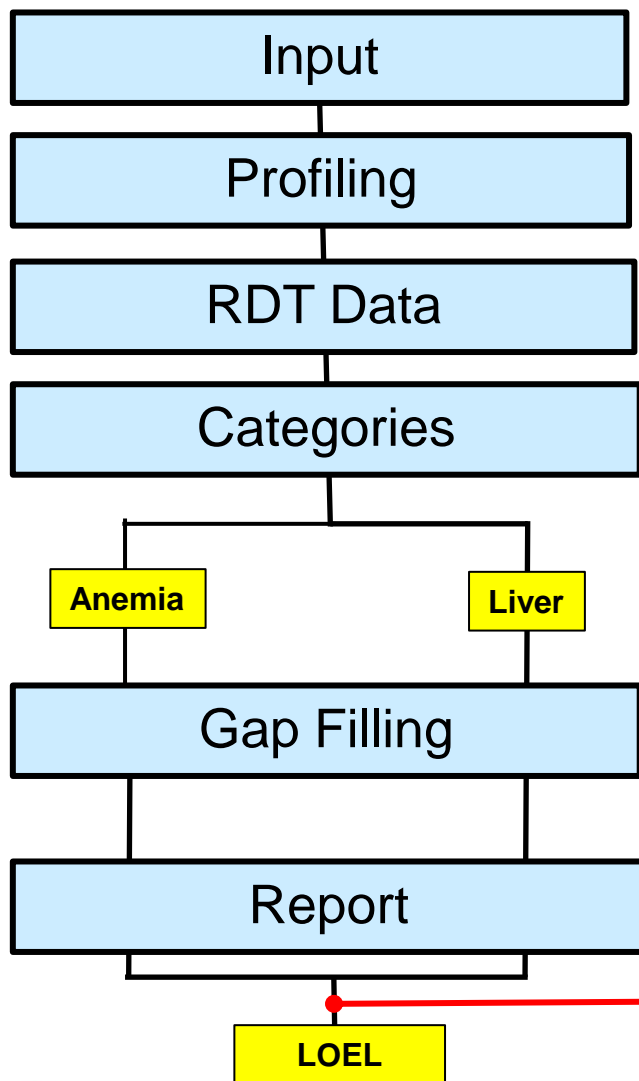
Average

based on 5 neighbours

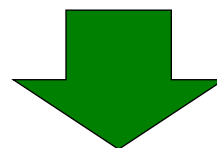
OK

Cancel

全身のLOELに対するデータギャップ補完



Min. { 溶血性貧血に対するLOEL
: 36.7 mg/kg/day
肝毒性に対するLOEL
: 44.3 mg/kg/day



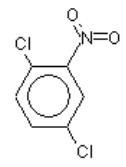
全身に対する LOEL
: 36.7 mg/kg/day

最小値を選択

Hazard Evaluation Support System

Reset Options

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



Chemical name: **1,4-dichloro-2-nitrobenzene**
 CAS No **89-61-2**
 SMILES **c1(Cl)c(N(=O)=O)cc(Cl)cc1**

to data matrix ->

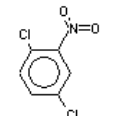

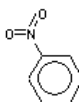
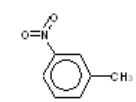
Data Gap Filling Method

- Read-across
- Trend analysis
- (Q)SAR models

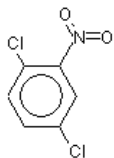
Apply

Target Endpoint

Repeated Dose Toxicity LOEL

Filter endpoint tree...	1 (Target)	2	3	4	5
Structure					
<input checked="" type="checkbox"/> Substance Identity <input type="checkbox"/> Repeated Dose Toxicity <ul style="list-style-type: none"> <input type="checkbox"/> LOEL (11/140) Min R: 17.7 mg/kg/day <input type="checkbox"/> NOEL (11/249) 		M: 15 mg/kg/day	M: 5 mg/kg/day	M: 48.1 mg/kg/day	M:
<input type="checkbox"/> Profile		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 5 ...	M: 96.2 mg/kg/day, ...	M:

Input
Profiling



Chemical name: 1,4-dichloro-2-nitrobenzene

CAS No 89-61-2

SMILES c1ccc(Cl)cc(Cl)[N+](=O)[O-]

to data matrix

これまでのデータギャップ補完の操作が記録されており、レポートが自動的に作成される。

RDT Data

Categories

Gap Filling

Report

Metabolism

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

Reports

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

Repository

Available data to report

Predictions
[1] NEDO HESS prediction for LOEL
(Q.SAR)
Categories

Available report templates

Standard (predefined)
Prediction Report (TPRF v.1.0.1)
Custom (user defined)

 show only relevant templates

Prediction [1]

Prediction of LOEL for 1,4-dichloro-2-nitrobenzene

1 / 18

NEDO HESS prediction based on read-across

Prediction of LOEL for 1,4-dichloro-2-nitrobenzene

The template of the current report is based on "GUIDANCE DOCUMENT ON THE VALIDATION OF (QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIPS MODELS" published by OECD (September, 2007) and "GUIDANCE ON INFORMATION REQUIREMENTS AND CHEMICAL SAFETY ASSESSMENT / CHAPTER R.6: QSARS AND GROUPING OF CHEMICALS" published by ECHA (May, 2008).

