評価事例1
～溶血性貧血を対象とした化学物質の毒性評価～

2013年12月10-11日

（独）製品評価技術基盤機構
化学物質管理センター

溶血性貧血について

赤血球が破壊されることにより貧血となる病変。

化審法試験で認められる主な関連所見：

血液学検査：RBC↓（赤血球数）、HGB（ヘモグロビン数）↓、
HCT（ヘマトクリット値）↓、Reticulo.（網状血球数）↑

血液生化学検査：T–bil（総ビリルビン）↑

病理組織学検査：Spleen (脾臓)や Liver (肝臓)における
Pigmentation(色素沈着)や
Extramedullary hematopoiesis（随外造血の亢進）

化審法試験においてはNOELの根拠になるケースが多い。

毒性発現のメカニズムに関する研究例が多く報告されており、カテゴリーの根拠となる情報が得られやすい。

HESSの溶血性貧血カテゴリー

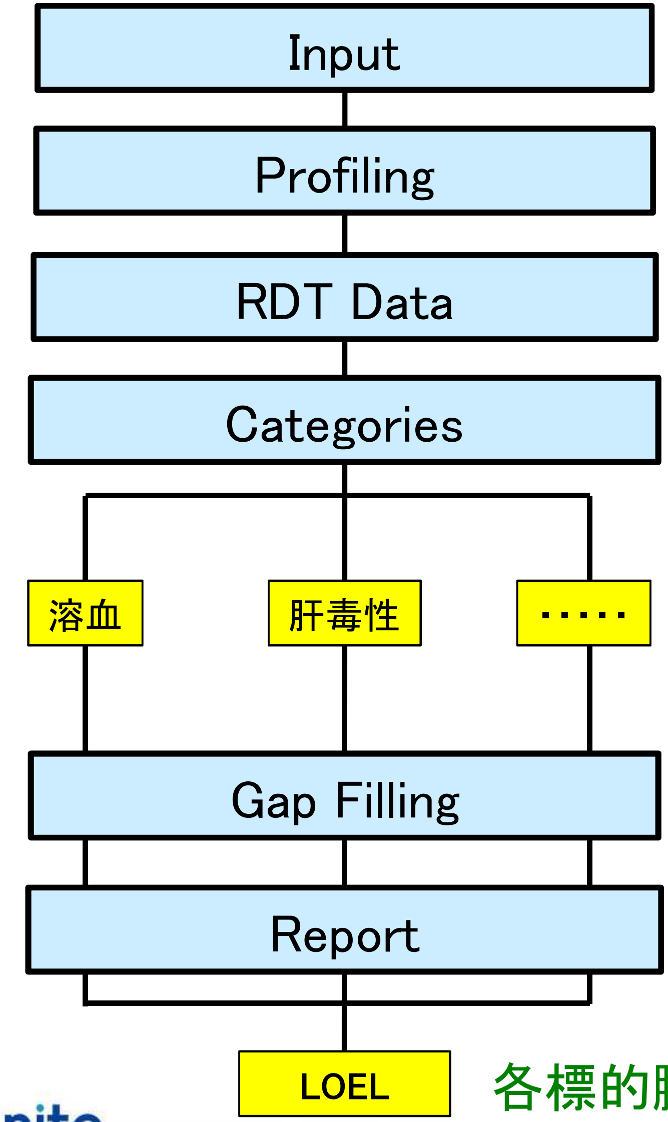
カテゴリー	物質数	対象影響の LOELの平均 (mg/kg/day)	信頼性ランク
1. Azobenzenes (Met-Hb生成)	2	0.6±5.7	B
2. Diphenyl disulfides (Met-Hb生成)	1	30	B
3. Hydrazines (Met-Hb生成)	2	20±127	B
4. Oximes (Met-Hb生成)	3	23±7	B
5. Nitrobenzenes (Met-Hb生成)	12	54±82	A
6. Anilines (Met-Hb生成)	18	72±40	A
7. N-Alkyl-N'-phenyl-p-phenylenediamine (Met-Hb生成)	2	100	B
8. Ethyleneglycol Alkylethers	5	110±192	A
9. o-/p-Aminophenols (Met-Hb生成)	3	254±606	B

溶血性貧血のメカニズムは、メトヘモグロビン(Met-Hb)生成の有無により大別できる。

HESSのカテゴリーの信頼性ランク

信頼性ランク	A	B	C
メカニズム情報	Molecular Initiating Eventからの毒性発現のメカニズムが説明されているもの。	Molecular Initiating Eventからの毒性発現のメカニズムが説明されているもの。	Molecular Initiating Eventからの毒性発現のメカニズムは説明されていないが、特定の構造的特徴を持つ物質に対し特定の毒性を発現することが文献等で報告されているもの。
構造領域	反復投与毒性試験データが多くの物質に対し得られており、反復投与毒性試験データを根拠に毒性が発現する構造領域を定義することが可能であるもの	反復投与毒性試験データが多くの物質に対し得られておらず、反復投与毒性試験データを根拠に毒性が発現する構造領域を定義することはできないが、in vitro試験等の別の試験の文献情報を根拠に毒性が発現する構造領域を定義できるもの	反復投与毒性試験データが多くの物質に対し得られており、反復投与毒性試験データを根拠に毒性が発現する構造領域を定義することが可能であるもの

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 (Q)SAR Toolboxに準拠）



Input

評価対象物質の入力

Profiling

プロファイリングの抽出（該当カテゴリー等）

RDT Data

反復投与毒性試験データの抽出
（ユーザデータ追加可能）

Categories

類似物質（カテゴリー候補）の抽出

溶血　肝毒性　・・・・・

HESS DB等によるカテゴリーのエビデンスの確認（専門家の知見活用）
→必要に応じてサブカテゴリー化

今回の講習対象

Gap Filling

各標的に対するLOELの推定

Report

レポートの自動作成

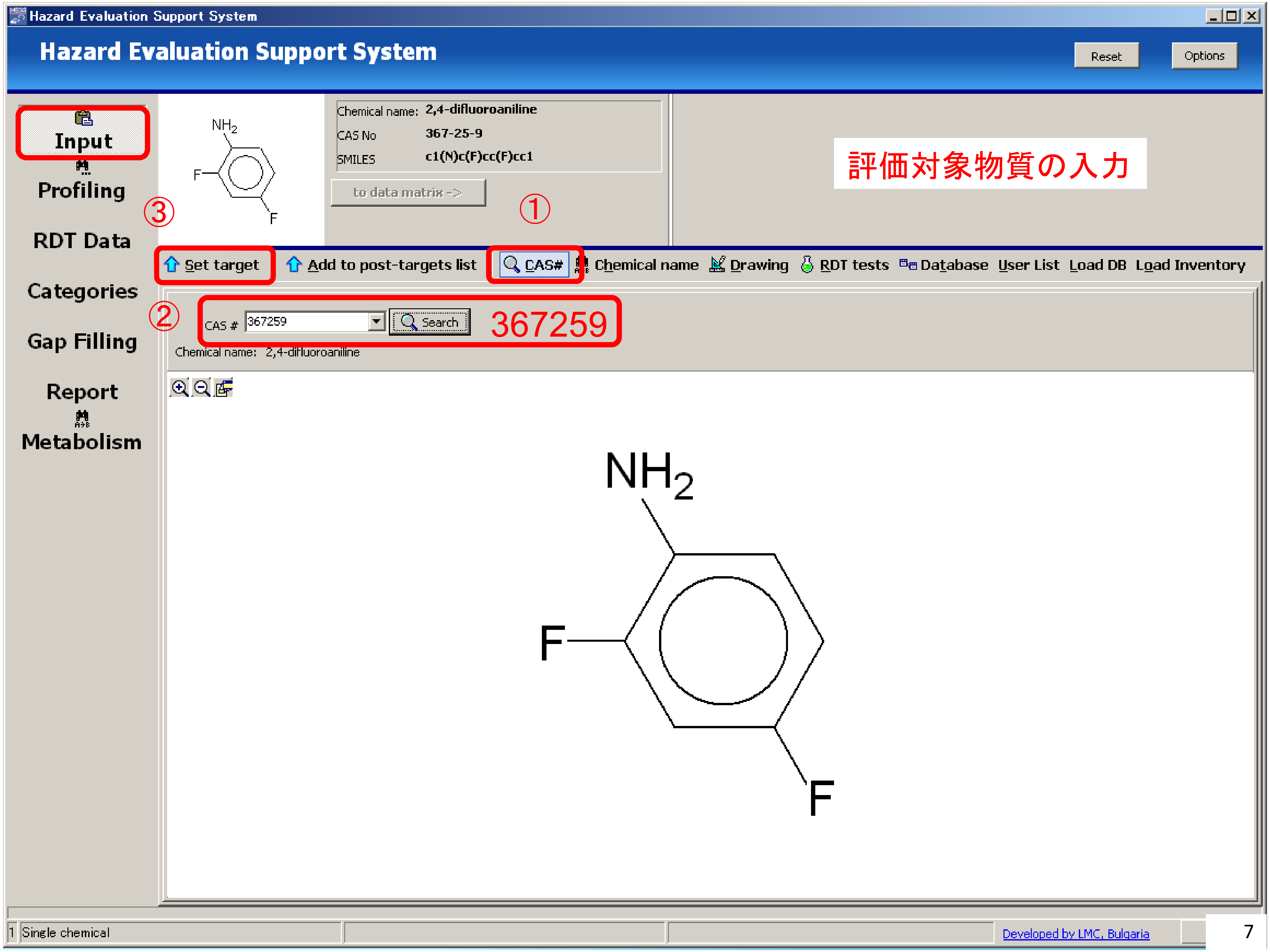
LOEL

各標的臓器に対するLOELの推定値の最少値を選択

A. 簡易予測

HESSが提示したカテゴリーの妥当性を大まかに確認し、特に問題がなければ、提示されたカテゴリーをそのまま用いて評価を行う。

1. 該当するカテゴリーレポートの確認（構造上の特徴、毒性の特徴の確認等）
2. 類似物質の構造類似性の確認
3. 類似物質の毒性の大まかな確認（フィルター機能の利用）
4. 類似物質の毒性強度の分布（logKowと対象毒性のLOELのプロット）の確認
5. 予測に使用する類似物質の選定→自動的に予測



評価対象物質の入力

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

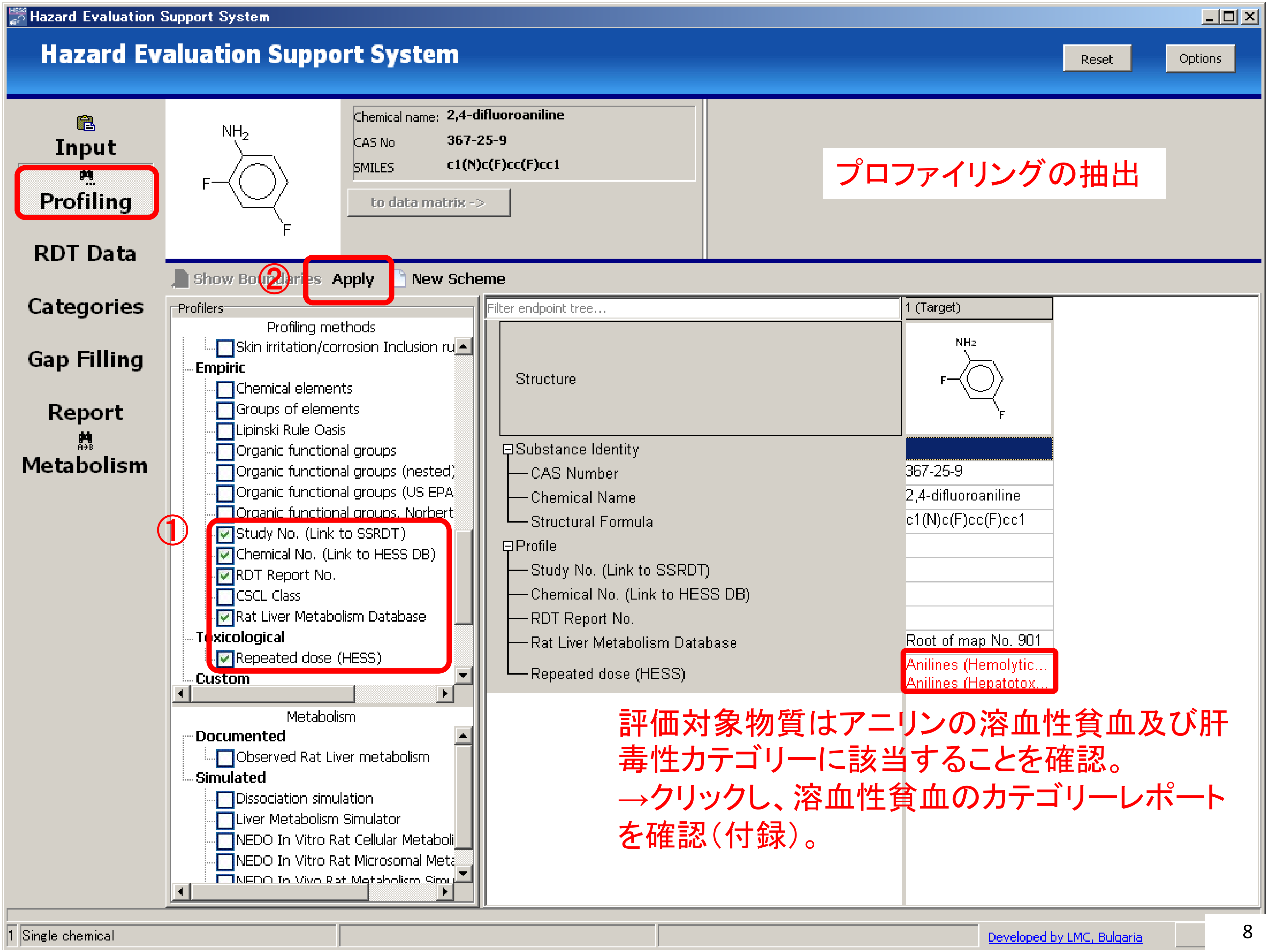
① CAS#

② CAS # 367259 Search 367259

Chemical name: 2,4-difluoroaniline

③ Set target

Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Add to post-targets list
Chemical name
Drawing
RDT tests
Database
User List
Load DB
Load Inventory
NH_2
F
F
1 Single chemical
Developed by LMC, Bulgaria


Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
NH2
F
F
to data matrix ->
Show Boundaries
②
Apply
New Scheme
①
Filter endpoint tree...
Structure
Single chemical
Developed by LMC, Bulgaria

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

プロファイリングの抽出

Profilers

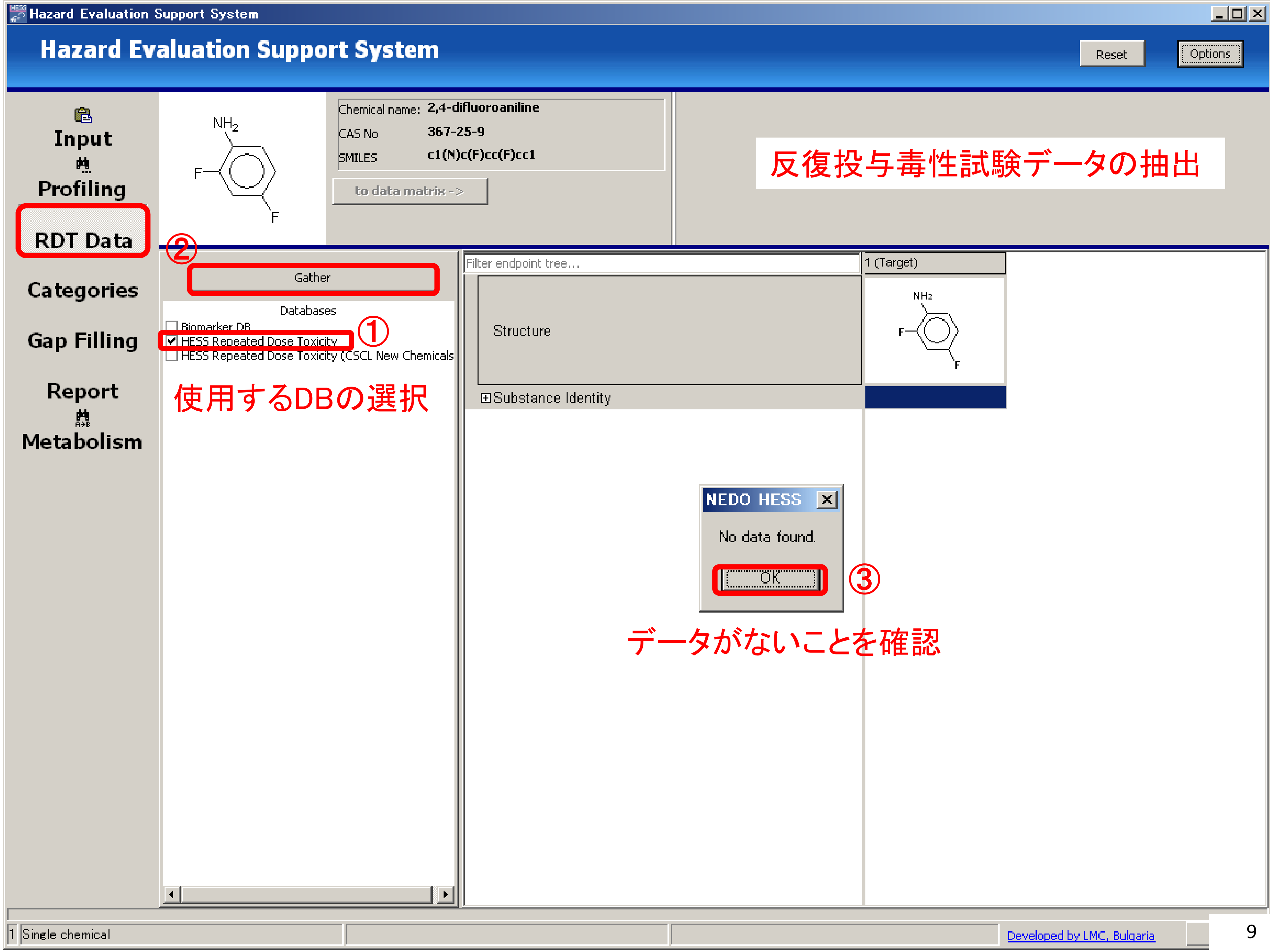
Profiling methods
- ☐ Skin irritation/corrosion Inclusion ru
- Empiric
  - ☐ Chemical elements
  - ☐ Groups of elements
  - ☐ Lipinski Rule Oasis
  - ☐ Organic functional groups
  - ☐ Organic functional groups (nested)
  - ☐ Organic functional groups (US EPA
  - ☐ Organic functional groups, Norbert
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

Metabolism
- Documented
  - ☐ Observed Rat Liver metabolism
- Simulated
  - ☐ Dissociation simulation
  - ☐ Liver Metabolism Simulator
  - ☐ NEDO In Vitro Rat Cellular Metaboli
  - ☐ NEDO In Vitro Rat Microsomal Meta
  - ☐ NEDO In Vivo Rat Metabolism Simu

	1 (Target)
Structure	
Substance Identity	
CAS Number	367-25-9
Chemical Name	2,4-difluoroaniline
Structural Formula	c1(N)c(F)cc(F)cc1
Profile	
Study No. (Link to SSRDT)	
Chemical No. (Link to HESS DB)	
RDT Report No.	
Rat Liver Metabolism Database	Root of map No. 901
Repeated dose (HESS)	Anilines (Hemolytic... Anilines (Hepatotox...

評価対象物質はアニリンの溶血性貧血及び肝毒性カテゴリーに該当することを確認。
→クリックし、溶血性貧血のカテゴリーレポートを確認（付録）。

反復投与毒性試験データの抽出


Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Gather
Filter endpoint tree...
1 (Target)
Structure
⊞Substance Identity
NEDO HESS
OK
Developed by LMC, Bulgaria

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

Databases
☐ Biomarker DB
☑ HESS Repeated Dose Toxicity ①
☐ HESS Repeated Dose Toxicity (CSCL New Chemicals

使用するDBの選択

② Gather

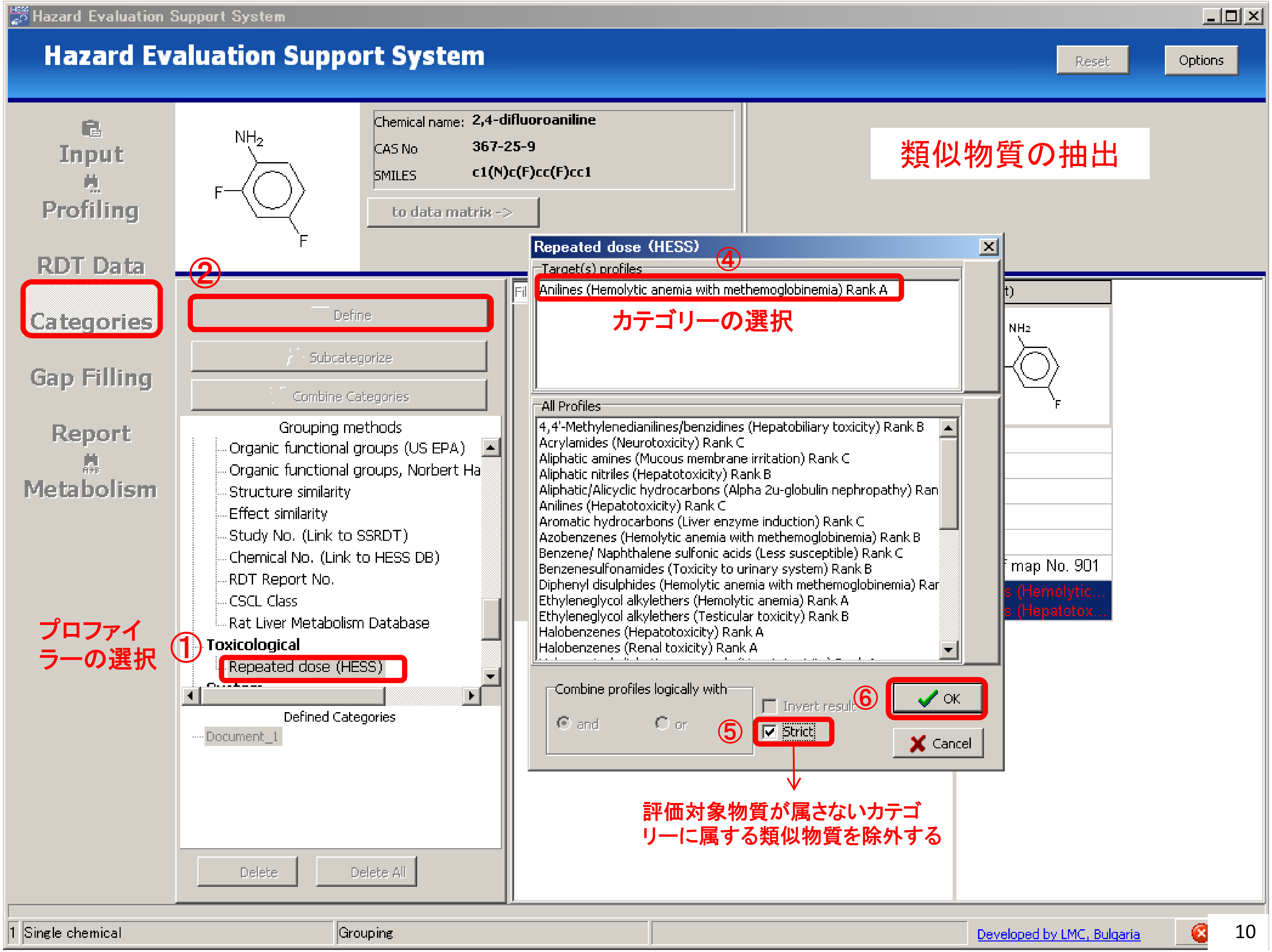
No data found.

③ OK

データがないことを確認

1 Single chemical

類似物質の抽出


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Define
Subcategorize
Combine Categories
Delete
Delete All
OK
Cancel
Developed by LMC, Bulgaria
NH2
F
F

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

Grouping methods
- Organic functional groups (US EPA)
- Organic functional groups, Norbert Ha
- 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)

Defined Categories
- Document_1

Repeated dose (HESS)

Target(s) profiles
Anilines (Hemolytic anemia with methemoglobinemia) Rank A

All Profiles
4,4'-Methylenedianilines/benzidines (Hepatobiliary toxicity) Rank B
Acrylamides (Neurotoxicity) Rank C
Aliphatic amines (Mucous membrane irritation) Rank C
Aliphatic nitriles (Hepatotoxicity) Rank B
Aliphatic/Alicyclic hydrocarbons (Alpha 2u-globulin nephropathy) Ran
Anilines (Hepatotoxicity) Rank C
Aromatic hydrocarbons (Liver enzyme induction) 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) Rar
Ethyleneglycol alkylethers (Hemolytic anemia) Rank A
Ethyleneglycol alkylethers (Testicular toxicity) Rank B
Halobenzenes (Hepatotoxicity) Rank A
Halobenzenes (Renal toxicity) Rank A

Combine profiles logically with ● and ○ or

☐ Invert result
☑ Strict

map No. 901
s (Hemolytic...
s (Hepatotox...

1 Single chemical | Grouping

①

プロファイラーの選択

②

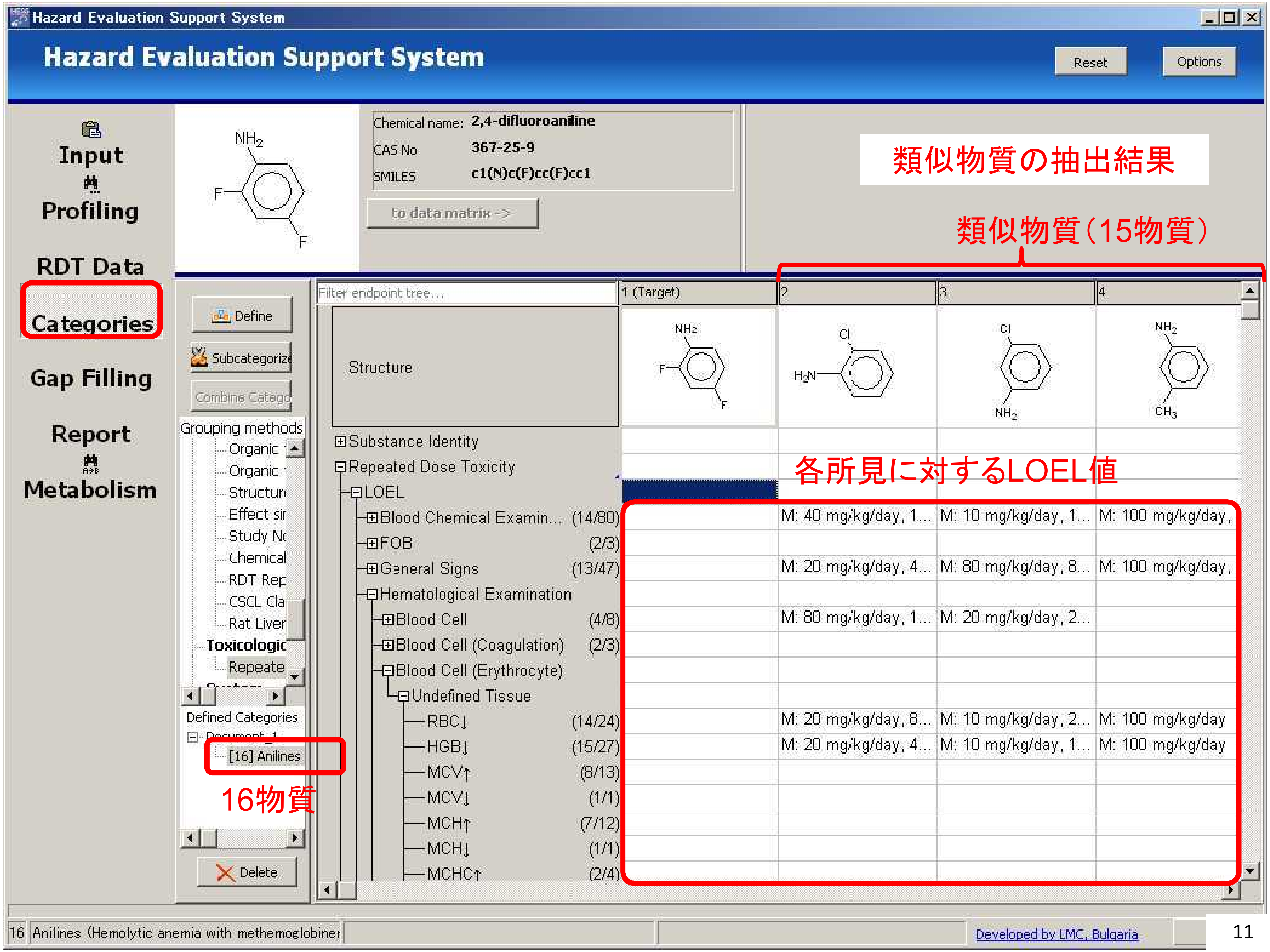
④

カテゴリーの選択

⑤

⑥

評価対象物質が属さないカテゴリーに属する類似物質を除外する


Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Define
Subcategorize
Combine Catego
Grouping methods
Organic
Organic
Structur
Effect sir
Study Nc
Chemical
RDT Rep
CSCL Cla
Rat Liver
Toxicologic
Repeate
Defined Categories
Document_1
Delete
Filter endpoint tree...
Developed by LMC, Bulgaria

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

類似物質の抽出結果

類似物質（15物質）

各所見に対するLOEL値

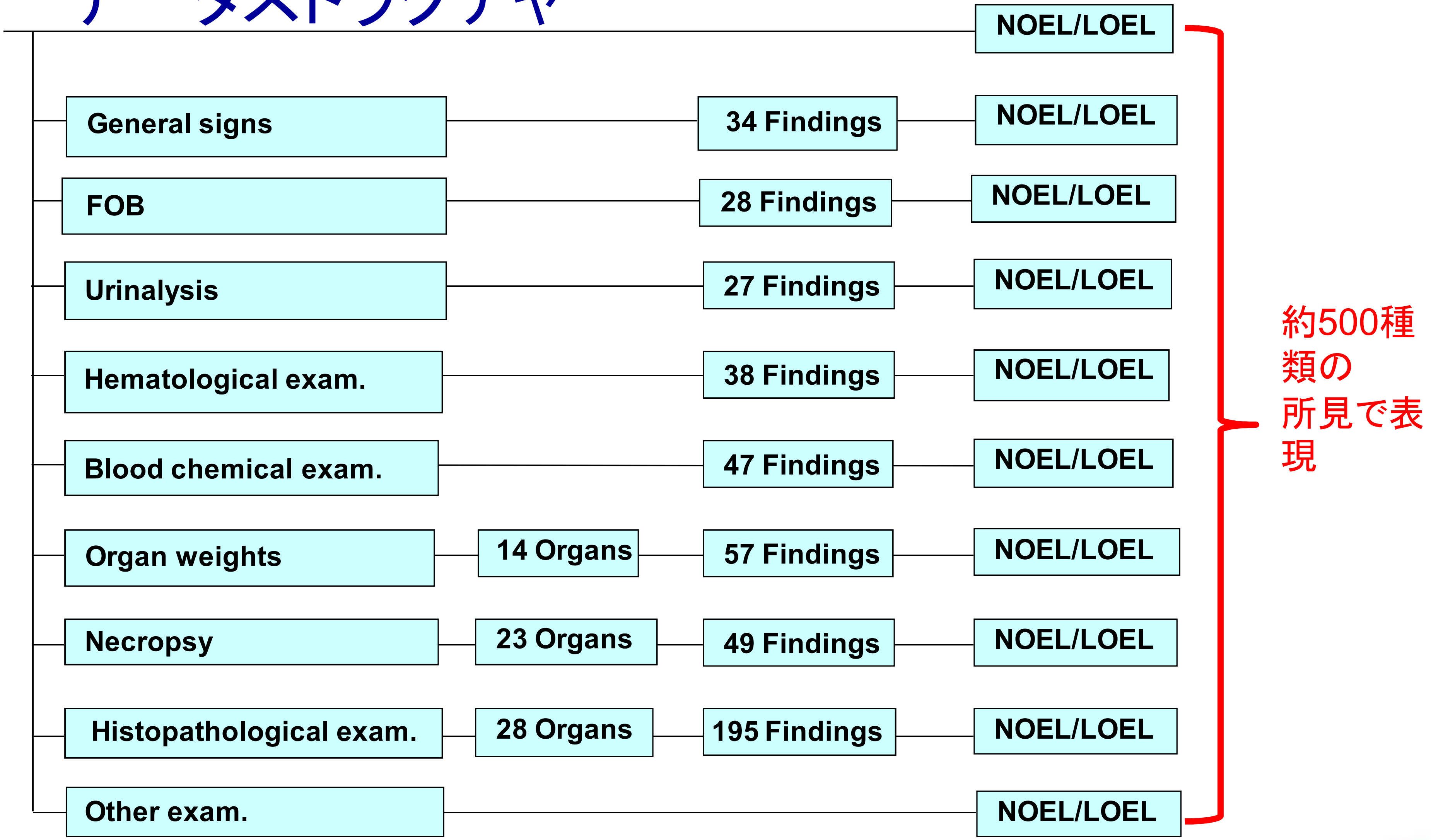
[16] Anilines

16物質

	1 (Target)	2	3	4
Structure				
⊞Substance Identity				
⊟Repeated Dose Toxicity				
⊟LOEL				
⊞Blood Chemical Examin... (14/80)		M: 40 mg/kg/day, 1...	M: 10 mg/kg/day, 1...	M: 100 mg/kg/day,
⊞FOB (2/3)				
⊞General Signs (13/47)		M: 20 mg/kg/day, 4...	M: 80 mg/kg/day, 8...	M: 100 mg/kg/day,
⊟Hematological Examination				
⊞Blood Cell (4/8)		M: 80 mg/kg/day, 1...	M: 20 mg/kg/day, 2...	
⊞Blood Cell (Coagulation) (2/3)				
⊟Blood Cell (Erythrocyte)				
⊟Undefined Tissue				
RBC↓ (14/24)		M: 20 mg/kg/day, 8...	M: 10 mg/kg/day, 2...	M: 100 mg/kg/day
HGB↓ (15/27)		M: 20 mg/kg/day, 4...	M: 10 mg/kg/day, 1...	M: 100 mg/kg/day
MCV↑ (8/13)				
MCV↓ (1/1)				
MCH↑ (7/12)				
MCH↓ (1/1)				
MCHC↑ (2/4)				