The report provides information about the target substance, chemical characteristics used for the grouping, the resulting boundaries of the group of chemicals (applicability domain), the type of data gap filling approach that was applied (read-across, trend analysis or QSAR models), the predicted result(s) and in the Annex information about the category members or training set and test set chemicals.

The chemicals are ordered by the distance to the target substance within the

～HESSの運用状況～

HESSについて

未試験化学物質の反復投与毒性を類似物質の試験データから推定すること(カテゴリーアプローチ)を支援するシステム。

NEDO/METIプロジェクト(H19-H23年度)*で開発。国際整合性を重視し、OECD QSAR Toolboxと互換性のあるシステムとして開発。

開発機関を代表して、当機構がH24年度より公開し運用を開始した。

<http://www.safe.nite.go.jp/kasinn/qsar/hess.html>

平成24年度の主な活動

ユーザとの交流を重視した運用を実施

HPを開設し、ユーザからの問い合わせに常時対応

操作方法の講習会の実施（3回）

操作方法の動画の配信

システムの更新（データ追加、バグ修正等；2回）

個別ユーザとの意見交換会の実施

HESSの利用方法

平成24年度講習会アンケートより（有効回答数46人）

1. 実測試験を行う際の参考情報（用量設定の参考など）	12 人
2. 評価対象物質の安全性情報（実測試験の有無）の確認	21 人
3. 類似物質の安全性情報（実測試験の有無）の確認	27 人
4. 代謝情報または作用機序情報の検索	13 人
5. Read-acrossによる化学物質のハザード評価	24 人

（その他の利用法）

- ・ 実試験結果（自社データ）と予測結果の比較
- ・ 医薬品シーズのドラッグデザイン
- ・ SDS有害性情報の調査等（GHS評価結果の無い化学物質等）

ユーザからの主要望

1. 収載データの拡充

- ・ 一般化合物以外にも医薬品などの化合物データも取り込んで欲しい。
 - ・ 自分たちの評価したい化合物の類似化合物が少ないという問題に直面した。今後のデータの充実を期待する。
 - ・ 適切な類似物が抽出できず、カテゴリーが上手く作成できないことが多い。
 - ・ 複雑な構造を持った農薬などを入力した場合、ほとんどカテゴリーに当てはまらないため、そういった化合物のHESSを用いた毒性予測には相当の工夫が必要と感じた。
- 現状のHESSの収載データは化審法既存化学物質が中心であり、他のデータを拡充することが必要。

2. 具体的な評価事例の提示

- ・ お手本となるような妥当性評価結果の例がない。(少なくとも「それ」で必要とされている要件が満たせれば、一般的には妥当である、といえるような要件の明示が欲しい。)
 - ・ カテゴリーの選び方、考慮すべき点など、実例での操作講習時間を増やした方が良い。
 - ・ 今後、一年に1回程度、講習会、可能であれば事例紹介等を開催していただきたい。
- これまでも、論文や学会において、いくつかの評価事例を提示してきたが、普及拡大のためには、講習会等において相当数の評価事例を提示することが必要。

平成25年度の主な対応

定常的に更新している化審法試験データに加え、ユーザが希望するデータについても検討の上、公開システムに取り込む(データ作成について協力が得られる場合)。

現在、花王(株)の協力を得て肝毒性カテゴリーの拡充を実施中。また、田辺三菱製薬(株)の協力を得て医薬品の毒性試験データを、米国環境保護局(US EPA)の協力を得て農薬の毒性試験データ(ToxRefデータ)を、EU COSMOSプロジェクトの協力を得て化粧品・食品添加物のデータシステムに取り込むことを計画中。

評価事例を主体とした無料の講習会を3度開催。

海外への普及を目的に国際学会でのブース展示を実施(EuroTox2013, SOT2014)。

ユーザからの要望を踏まえて操作性を向上させるためシステムの改修を実施中(HESS:Undo機能、HESS DB:64bit対応など)。新システムには、上述の拡充データの一部を取り込み、**平成26年3月**にリリースする予定。

HESSの入手

- HESS/HESS DBのインストールファイル一式
- 操作法に関する説明動画
- NITEが開催したHESS講習会の資料
- NITEのHPから入手できます。

<http://www.safe.nite.go.jp/kasinn/qsar/hess.html>

(検索キーワード“NITE”, “HESS”)