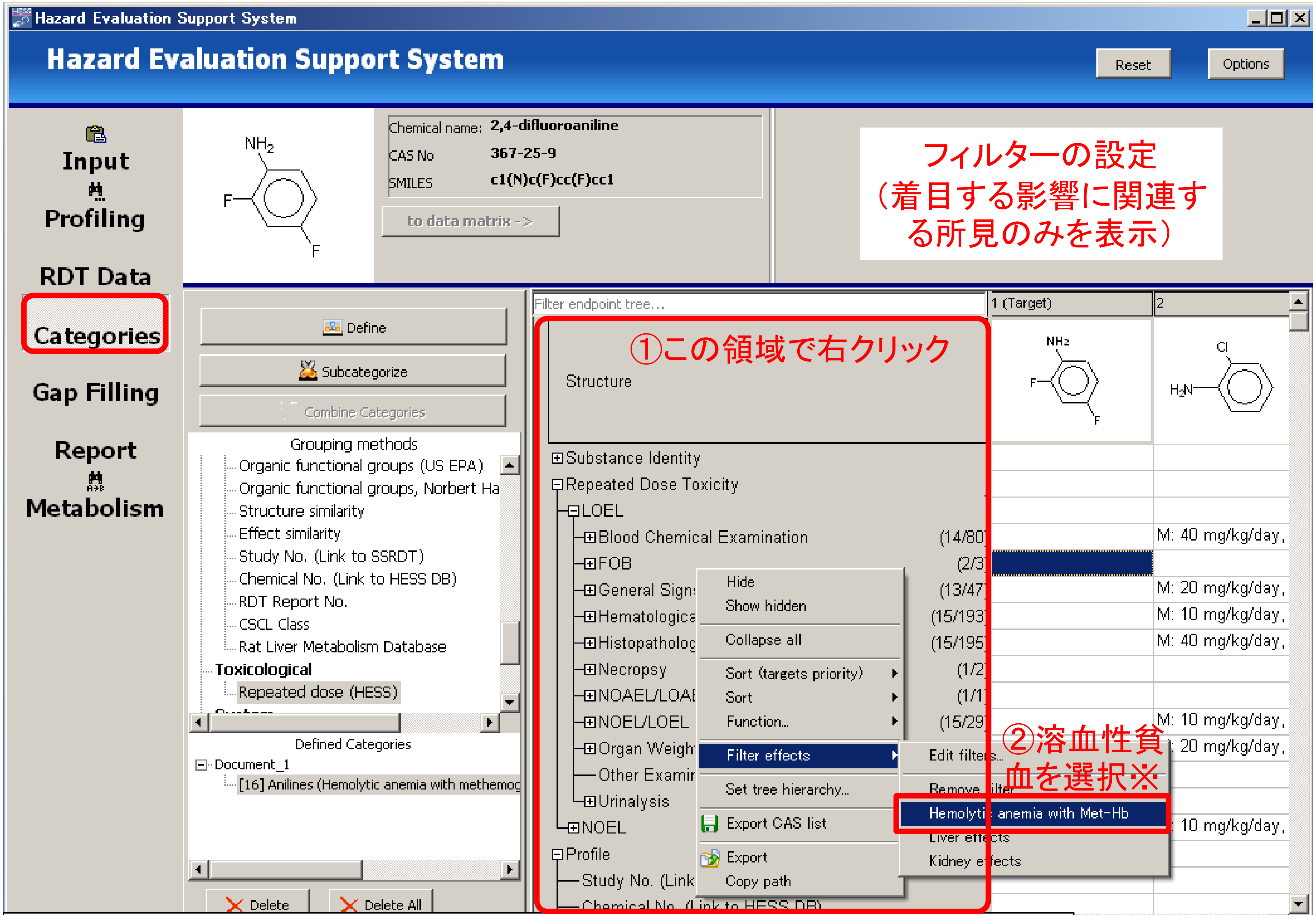
16 Anilines (Hemolytic anemia with methemoglobine

HESSにおける反復投与毒性試験データのデータストラクチャー



			NOEL/LOEL
General signs		34 Findings	NOEL/LOEL
FOB		28 Findings	NOEL/LOEL
Urinalysis		27 Findings	NOEL/LOEL
Hematological exam.		38 Findings	NOEL/LOEL
Blood chemical exam.		47 Findings	NOEL/LOEL
Organ weights	14 Organs	57 Findings	NOEL/LOEL
Necropsy	23 Organs	49 Findings	NOEL/LOEL
Histopathological exam.	28 Organs	195 Findings	NOEL/LOEL
Other exam.			NOEL/LOEL

約500種
類の
所見で表
現


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Define
Subcategorize
Combine Categories
Grouping methods
Organic functional groups (US EPA)
Organic functional groups, Norbert Ha
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)
Defined Categories
Document_1
[16] Anilines (Hemolytic anemia with methemog
Delete
Delete All
Filter endpoint tree...
1 (Target)
2
Structure
Substance Identity
Repeated Dose Toxicity
LOEL
Blood Chemical Examination (14/80
FOB (2/3
General Signs (13/47
Hematological (15/193
Histopathology (15/195
Necropsy (1/2
NOAEL/LOAEL (1/1
NOEL/LOEL (15/29
Organ Weight
Other Examin
Urinalysis
NOEL
Profile
Study No. (Link
Chemical No. (Link to HESS DB)
Hide
Show hidden
Collapse all
Sort (targets priority)
Sort
Function...
Filter effects
Set tree hierarchy...
Export CAS list
Export
Copy path
Edit filters...
Remove filter
Hemolytic anemia with Met-Hb
Liver effects
Kidney effects
M: 40 mg/kg/day,
M: 20 mg/kg/day,
M: 10 mg/kg/day,
M: 40 mg/kg/day,
M: 10 mg/kg/day,
20 mg/kg/day,
10 mg/kg/day,
NH2
F
Cl
H2N
by LMC, Bulgaria

Chemical name: 2,4-difluoroaniline

CAS No 367-25-9

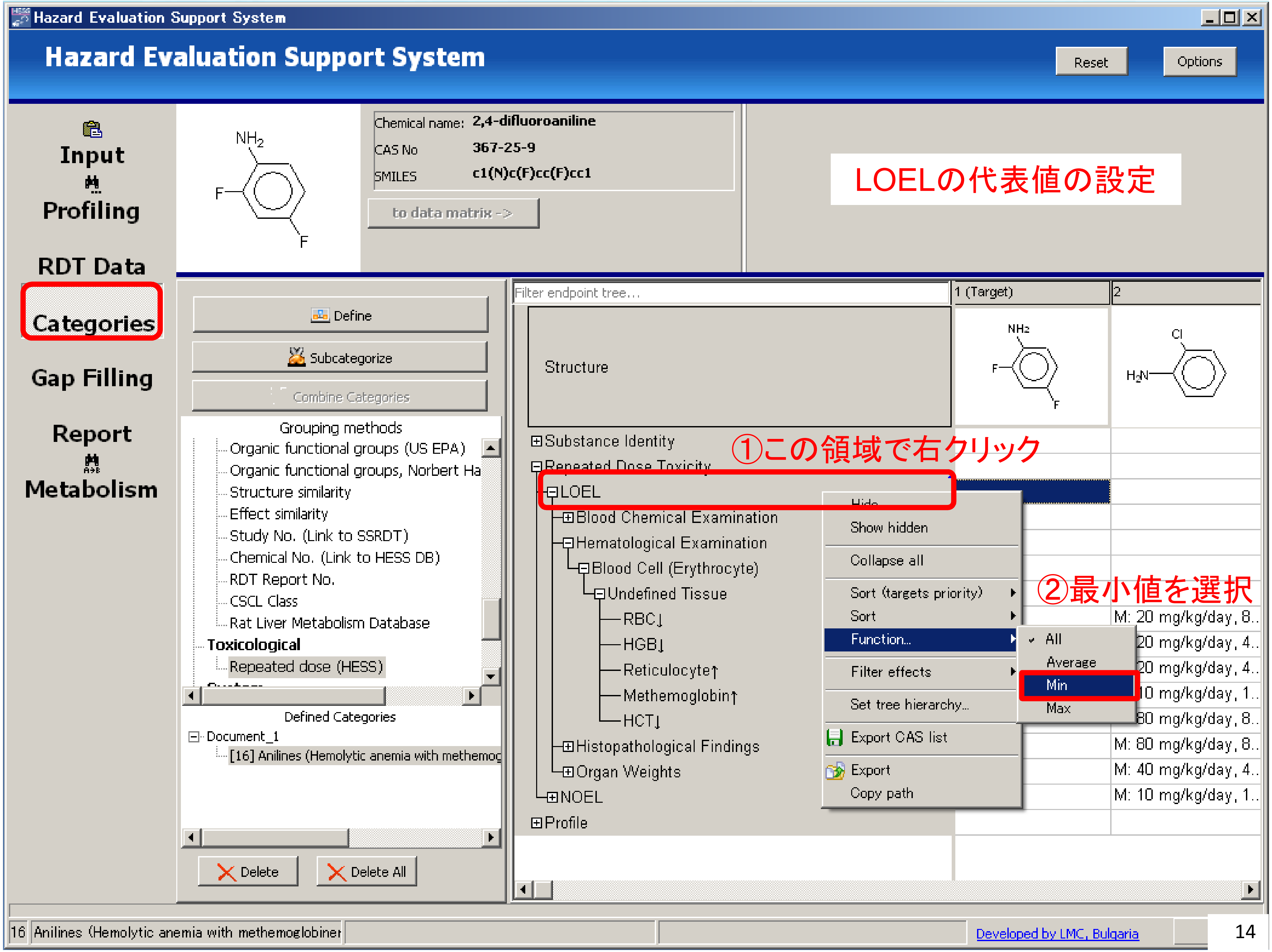
SMILES c1(N)c(F)cc(F)cc1

フィルターの設定
（着目する影響に関連する所見のみを表示）

①この領域で右クリック

②溶血性貧血を選択※

※フィルターの登録方法については昨年度講習会資料又は基本操作の動画を参照（HESSのWebサイトで公開）。
今回の講習会で使用するPCには登録済。



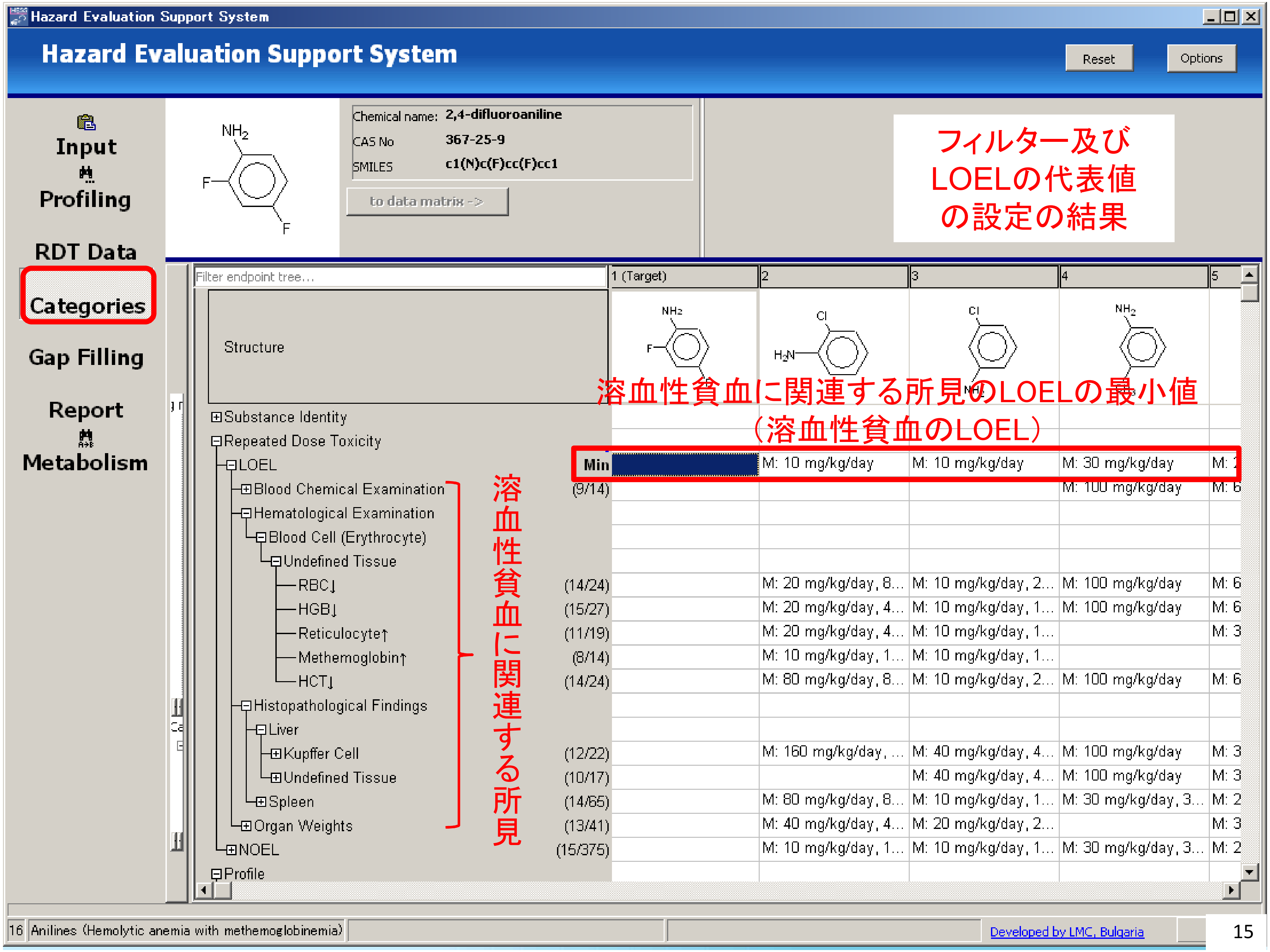
LOELの代表値の設定

①この領域で右クリック

②最小値を選択

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

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
NH_2
F
F
to data matrix ->
Define
Subcategorize
Combine Categories
Grouping methods
Organic functional groups (US EPA)
Organic functional groups, Norbert Ha
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)
Defined Categories
Document_1
[16] Anilines (Hemolytic anemia with methemog
Delete
Delete All
Filter endpoint tree...
1 (Target)
2
Structure
Substance Identity
Repeated Dose Toxicity
LOEL
Blood Chemical Examination
Hematological Examination
Blood Cell (Erythrocyte)
Undefined Tissue
RBC↓
HGB↓
Reticulocyte↑
Methemoglobin↑
HCT↓
Histopathological Findings
Organ Weights
NOEL
Profile
Hide
Show hidden
Collapse all
Sort (targets priority)
Sort
Function...
Filter effects
Set tree hierarchy...
Export CAS list
Export
Copy path
All
Average
Min
Max
M: 20 mg/kg/day, 8..
20 mg/kg/day, 4..
20 mg/kg/day, 4..
10 mg/kg/day, 1..
80 mg/kg/day, 8..
M: 80 mg/kg/day, 8..
M: 40 mg/kg/day, 4..
M: 10 mg/kg/day, 1..
Cl
H_2N
16 Anilines (Hemolytic anemia with methemoglobiner
Developed by LMC, Bulgaria


Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Filter endpoint tree…
NH2
F
F
Cl
H2N
Cl
NH2
NH2

Hazard Evaluation Support System

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

フィルター及び
LOELの代表値
の設定の結果

溶血性貧血に関連する所見のLOELの最小値
（溶血性貧血のLOEL）

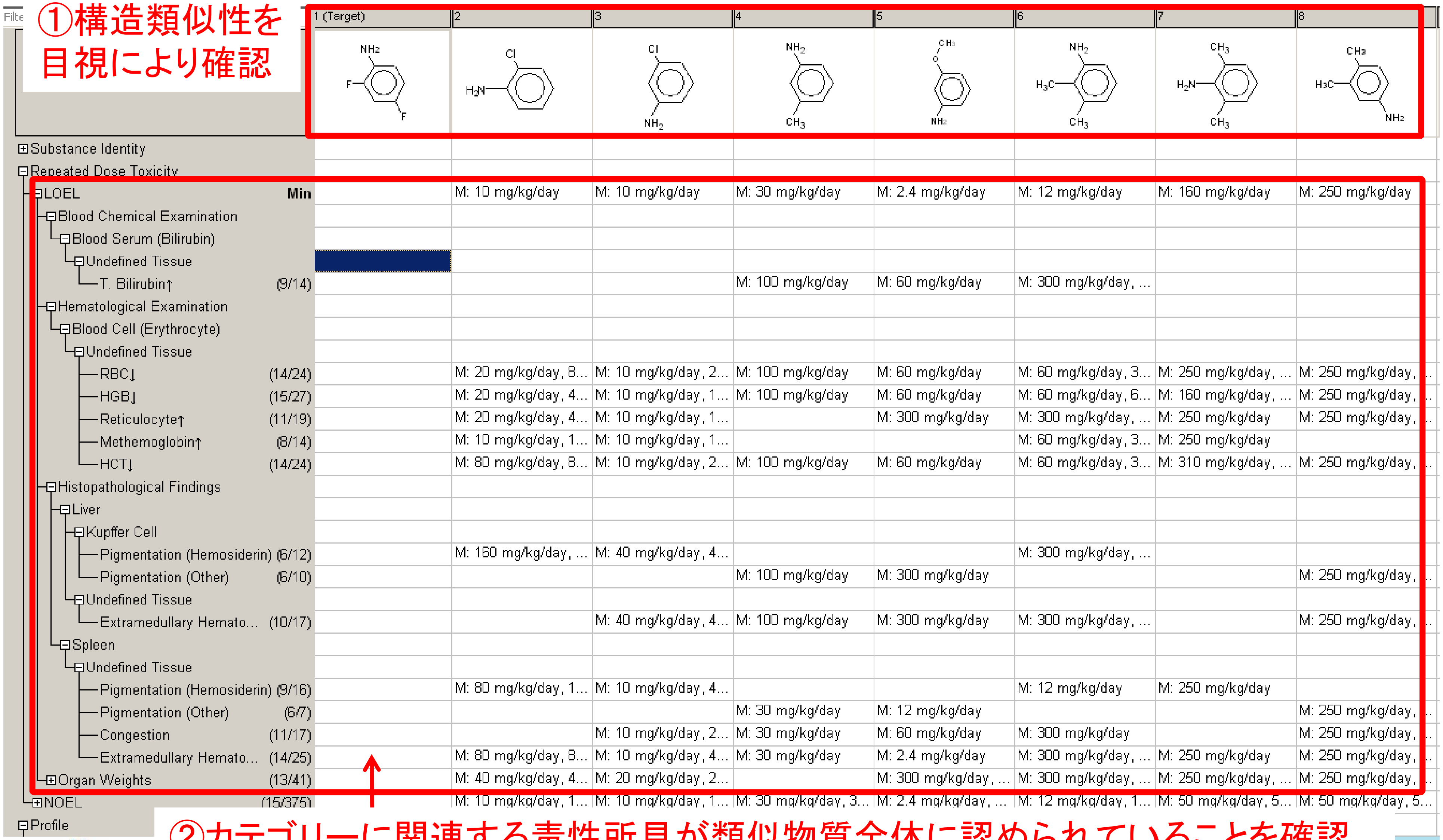
		1 (Target)	2	3	4	5
Structure						
⊞Substance Identity						
⊟Repeated Dose Toxicity						
⊟LOEL	**Min**		M: 10 mg/kg/day	M: 10 mg/kg/day	M: 30 mg/kg/day	M:
⊞Blood Chemical Examination	(9/14)				M: 100 mg/kg/day	M: 6
⊟Hematological Examination						
⊟Blood Cell (Erythrocyte)						
⊟Undefined Tissue						
RBC↓	(14/24)		M: 20 mg/kg/day, 8…	M: 10 mg/kg/day, 2…	M: 100 mg/kg/day	M: 6
HGB↓	(15/27)		M: 20 mg/kg/day, 4…	M: 10 mg/kg/day, 1…	M: 100 mg/kg/day	M: 6
Reticulocyte↑	(11/19)		M: 20 mg/kg/day, 4…	M: 10 mg/kg/day, 1…		M: 3
Methemoglobin↑	(8/14)		M: 10 mg/kg/day, 1…	M: 10 mg/kg/day, 1…		
HCT↓	(14/24)		M: 80 mg/kg/day, 8…	M: 10 mg/kg/day, 2…	M: 100 mg/kg/day	M: 6
⊟Histopathological Findings						
⊟Liver						
⊞Kupffer Cell	(12/22)		M: 160 mg/kg/day, …	M: 40 mg/kg/day, 4…	M: 100 mg/kg/day	M: 3
⊞Undefined Tissue	(10/17)			M: 40 mg/kg/day, 4…	M: 100 mg/kg/day	M: 3
⊞Spleen	(14/65)		M: 80 mg/kg/day, 8…	M: 10 mg/kg/day, 1…	M: 30 mg/kg/day, 3…	M: 2
⊞Organ Weights	(13/41)		M: 40 mg/kg/day, 4…	M: 20 mg/kg/day, 2…		M: 3
⊞NOEL	(15/375)		M: 10 mg/kg/day, 1…	M: 10 mg/kg/day, 1…	M: 30 mg/kg/day, 3…	M: 2
⊟Profile						

溶血性貧血に関連する所見

16 Anilines (Hemolytic anemia with methemoglobinemia)

Developed by LMC, Bulgaria

簡易予測おけるカテゴリーの確認



①構造類似性を目視により確認

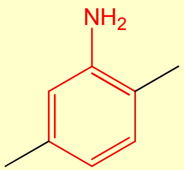
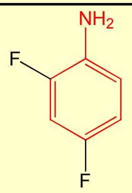
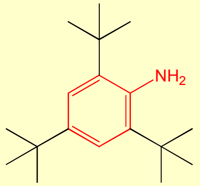
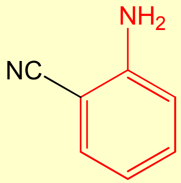
Filte

		1 (Target)	2	3	4	5	6	7	8
⊞Substance Identity									
⊟Repeated Dose Toxicity									
⊟LOEL	**Min**		M: 10 mg/kg/day	M: 10 mg/kg/day	M: 30 mg/kg/day	M: 2.4 mg/kg/day	M: 12 mg/kg/day	M: 160 mg/kg/day	M: 250 mg/kg/day
⊟Blood Chemical Examination									
⊟Blood Serum (Bilirubin)									
⊟Undefined Tissue									
T. Bilirubin↑	(9/14)				M: 100 mg/kg/day	M: 60 mg/kg/day	M: 300 mg/kg/day, ...		
⊟Hematological Examination									
⊟Blood Cell (Erythrocyte)									
⊟Undefined Tissue									
RBC↓	(14/24)		M: 20 mg/kg/day, 8...	M: 10 mg/kg/day, 2...	M: 100 mg/kg/day	M: 60 mg/kg/day	M: 60 mg/kg/day, 3...	M: 250 mg/kg/day, ...	M: 250 mg/kg/day, ..
HGB↓	(15/27)		M: 20 mg/kg/day, 4...	M: 10 mg/kg/day, 1...	M: 100 mg/kg/day	M: 60 mg/kg/day	M: 60 mg/kg/day, 6...	M: 160 mg/kg/day, ...	M: 250 mg/kg/day, ..
Reticulocyte↑	(11/19)		M: 20 mg/kg/day, 4...	M: 10 mg/kg/day, 1...		M: 300 mg/kg/day	M: 300 mg/kg/day, ...	M: 250 mg/kg/day	M: 250 mg/kg/day, ..
Methemoglobin↑	(8/14)		M: 10 mg/kg/day, 1...	M: 10 mg/kg/day, 1...			M: 60 mg/kg/day, 3...	M: 250 mg/kg/day	
HCT↓	(14/24)		M: 80 mg/kg/day, 8...	M: 10 mg/kg/day, 2...	M: 100 mg/kg/day	M: 60 mg/kg/day	M: 60 mg/kg/day, 3...	M: 310 mg/kg/day, ...	M: 250 mg/kg/day, ..
⊟Histopathological Findings									
⊟Liver									
⊟Kupffer Cell									
Pigmentation (Hemosiderin)	(6/12)		M: 160 mg/kg/day, ...	M: 40 mg/kg/day, 4...			M: 300 mg/kg/day, ...		
Pigmentation (Other)	(6/10)				M: 100 mg/kg/day	M: 300 mg/kg/day			M: 250 mg/kg/day, ..
⊟Undefined Tissue									
Extramedullary Hemato...	(10/17)			M: 40 mg/kg/day, 4...	M: 100 mg/kg/day	M: 300 mg/kg/day	M: 300 mg/kg/day, ...		M: 250 mg/kg/day, ..
⊟Spleen									
⊟Undefined Tissue									
Pigmentation (Hemosiderin)	(9/16)		M: 80 mg/kg/day, 1...	M: 10 mg/kg/day, 4...			M: 12 mg/kg/day	M: 250 mg/kg/day	
Pigmentation (Other)	(6/7)				M: 30 mg/kg/day	M: 12 mg/kg/day			M: 250 mg/kg/day, ..
Congestion	(11/17)			M: 10 mg/kg/day, 2...	M: 30 mg/kg/day	M: 60 mg/kg/day	M: 300 mg/kg/day		M: 250 mg/kg/day, ..
Extramedullary Hemato...	(14/25)		M: 80 mg/kg/day, 8...	M: 10 mg/kg/day, 4...	M: 30 mg/kg/day	M: 2.4 mg/kg/day	M: 300 mg/kg/day, ...	M: 250 mg/kg/day	M: 250 mg/kg/day, ..
⊞Organ Weights	(13/41)		M: 40 mg/kg/day, 4...	M: 20 mg/kg/day, 2...		M: 300 mg/kg/day, ...	M: 300 mg/kg/day, ...	M: 250 mg/kg/day, ...	M: 250 mg/kg/day, ..
⊞NOEL	(15/375)		M: 10 mg/kg/day, 1...	M: 10 mg/kg/day, 1...	M: 30 mg/kg/day, 3...	M: 2.4 mg/kg/day, ...	M: 12 mg/kg/day, 1...	M: 50 mg/kg/day, 5...	M: 50 mg/kg/day, 5...
⊟Profile									

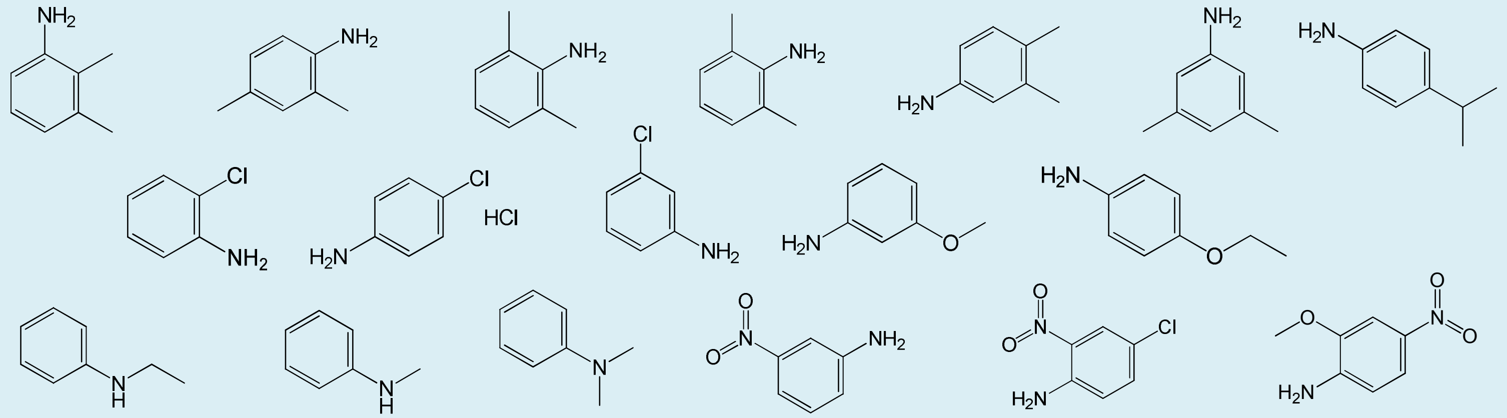
②カテゴリーに関連する毒性所見が類似物質全体に認められていることを確認

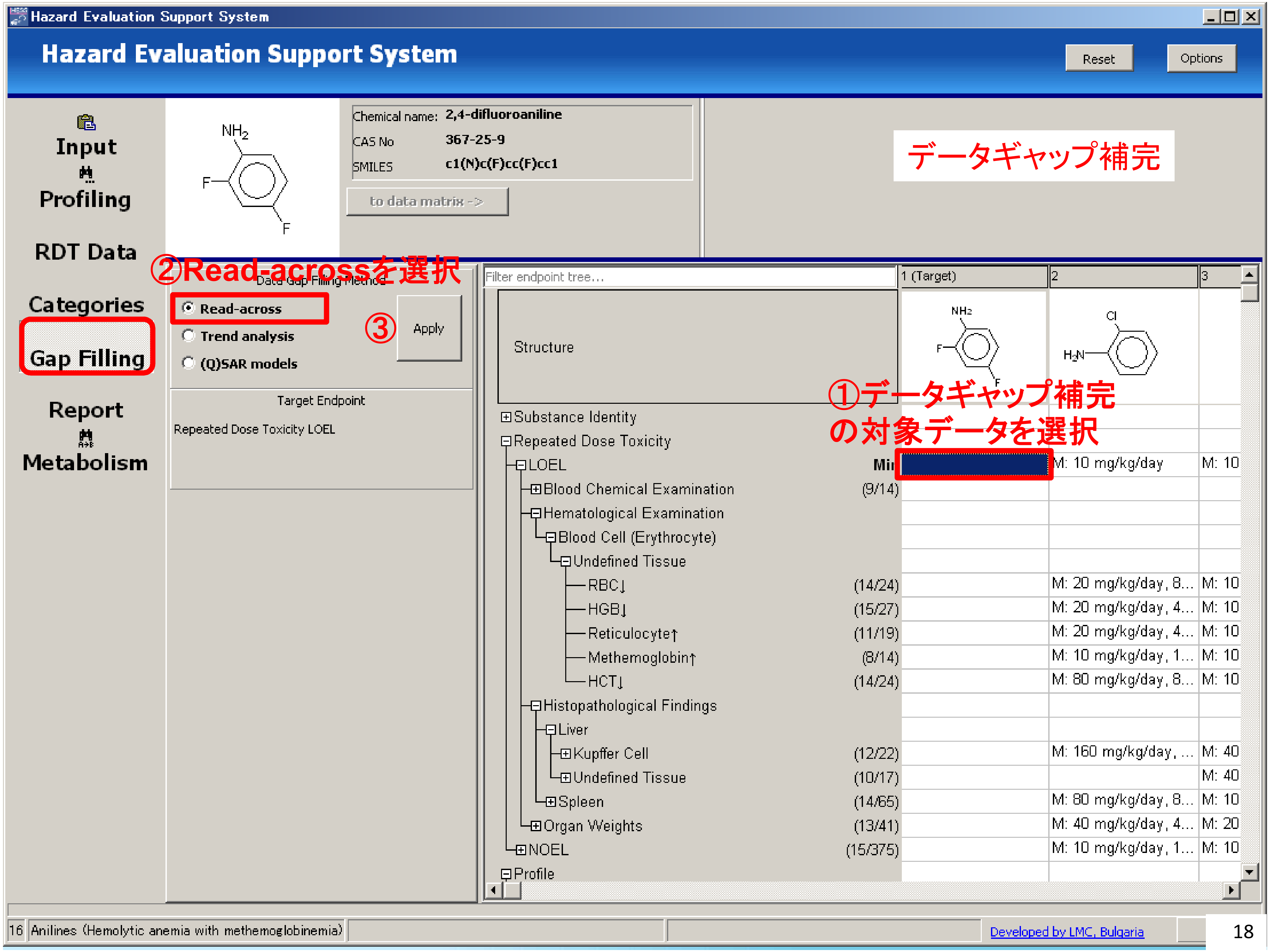
構造類似性の目視による確認の例

ポイント：毒性の原因となる部分構造を有し、かつ、それ以外の部分構造の差異が試験済みの類似物質と比較し大きくないか？

評価対象物質	1	2	3	4
				
HESSカテゴリーの該当性（プロファイラーによる自動認識）	該当	該当	該当	非該当
目視による構造類似性の確認の例（カテゴリーの該当性の評価結果の例）	構造類似性は非常に高い（該当）。	構造類似性は高いが、フッ素置換の影響が不確定要素（該当）。	嵩高い置換基があり、構造類似性は低い（非該当）。	–

試験済みの類似物質




Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Apply
Filter endpoint tree...

データギャップ補完

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

②Read-acrossを選択

Data Gap Filling Method
● Read-across
○ Trend analysis
○ (Q)SAR models

③

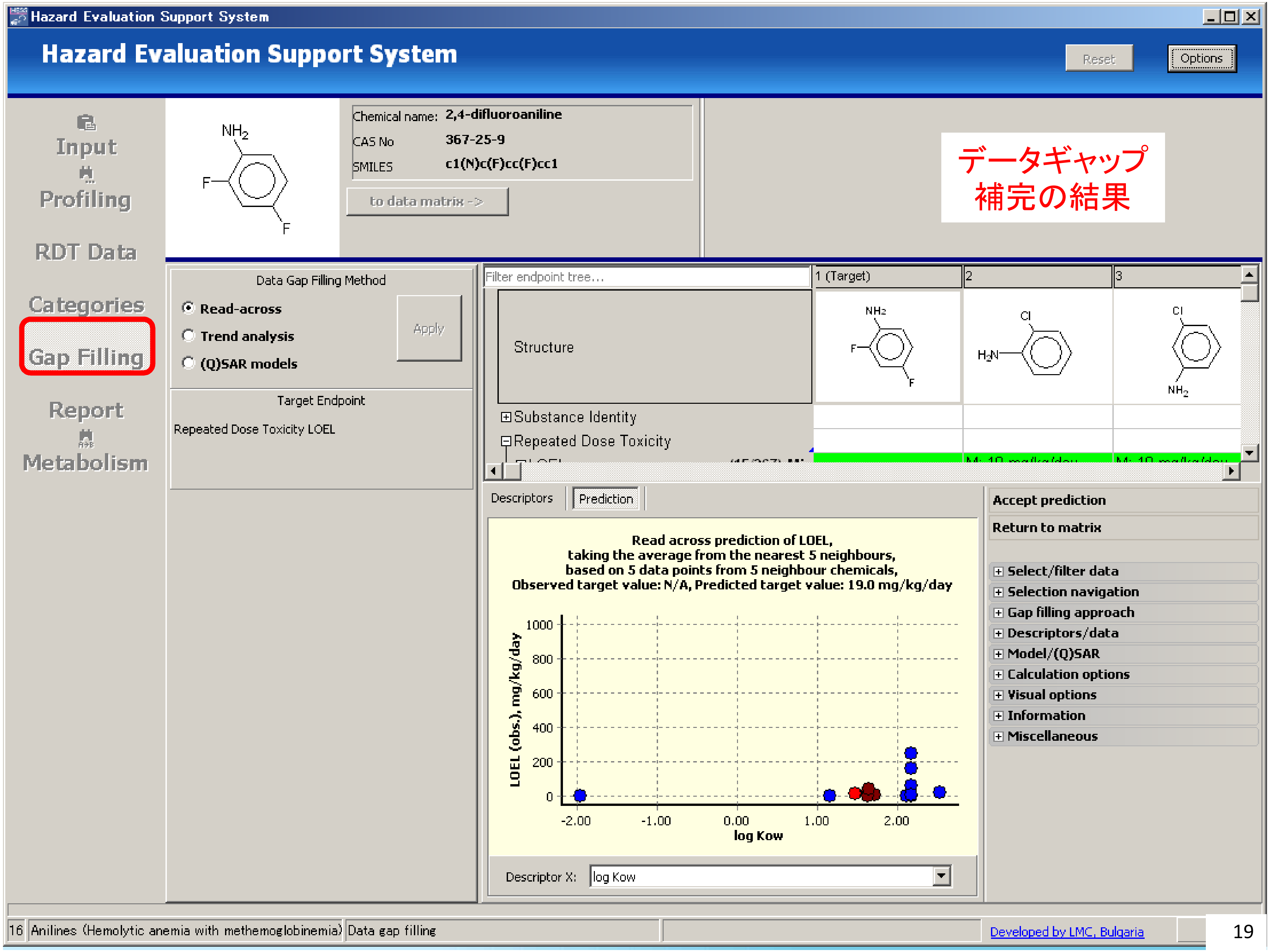
Target Endpoint
Repeated Dose Toxicity LOEL

①データギャップ補完の対象データを選択

		1 (Target)	2	3
Structure				
⊞Substance Identity				
⊟Repeated Dose Toxicity				
⊟LOEL	Mi		M: 10 mg/kg/day	M: 10
⊞Blood Chemical Examination	(9/14)			
⊟Hematological Examination				
⊟Blood Cell (Erythrocyte)				
⊟Undefined Tissue				
RBC↓	(14/24)		M: 20 mg/kg/day, 8...	M: 10
HGB↓	(15/27)		M: 20 mg/kg/day, 4...	M: 10
Reticulocyte↑	(11/19)		M: 20 mg/kg/day, 4...	M: 10
Methemoglobin↑	(8/14)		M: 10 mg/kg/day, 1...	M: 10
HCT↓	(14/24)		M: 80 mg/kg/day, 8...	M: 10
⊟Histopathological Findings				
⊟Liver				
⊞Kupffer Cell	(12/22)		M: 160 mg/kg/day, ...	M: 40
⊞Undefined Tissue	(10/17)			M: 40
⊞Spleen	(14/65)		M: 80 mg/kg/day, 8...	M: 10
⊞Organ Weights	(13/41)		M: 40 mg/kg/day, 4...	M: 20
⊞NOEL	(15/375)		M: 10 mg/kg/day, 1...	M: 10
⊟Profile				

16 Anilines (Hemolytic anemia with methemoglobinemia)

Developed by LMC, Bulgaria


Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
Apply
Filter endpoint tree...
1 (Target)
2
3
Structure
⊞Substance Identity
⊟Repeated Dose Toxicity
Descriptors
Prediction
Accept prediction
Return to matrix
⊞ Select/filter data
⊞ Selection navigation
⊞ Gap filling approach
⊞ Descriptors/data
⊞ Model/(Q)SAR
⊞ Calculation options
⊞ Visual options
⊞ Information
⊞ Miscellaneous
1000
800
600
400
200
0
LOEL (obs.), mg/kg/day
-2.00
-1.00
0.00
1.00
2.00
log Kow
Developed by LMC, Bulgaria

データギャップ
補完の結果

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

Data Gap Filling Method
- ● Read-across
- ○ Trend analysis
- ○ (Q)SAR models

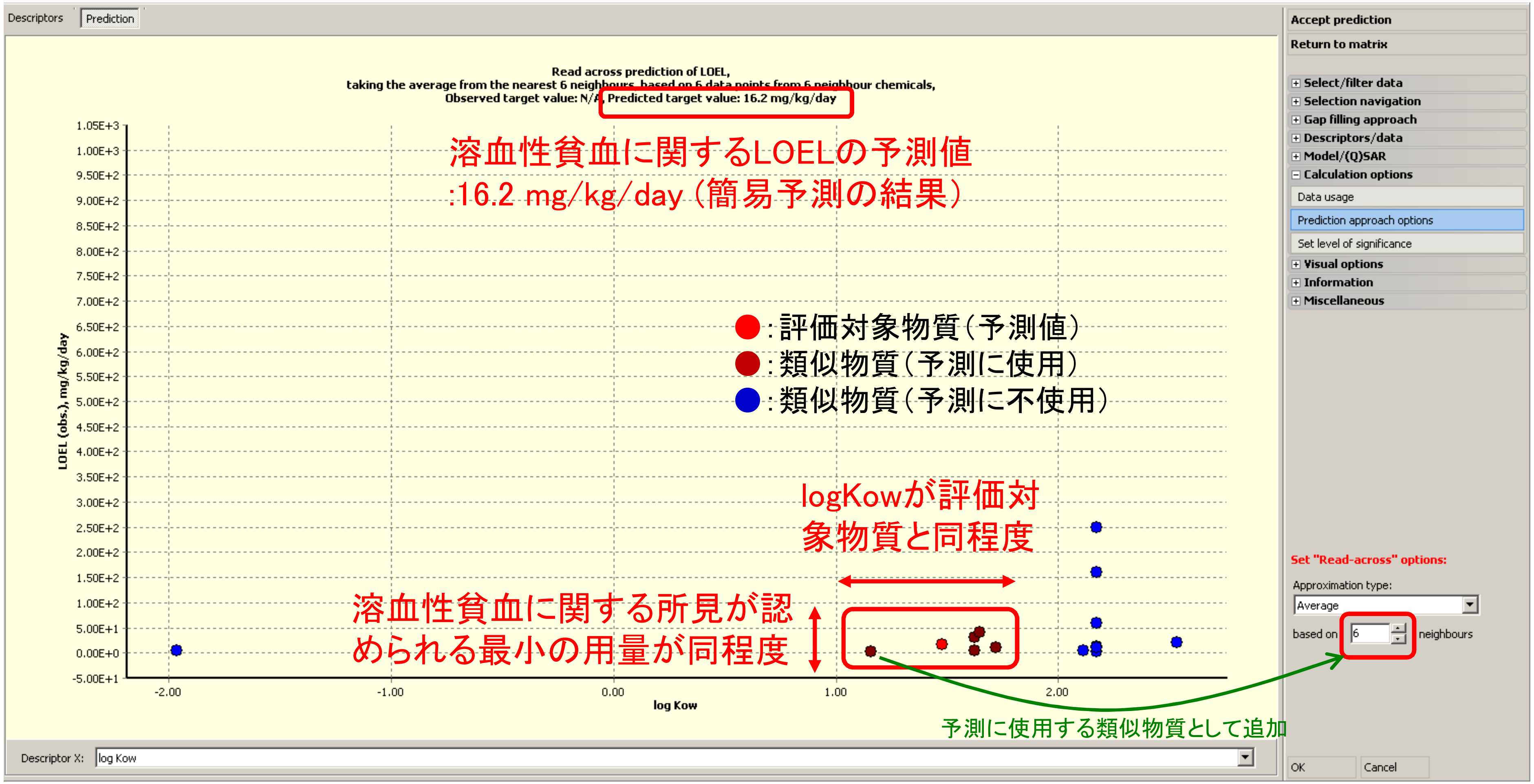
Target Endpoint
Repeated Dose Toxicity LOEL

Read across prediction of LOEL,
taking the average from the nearest 5 neighbours,
based on 5 data points from 5 neighbour chemicals,
Observed target value: N/A, Predicted target value: 19.0 mg/kg/day

Descriptor X: log Kow

16 Anilines (Hemolytic anemia with methemoglobinemia) Data gap filling

予測に使用する類似物質の確定と予測結果


Descriptors
Prediction
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
Miscellaneous
LOEL (obs.), mg/kg/day
1.05E+3
1.00E+3
9.50E+2
9.00E+2
8.50E+2
8.00E+2
7.50E+2
7.00E+2
6.50E+2
6.00E+2
5.50E+2
5.00E+2
4.50E+2
4.00E+2
3.50E+2
3.00E+2
2.50E+2
2.00E+2
1.50E+2
1.00E+2
5.00E+1
0.00E+0
-5.00E+1
-2.00
-1.00
0.00
1.00
2.00
log Kow
OK
Cancel

Read across prediction of LOEL,
taking the average from the nearest 6 neighbours, based on 6 data points from 6 neighbour chemicals,
Observed target value: N/A, Predicted target value: 16.2 mg/kg/day

溶血性貧血に関するLOELの予測値
:16.2 mg/kg/day（簡易予測の結果）

🔴:評価対象物質（予測値）
●:類似物質（予測に使用）
🔵:類似物質（予測に不使用）

logKowが評価対象物質と同程度

溶血性貧血に関する所見が認められる最小の用量が同程度

Set "Read-across" options:

Approximation type: Average

based on 6 neighbours

予測に使用する類似物質として追加

Descriptor X: log Kow

予測の信頼性は毒性強度の分布に依存する。→利用目的に応じて指標を考慮。
化審法判定の場合、25mg/kg/day、250mg/kg/dayに基準があり、この範囲に収まっているかどうかが、一つの評価指標となり得る。

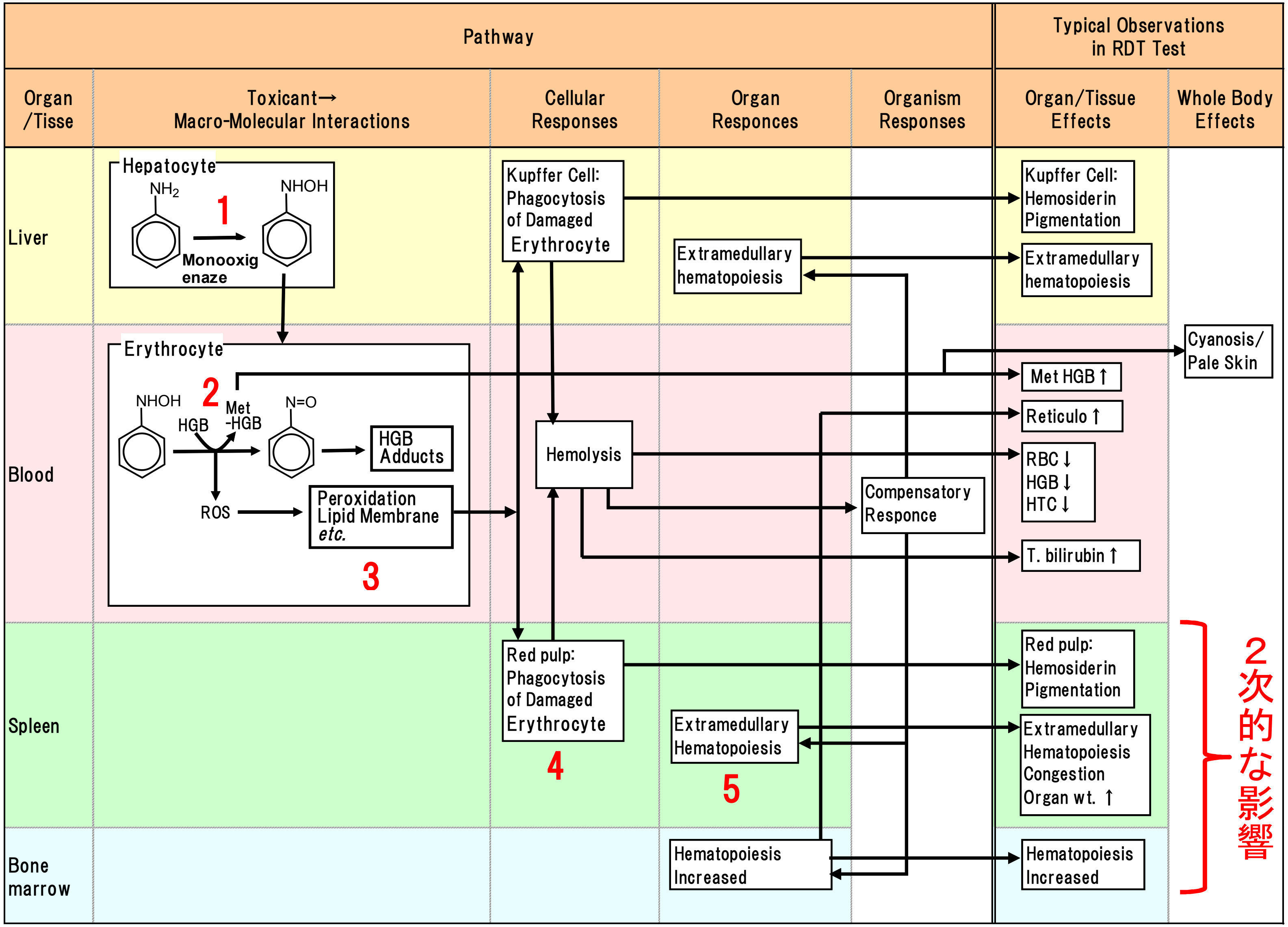
nite

B. 詳細予測

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

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

アニリンの溶血性貧血のAOP



Pathway					Typical Observations in RDT Test	
Organ /Tisse	Toxicant→ Macro-Molecular Interactions	Cellular Responses	Organ Responces	Organism Responses	Organ/Tissue Effects	Whole Body Effects
Liver	Hepatocyte NH₂ 1 Monooxigenaze NHOH	Kupffer Cell: Phagocytosis of Damaged Erythrocyte	Extramedullary hematopoiesis		Kupffer Cell: Hemosiderin Pigmentation Extramedullary hematopoiesis	
Blood	Erythrocyte NHOH HGB 2 Met -HGB N=O HGB Adducts ROS Peroxidation Lipid Membrane *etc.* 3	Hemolysis		Compensatory Responce	Met HGB ↑ Reticulo ↑ RBC ↓ HGB ↓ HTC ↓ T. bilirubin ↑	Cyanosis/ Pale Skin
Spleen		Red pulp: Phagocytosis of Damaged Erythrocyte 4	Extramedullary Hematopoiesis 5		Red pulp: Hemosiderin Pigmentation Extramedullary Hematopoiesis Congestion Organ wt. ↑	２次的な影響
Bone marrow			Hematopoiesis Increased		Hematopoiesis Increased	

Hayashi, M. and Sakuratani, Y. 2011. Hemolytic anemia induced by anilines and nephrotoxicity induced by 4-aminophenols. In: OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 138 , Report of the Workshop on Using Mechanistic Information in Forming Chemical Categories: Annex 8.

溶血性貧血の内容の吟味

簡易評価：

溶血性貧血に関連する所見が認められているかをフィルター機能を利用して確認。

詳細評価：

①**標的としての確度**：血液学検査における、RBC（赤血球数）、HGB（ヘモグロビン数）及びHCT（ヘマトクリット値）の3つの検査値が、減少していれば、溶血性貧血の可能性は高いと考えられる。

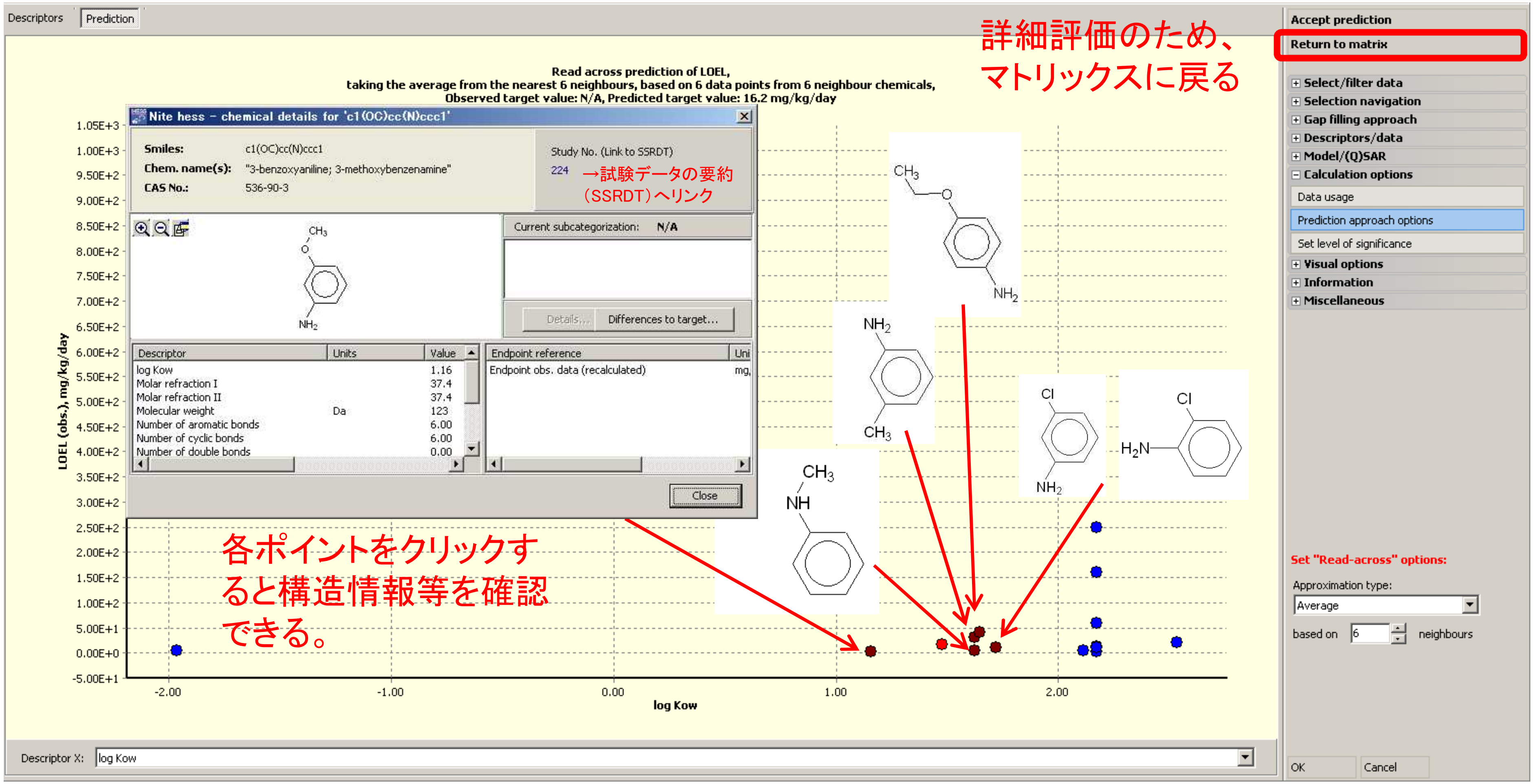
但し、赤血球と共に白血球及び血小版に関する血液学検査値も変動し、脾臓や肝臓における色素沈着が認められない場合については、骨髄が標的となっている可能性があるため、このようなケースに該当しないか、確認する必要がある。

Met-Hbはメカニズムを示唆する重要なパラメータだが測定されていない試験が多い。

②**毒性の強さ**

用量やRBC値の減少の大きさを確認し、構造との関係を検討

プロットから試験データの要約へのリンク



Descriptors
Prediction
1.05E+3
1.00E+3
9.50E+2
9.00E+2
8.50E+2
8.00E+2
7.50E+2
7.00E+2
6.50E+2
6.00E+2
5.50E+2
5.00E+2
4.50E+2
4.00E+2
3.50E+2
3.00E+2
2.50E+2
2.00E+2
1.50E+2
1.00E+2
5.00E+1
0.00E+0
-5.00E+1
LOEL (obs.), mg/kg/day
-2.00
-1.00
0.00
1.00
2.00
log Kow
CH_3
O
NH_2
NH
Cl
H_2N
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
Miscellaneous
Details...
Differences to target...
Close
OK
Cancel

Read across prediction of LOEL,
taking the average from the nearest 6 neighbours, based on 6 data points from 6 neighbour chemicals,
Observed target value: N/A, Predicted target value: 16.2 mg/kg/day

Nite hess – chemical details for 'c1(OC)cc(N)ccc1'

Smiles: c1(OC)cc(N)ccc1
Chem. name(s): "3-benzoxyaniline; 3-methoxybenzenamine"
CAS No.: 536-90-3

Study No. (Link to SSRDT)
224 →試験データの要約（SSRDT）へリンク

Current subcategorization: **N/A**

Descriptor	Units	Value
log Kow		1.16
Molar refraction I		37.4
Molar refraction II		37.4
Molecular weight	Da	123
Number of aromatic bonds		6.00
Number of cyclic bonds		6.00
Number of double bonds		0.00

Endpoint reference	Uni
Endpoint obs. data (recalculated)	mg,

詳細評価のため、マトリックスに戻る

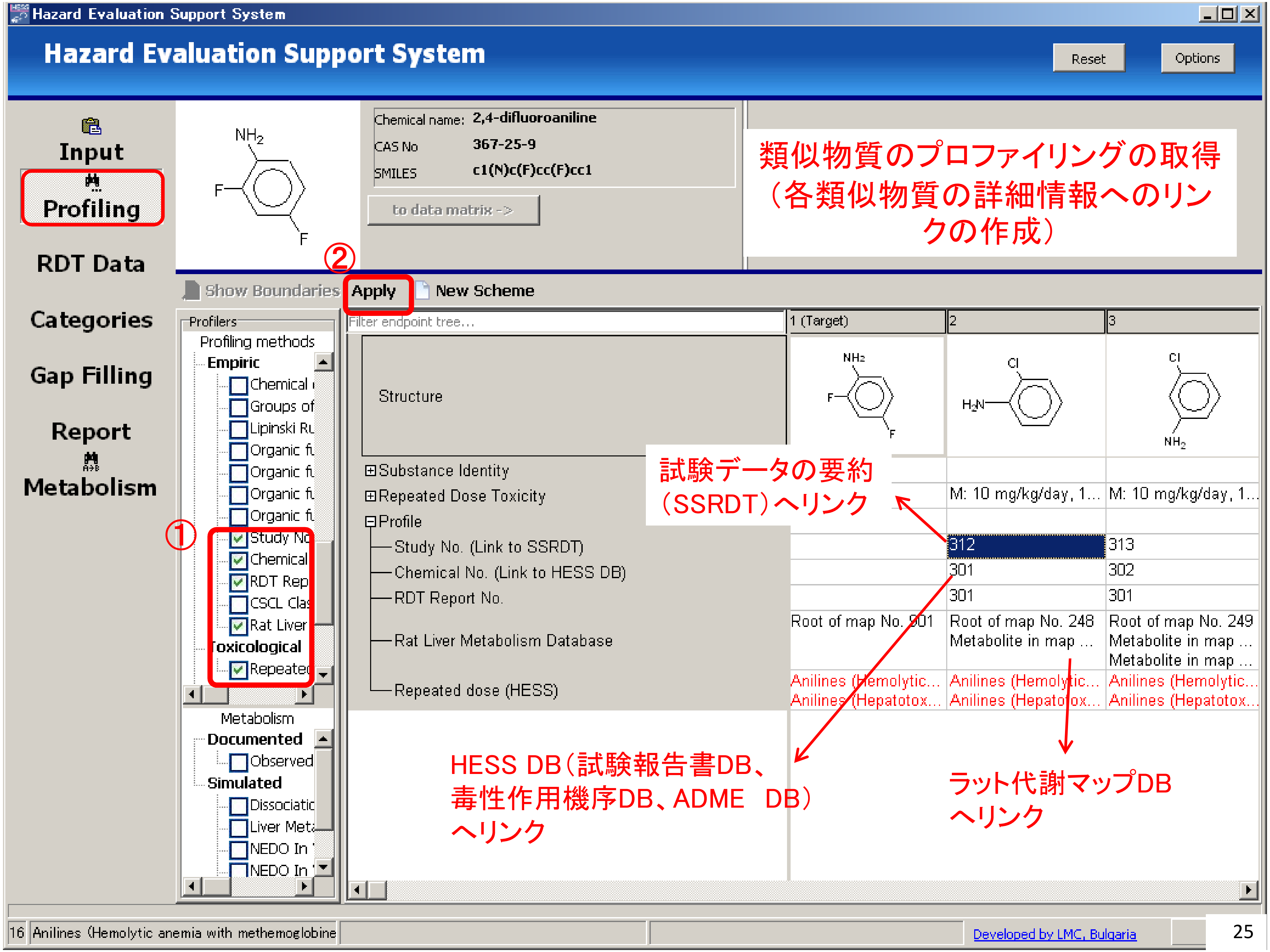
各ポイントをクリックすると構造情報等を確認できる。

Set "Read-across" options:

Approximation type: Average

based on 6 neighbours

Descriptor X: log Kow


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
to data matrix ->
②
Show Boundaries
Apply
New Scheme
Filter endpoint tree...
①

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

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）

Profilers

Profiling methods

Empiric
- ☐ Chemical
- ☐ Groups of
- ☐ Lipinski Ru
- ☐ Organic fu
- ☐ Organic fu
- ☐ Organic fu
- ☐ Organic fu
- ☑ Study No
- ☑ Chemical
- ☑ RDT Rep
- ☐ CSCL Clas
- ☑ Rat Liver

Toxicological
- ☑ Repeated

Metabolism

Documented
- ☐ Observed

Simulated
- ☐ Dissociatio
- ☐ Liver Meta
- ☐ NEDO In
- ☐ NEDO In

	1 (Target)	2	3
Structure			
⊞Substance Identity			
⊞Repeated Dose Toxicity		M: 10 mg/kg/day, 1...	M: 10 mg/kg/day, 1...
⊟Profile			
Study No. (Link to SSRDT)		312	313
Chemical No. (Link to HESS DB)		301	302
RDT Report No.		301	301
Rat Liver Metabolism Database	Root of map No. 901	Root of map No. 248 Metabolite in map ...	Root of map No. 249 Metabolite in map ... Metabolite in map ...
Repeated dose (HESS)	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...	Anilines (Hemolytic... Anilines (Hepatotox...

試験データの要約（SSRDT）へリンク

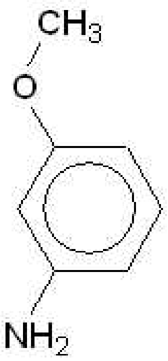
HESS DB（試験報告書DB、毒性作用機序DB、ADME　DB）へリンク

ラット代謝マップDBへリンク

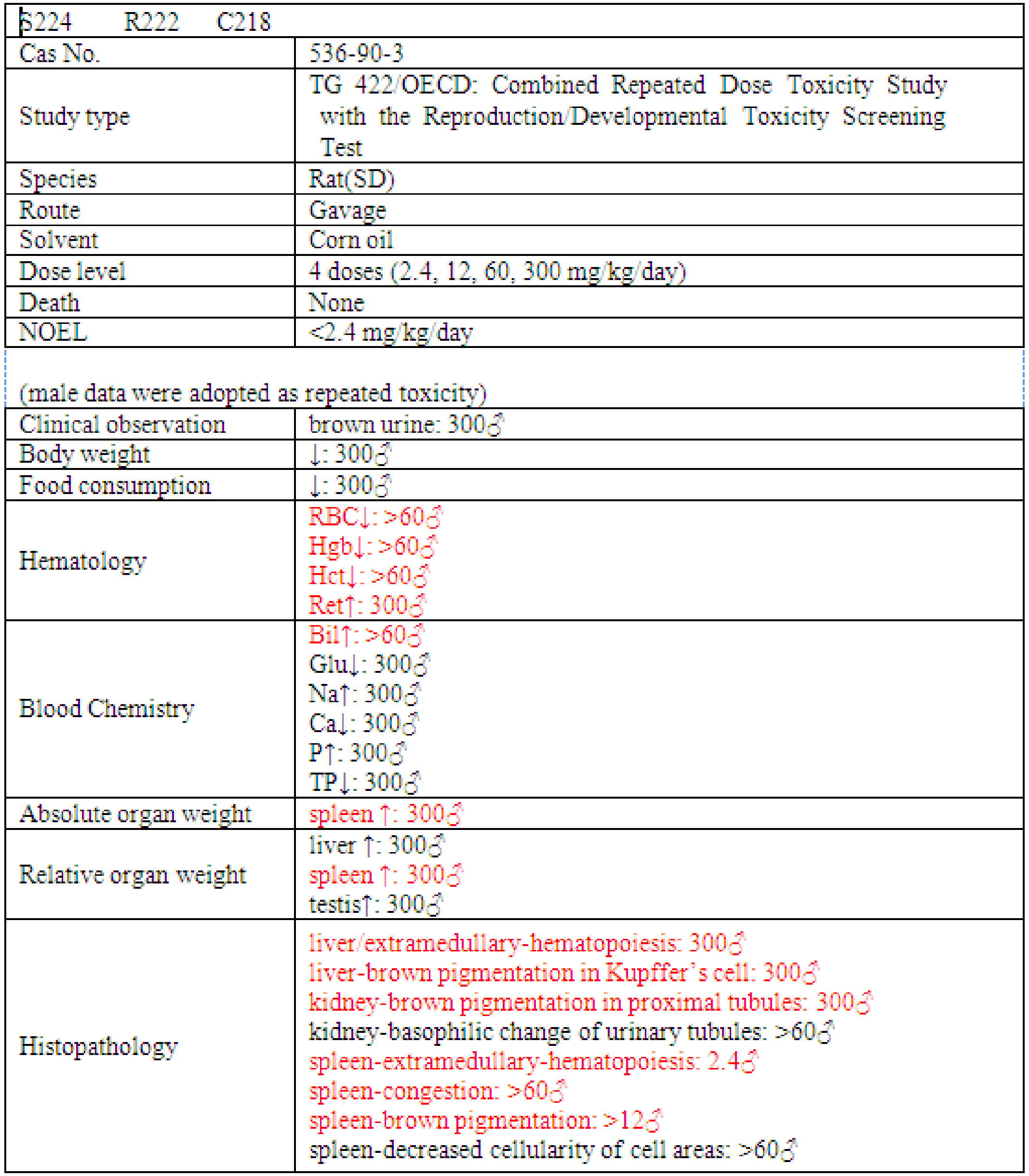
16 Anilines (Hemolytic anemia with methemoglobine

Developed by LMC, Bulgaria

SSRDTの確認(1)



溶血性貧血を明確に示唆

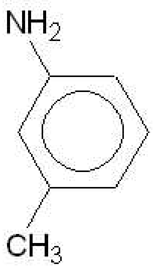


S224　R222　C218	
Cas No.	536-90-3
Study type	TG 422/OECD: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Species	Rat(SD)
Route	Gavage
Solvent	Corn oil
Dose level	4 doses (2.4, 12, 60, 300 mg/kg/day)
Death	None
NOEL	<2.4 mg/kg/day

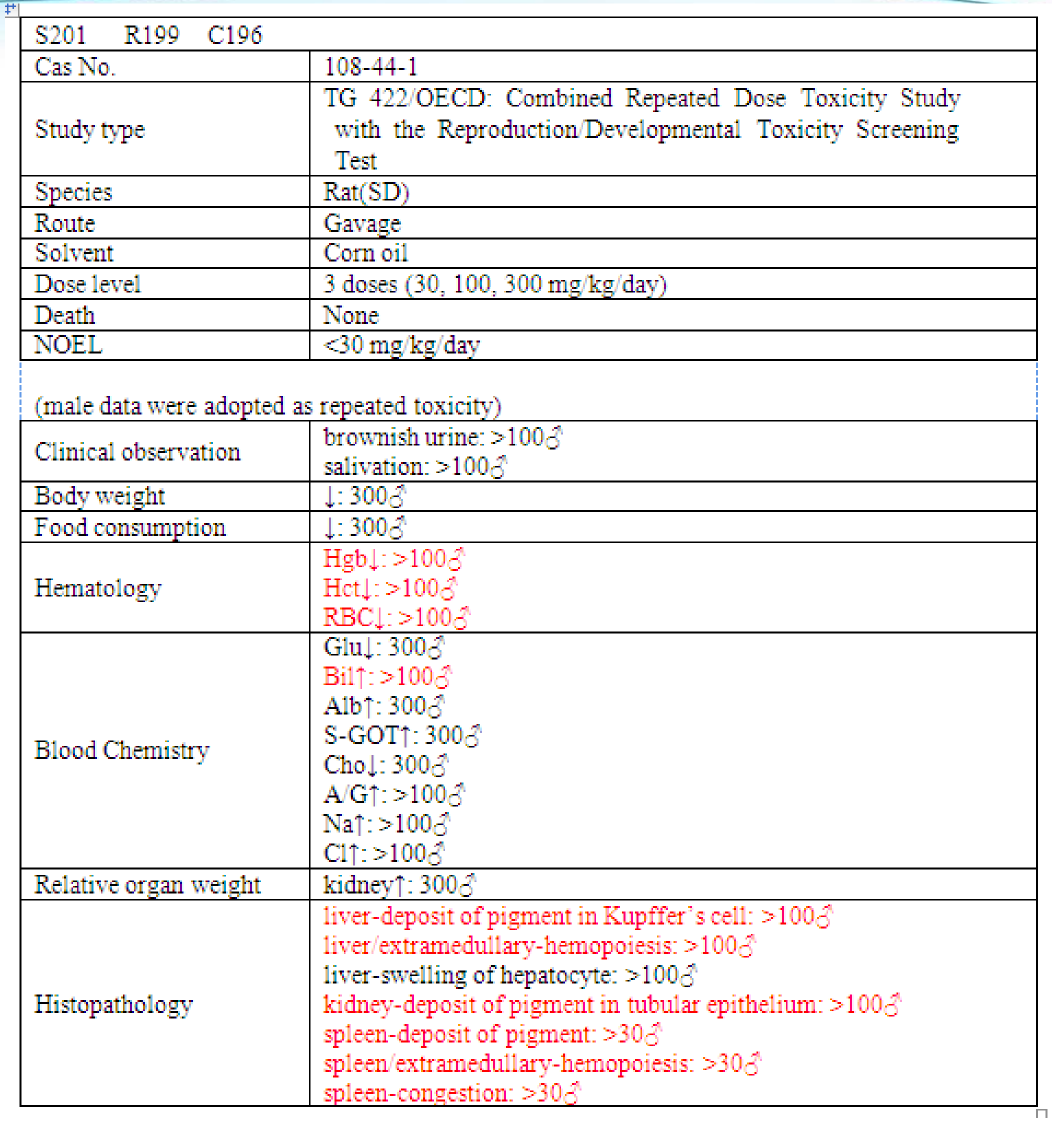
(male data were adopted as repeated toxicity)

Clinical observation	brown urine: 300♂
Body weight	↓: 300♂
Food consumption	↓: 300♂
Hematology	RBC↓: >60♂ Hgb↓: >60♂ Hct↓: >60♂ Ret↑: 300♂
Blood Chemistry	Bil↑: >60♂ Glu↓: 300♂ Na↑: 300♂ Ca↓: 300♂ P↑: 300♂ TP↓: 300♂
Absolute organ weight	spleen ↑: 300♂
Relative organ weight	liver ↑: 300♂ spleen ↑: 300♂ testis↑: 300♂
Histopathology	liver/extramedullary-hematopoiesis: 300♂ liver-brown pigmentation in Kupffer’s cell: 300♂ kidney-brown pigmentation in proximal tubules: 300♂ kidney-basophilic change of urinary tubules: >60♂ spleen-extramedullary-hematopoiesis: 2.4♂ spleen-congestion: >60♂ spleen-brown pigmentation: >12♂ spleen-decreased cellularity of cell areas: >60♂

SSRDTの確認(2)



溶血性貧血を明確に示唆

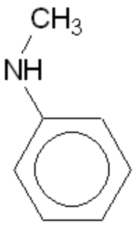


S201 R199 C196	
Cas No.	108-44-1
Study type	TG 422/OECD: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Species	Rat(SD)
Route	Gavage
Solvent	Corn oil
Dose level	3 doses (30, 100, 300 mg/kg/day)
Death	None
NOEL	<30 mg/kg/day

(male data were adopted as repeated toxicity)

Clinical observation	brownish urine: >100♂ salivation: >100♂
Body weight	↓: 300♂
Food consumption	↓: 300♂
Hematology	Hgb↓: >100♂ Hct↓: >100♂ RBC↓: >100♂
Blood Chemistry	Glu↓: 300♂ Bil↑: >100♂ Alb↑: 300♂ S-GOT↑: 300♂ Cho↓: 300♂ A/G↑: >100♂ Na↑: >100♂ Cl↑: >100♂
Relative organ weight	kidney↑: 300♂
Histopathology	liver-deposit of pigment in Kupffer's cell: >100♂ liver/extramedullary-hemopoiesis: >100♂ liver-swelling of hepatocyte: >100♂ kidney-deposit of pigment in tubular epithelium: >100♂ spleen-deposit of pigment: >30♂ spleen/extramedullary-hemopoiesis: >30♂ spleen-congestion: >30♂

SSRDTの確認（3）

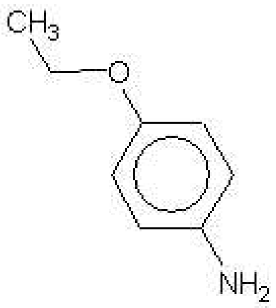


溶血性貧血を明確に示唆

S002　R002　C002	
Cas No.	100-61-8
Study type	TG407OECD: Repeated Dose 28-day Oral Toxicity Study in Rodents
Species	Rat (SD)
Route	Gavage
Solvent	Corn oil
Dose level	3 doses (5, 25, 125 mg/kg/day)
Death	None
NOEL	＜5 mg/kg/day

Clinical observation	Cyanosis: 125♂♀
Urinalysis	Ketone body↑: >5♂♀ Yellowish brown colored: 125♂♀
Hematology	Hgb↓: >5♀, >25♂ Hct↓: >25♂♀ RBC↓: >25♂♀ Ret↑: >25♂♀ MCV↑: 125♂♀ MCH↑: 125♂♀ MCHC↑: 125♂♀
Blood chemistry	Crn↑: >5♀, 125♂ Bil↑: 125♂♀ GOT↑:125♂
Absolute organ weight	Spleen↑: 125♂♀
Relative organ weight	Spleen↑: 125♂♀
Histopathology	Bone marrow-hematopoiesis, increased: >25♀, 125♂ Spleen-deposit of pigment: >25♂ Spleen-hematopoiesis, increased: >25♂♀ Spleen-congestion: >5♂, >25♀ Liver-deposit of pigment: >25♂♀ Liver - extramedullary hematopoiesis: >25♀, 125♂ Kidney-deposit of pigment: 125♂♀ Kidney-hyaline droplet: >25♂

SSRDTの確認（4）

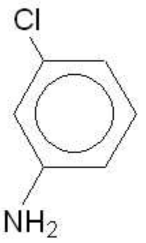


溶血性貧血を明確に示唆

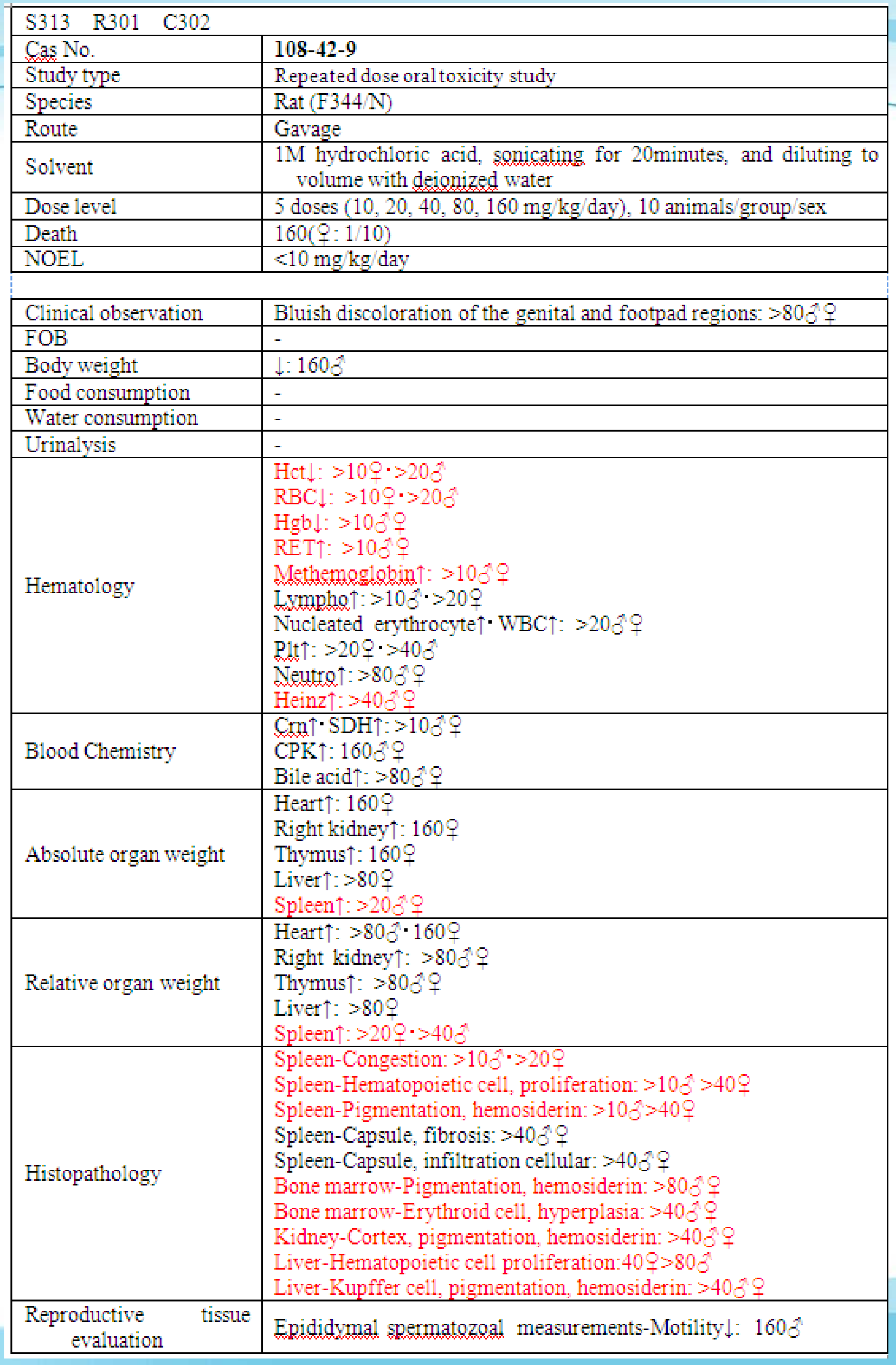
S007　R007　C007	
Cas No.	156-43-4
Study type	TG407OECD: Repeated Dose 28-day Oral Toxicity Study in Rodents
Species	Rat (F344)
Route	Gavage
Solvent	Olive oil
Dose level	3 doses (10, 40, 160 mg/kg/day)
Death	None
NOEL	10 mg/kg/day

Urinalysis	Urobilinogen↑: >40♂♀
Hematology	RBC↓: >40♂♀ Hgb↓: >40♂♀ Hct↓: >40♂♀ Ret↑: >40♂♀ MCH↑: >40♀, 160♂ MCHC↑: 160♂♀
Blood chemistry	Cho↓: 160♂
Absolute organ weight	Spleen↑: >40♂♀
Relative organ weight	Spleen↑: >40♂♀
Histopathology	Spleen-hemosiderosis: >40♂♀ Spleen-extramedullary hemopoiesis: >40♂♀ Spleen-congestion: >40♂♀ Bone marrow-myeloid hyperplasia: >40♂♀ Liver-hemosiderin deposition: 160♂♀ Liver-extramedullary hemopoiesis: 160♂♀

SSRDTの確認(5)

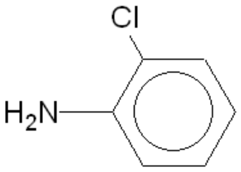


溶血性貧血を明確に示唆

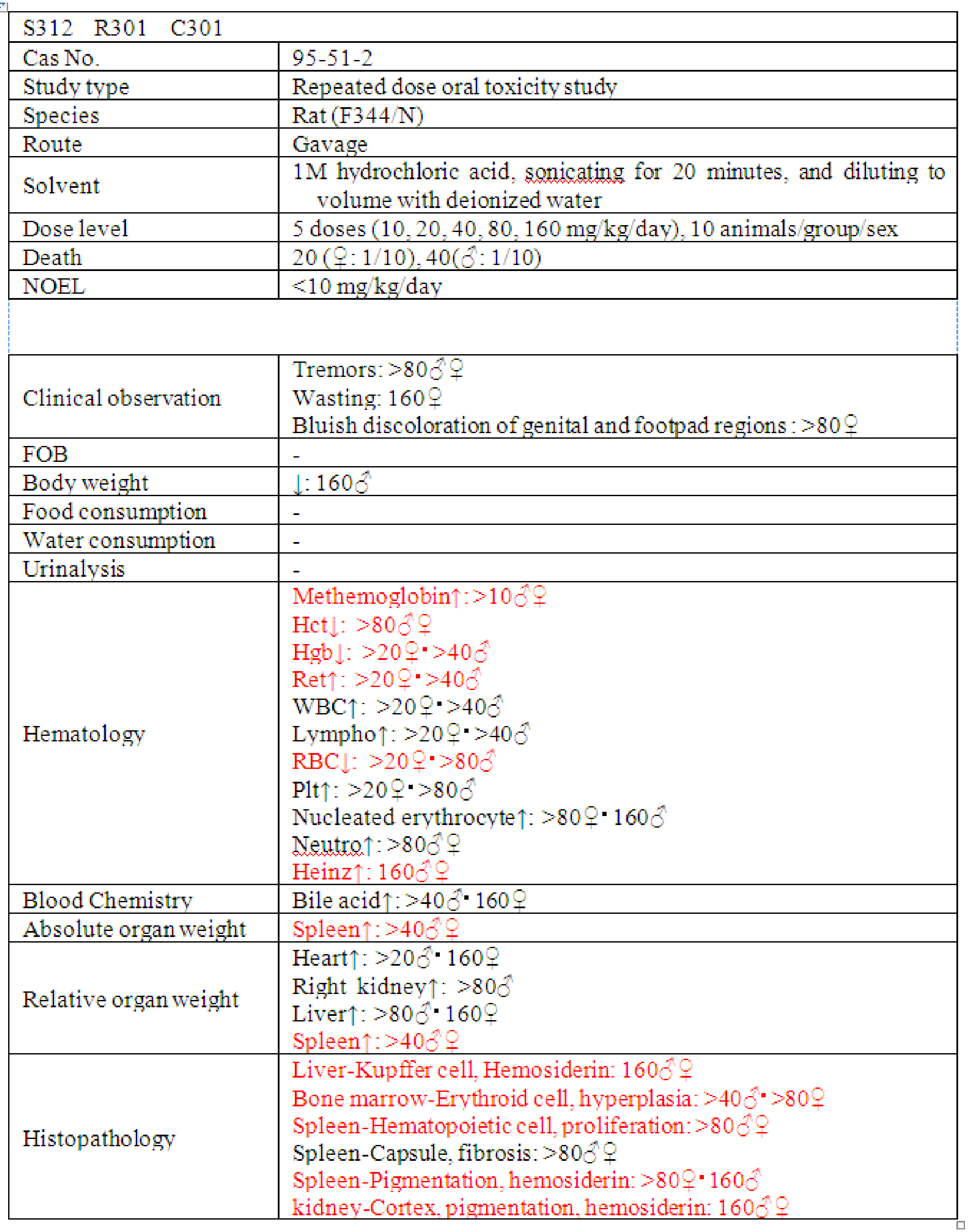


S313 R301 C302	
Cas No.	**108-42-9**
Study type	Repeated dose oral toxicity study
Species	Rat (F344/N)
Route	Gavage
Solvent	1M hydrochloric acid, sonicating for 20minutes, and diluting to volume with deionized water
Dose level	5 doses (10, 20, 40, 80, 160 mg/kg/day), 10 animals/group/sex
Death	160(♀: 1/10)
NOEL	<10 mg/kg/day
Clinical observation	Bluish discoloration of the genital and footpad regions: >80♂♀
FOB	-
Body weight	↓: 160♂
Food consumption	-
Water consumption	-
Urinalysis	-
Hematology	Hct↓: >10♀･>20♂ RBC↓: >10♀･>20♂ Hgb↓: >10♂♀ RET↑: >10♂♀ Methemoglobin↑: >10♂♀ Lympho↑: >10♂･>20♀ Nucleated erythrocyte↑･WBC↑: >20♂♀ Plt↑: >20♀･>40♂ Neutro↑: >80♂♀ Heinz↑: >40♂♀
Blood Chemistry	Crn↑･SDH↑: >10♂♀ CPK↑: 160♂♀ Bile acid↑: >80♂♀
Absolute organ weight	Heart↑: 160♀ Right kidney↑: 160♀ Thymus↑: 160♀ Liver↑: >80♀ Spleen↑: >20♂♀
Relative organ weight	Heart↑: >80♂･160♀ Right kidney↑: >80♂♀ Thymus↑: >80♂♀ Liver↑: >80♀ Spleen↑: >20♀･>40♂
Histopathology	Spleen-Congestion: >10♂･>20♀ Spleen-Hematopoietic cell, proliferation: >10♂ >40♀ Spleen-Pigmentation, hemosiderin: >10♂>40♀ Spleen-Capsule, fibrosis: >40♂♀ Spleen-Capsule, infiltration cellular: >40♂♀ Bone marrow-Pigmentation, hemosiderin: >80♂♀ Bone marrow-Erythroid cell, hyperplasia: >40♂♀ Kidney-Cortex, pigmentation, hemosiderin: >40♂♀ Liver-Hematopoietic cell proliferation:40♀>80♂ Liver-Kupffer cell, pigmentation, hemosiderin: >40♂♀
Reproductive tissue evaluation	Epididymal spermatozoal measurements-Motility↓: 160♂

SSRDTの確認(6)



溶血性貧血を明確に示唆

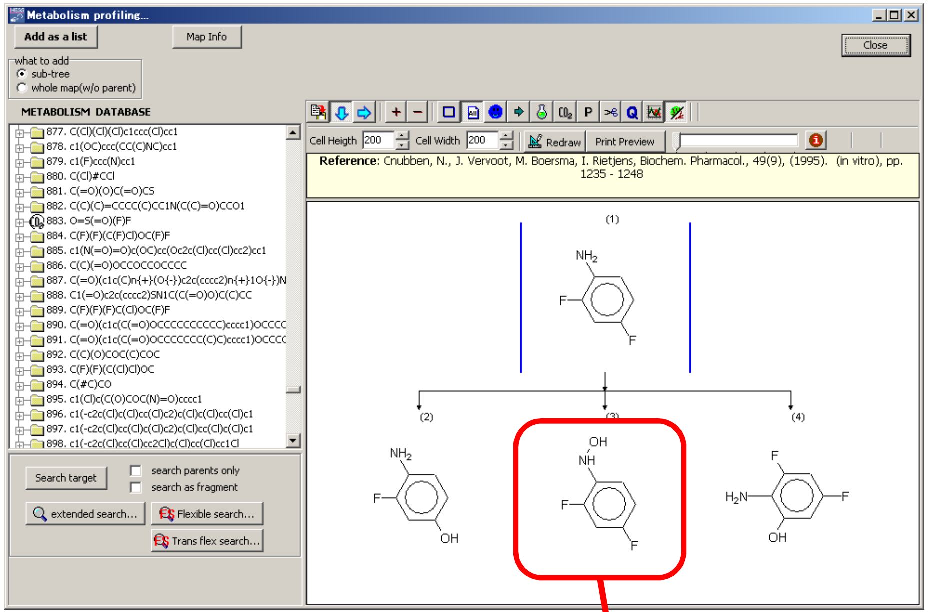


S312　R301　C301	
Cas No.	95-51-2
Study type	Repeated dose oral toxicity study
Species	Rat (F344/N)
Route	Gavage
Solvent	1M hydrochloric acid, sonicating for 20 minutes, and diluting to volume with deionized water
Dose level	5 doses (10, 20, 40, 80, 160 mg/kg/day), 10 animals/group/sex
Death	20 (♀: 1/10), 40(♂: 1/10)
NOEL	<10 mg/kg/day

Clinical observation	Tremors: >80♂♀ Wasting: 160♀ Bluish discoloration of genital and footpad regions : >80♀
FOB	-
Body weight	↓: 160♂
Food consumption	-
Water consumption	-
Urinalysis	-
Hematology	Methemoglobin↑: >10♂♀ Hct↓: >80♂♀ Hgb↓: >20♀･>40♂ Ret↑: >20♀･>40♂ WBC↑: >20♀･>40♂ Lympho↑: >20♀･>40♂ RBC↓: >20♀･>80♂ Plt↑: >20♀･>80♂ Nucleated erythrocyte↑: >80♀･160♂ Neutro↑: >80♂♀ Heinz↑: 160♂♀
Blood Chemistry	Bile acid↑: >40♂･160♀
Absolute organ weight	Spleen↑: >40♂♀
Relative organ weight	Heart↑: >20♂･160♀ Right kidney↑: >80♂ Liver↑: >80♂･160♀ Spleen↑: >40♂♀
Histopathology	Liver-Kupffer cell, Hemosiderin: 160♂♀ Bone marrow-Erythroid cell, hyperplasia: >40♂･>80♀ Spleen-Hematopoietic cell, proliferation: >80♂♀ Spleen-Capsule, fibrosis: >80♂♀ Spleen-Pigmentation, hemosiderin: >80♀･160♂ kidney-Cortex, pigmentation, hemosiderin: 160♂♀

ラット代謝マップDBの確認

評価対象物質

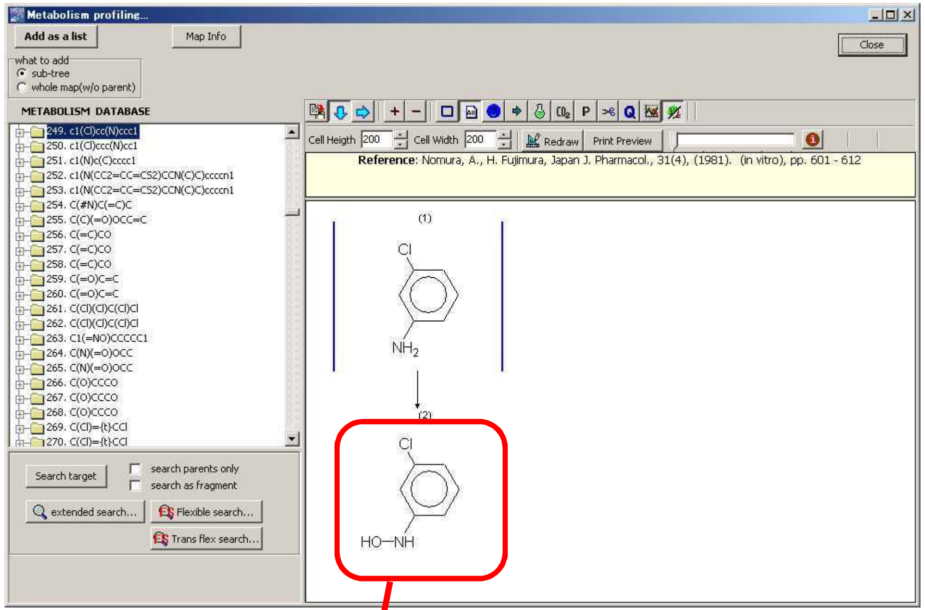

Metabolism profiling...
Add as a list
Map Info
Close
what to add
● sub-tree
○ whole map(w/o parent)
Search target
☐ search parents only
☐ search as fragment
extended search...
Flexible search...
Trans flex search...
Cell Heigth 200
Cell Width 200
Redraw
Print Preview
(1)
NH2
F
F
(2)
NH2
F
OH
(3)
OH
NH
F
F
(4)
F
H2N
F
OH

METABOLISM DATABASE

877. C(Cl)(Cl)(Cl)c1ccc(Cl)cc1
878. c1(OC)ccc(CC(C)NC)cc1
879. c1(F)ccc(N)cc1
880. C(Cl)#CCl
881. C(=O)(O)C(=O)CS
882. C(C)(C)=CCCC(C)CC1N(C(C)=O)CCO1
883. O=S(=O)(F)F
884. C(F)(F)(C(F)Cl)OC(F)F
885. c1(N(=O)=O)c(OC)cc(Oc2c(Cl)cc(Cl)cc2)cc1
886. C(C)(=O)OCCOCCOCCCC
887. C(=O)(c1c(C)n{+}(O{-})c2c(cccc2)n{+}1O{-})N
888. C1(=O)c2c(cccc2)SN1C(C(=O)O)C(C)CC
889. C(F)(F)(F)C(Cl)OC(F)F
890. C(=O)(c1c(C(=O)OCCCCCCCCCC)cccc1)OCCCC
891. C(=O)(c1c(C(=O)OCCCCCCC(C)C)cccc1)OCCCC
892. C(C)(O)COC(C)COC
893. C(F)(F)(C(Cl)Cl)OC
894. C(#C)CO
895. c1(Cl)c(C(O)COC(N)=O)cccc1
896. c1(-c2c(Cl)c(Cl)cc(Cl)c2)c(Cl)c(Cl)cc(Cl)c1
897. c1(-c2c(Cl)cc(Cl)c(Cl)c2)c(Cl)cc(Cl)c(Cl)c1
898. c1(-c2c(Cl)cc(Cl)cc2Cl)c(Cl)cc(Cl)cc1Cl

Reference: Cnubben, N., J. Vervoot, M. Boersma, I. Rietjens, Biochem. Pharmacol., 49(9), (1995). (in vitro), pp. 1235 - 1248

類似物質


Metabolism profiling...
Add as a list
Map Info
Close
what to add
● sub-tree
○ whole map(w/o parent)
Search target
☐ search parents only
☐ search as fragment
extended search...
Flexible search...
Trans flex search...
Cell Heigth 200
Cell Width 200
Redraw
Print Preview
(1)
Cl
NH2
(2)
Cl
HO—NH

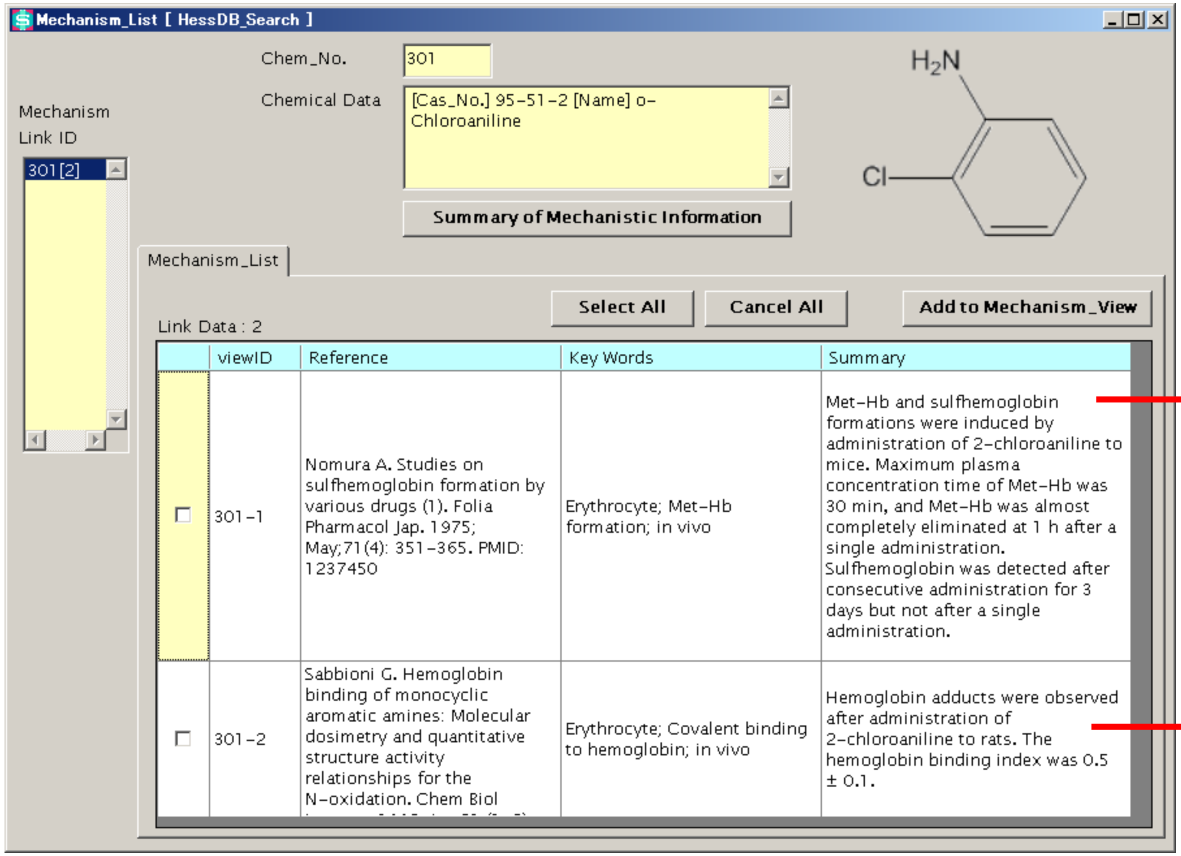
METABOLISM DATABASE

249. c1(Cl)cc(N)ccc1
250. c1(Cl)ccc(N)cc1
251. c1(N)c(C)cccc1
252. c1(N(CC2=CC=CS2)CCN(C)C)ccccn1
253. c1(N(CC2=CC=CS2)CCN(C)C)ccccn1
254. C(#N)C(=C)C
255. C(C)(=O)OCC=C
256. C(=C)CO
257. C(=C)CO
258. C(=C)CO
259. C(=O)C=C
260. C(=O)C=C
261. C(Cl)(Cl)C(Cl)Cl
262. C(Cl)(Cl)C(Cl)Cl
263. C1(=NO)CCCCC1
264. C(N)(=O)OCC
265. C(N)(=O)OCC
266. C(O)CCCO
267. C(O)CCCO
268. C(O)CCCO
269. C(Cl)={t}CCl
270. C(Cl)={t}CCl

Reference: Nomura, A., H. Fujimura, Japan J. Pharmacol., 31(4), (1981). (in vitro), pp. 601 - 612

対象とする毒性発現に関連する代謝物（カテゴリーレポートに記載）が実測試験で確認されている。対象とする反応が起こり得ることのエビデンス。

毒性作用機序DBの確認


Mechanism_List [HessDB_Search]
Summary of Mechanistic Information
Mechanism_List
Select All
Cancel All
Add to Mechanism_View

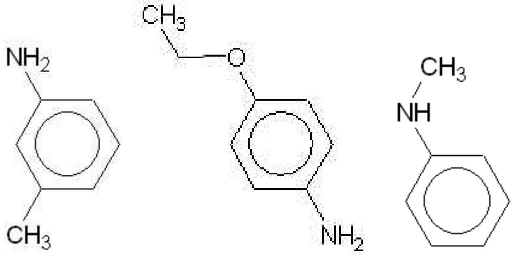
Chem_No. 301

Chemical Data [Cas_No.] 95-51-2 [Name] o-Chloroaniline

Mechanism Link ID 301 [2]

Link Data : 2

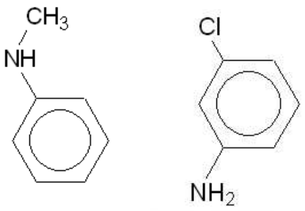
	viewID	Reference	Key Words	Summary
☐	301-1	Nomura A. Studies on sulfhemoglobin formation by various drugs (1). Folia Pharmacol Jap. 1975; May;71(4): 351-365. PMID: 1237450	Erythrocyte; Met-Hb formation; in vivo	Met-Hb and sulfhemoglobin formations were induced by administration of 2-chloroaniline to mice. Maximum plasma concentration time of Met-Hb was 30 min, and Met-Hb was almost completely eliminated at 1 h after a single administration. Sulfhemoglobin was detected after consecutive administration for 3 days but not after a single administration.
☐	301-2	Sabbioni G. Hemoglobin binding of monocyclic aromatic amines: Molecular dosimetry and quantitative structure activity relationships for the N-oxidation. Chem Biol	Erythrocyte; Covalent binding to hemoglobin; in vivo	Hemoglobin adducts were observed after administration of 2-chloroaniline to rats. The hemoglobin binding index was 0.5 ± 0.1.


NH$_2$
CH$_3$
CH$_3$
O
NH$_2$
CH$_3$
NH

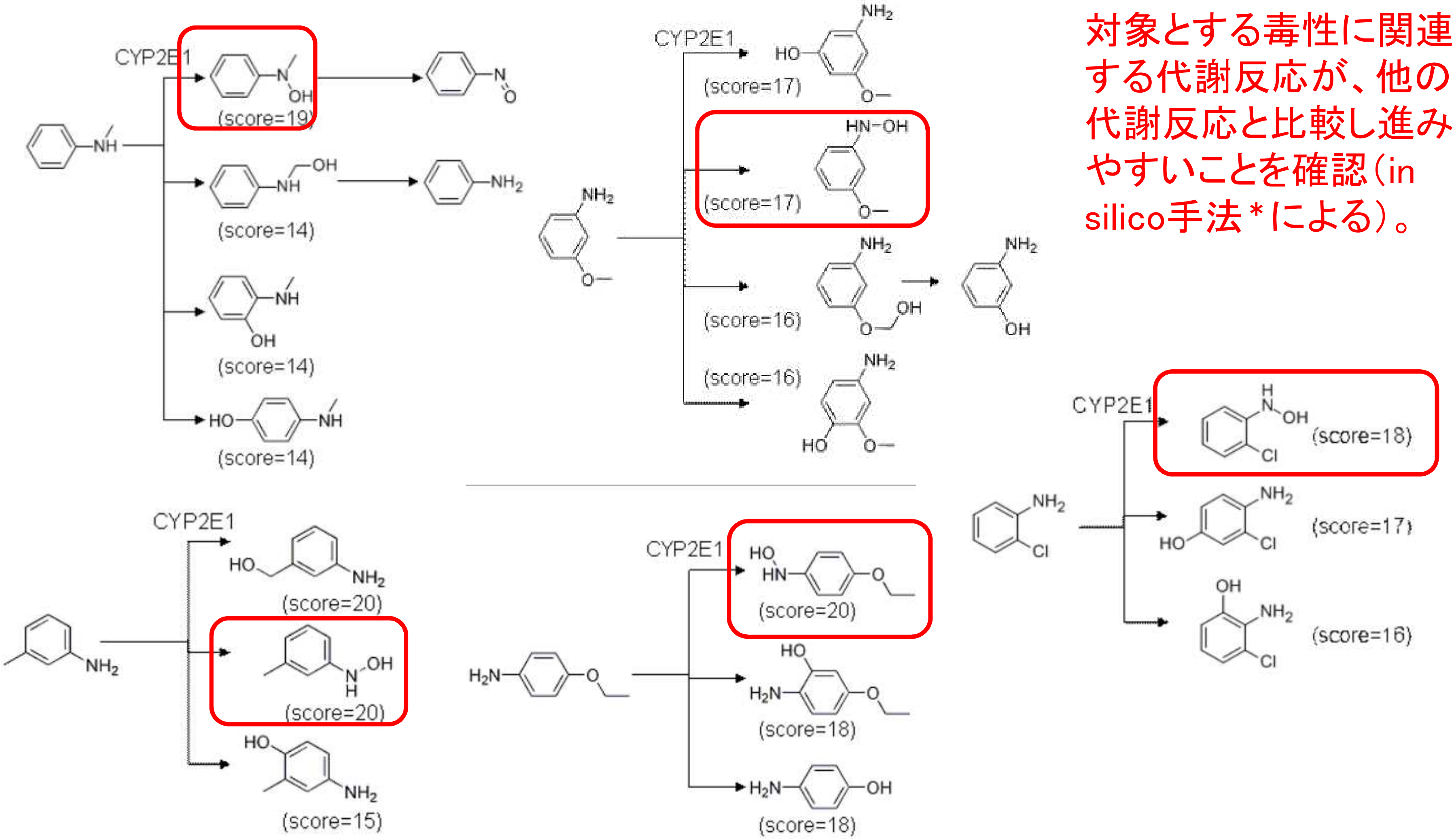
Met-Hb生成
の実験データ

ヘモグロビン
結合体生成
の実験データ

いくつかの類似物質においてカテゴリーレポートに記載されたメカニズムを示唆する実験データが得られてる。


CH$_3$
NH
Cl
NH$_2$

ADME DBの確認


CYP2E1
(score=19)
(score=14)
(score=14)
(score=14)
CYP2E1
(score=17)
(score=17)
(score=16)
(score=16)
CYP2E1
(score=18)
(score=17)
(score=16)
CYP2E1
(score=20)
(score=20)
(score=15)
CYP2E1
(score=20)
(score=18)
(score=18)

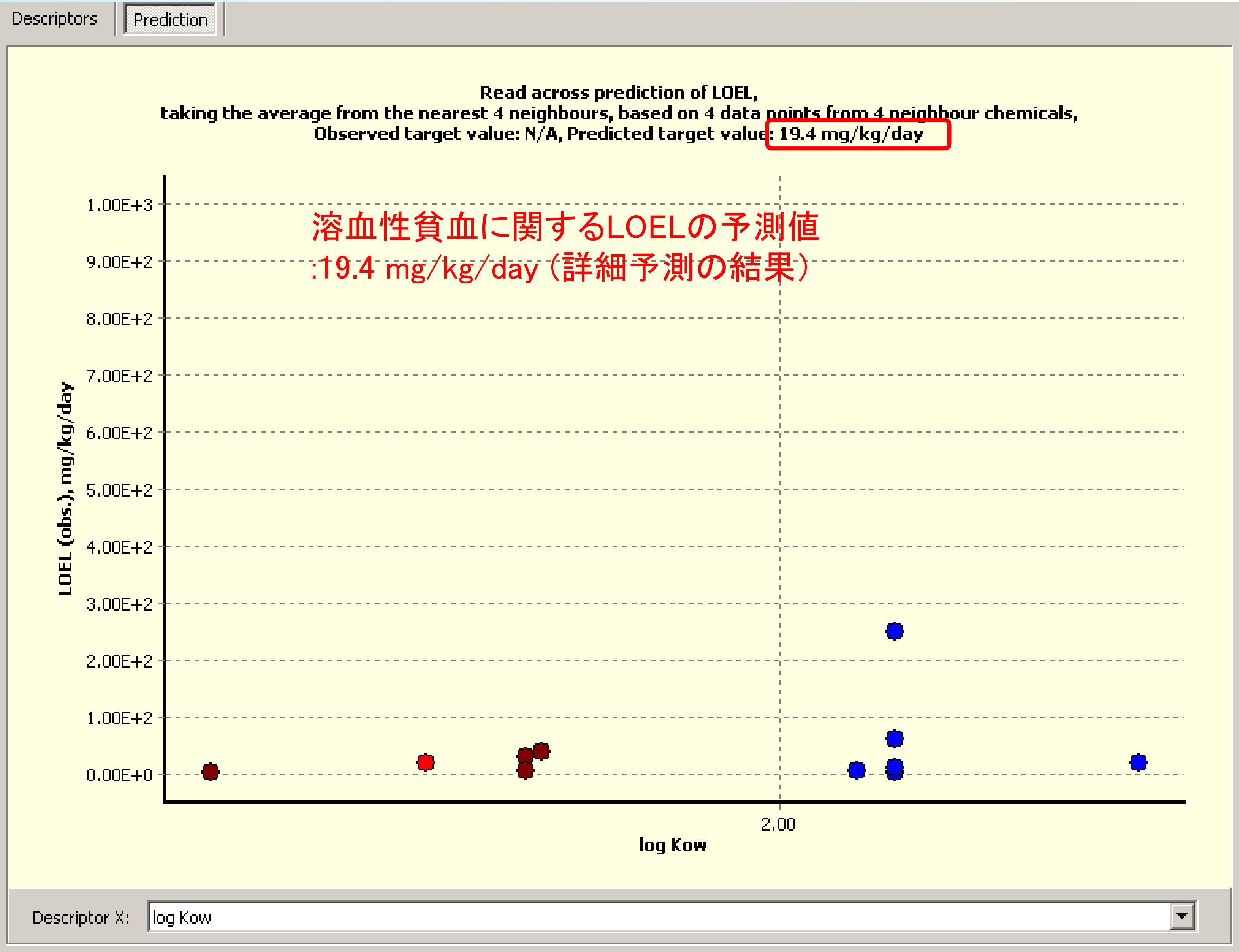
対象とする毒性に関連する代謝反応が、他の代謝反応と比較し進みやすいことを確認（in silico手法＊による）。

*Yamazoe, Y. Ito, K. and Yoshinari, K. 2011. Construction of a CYP2E1-template system for prediction of the metabolism on both site and preference order Drug Metabol. Rev. 43:409-439.

評価例（詳細予測の結果）

類似6物質全てにおいて溶血性貧血が主要毒性であり、NOELの根拠となっていることを確認。
但し、試験期間が長い、NTPの２物質については、他臓器への影響も比較的多く認められていることから、類似物質から、除外した。
代謝経路やヘモグロビン結合性など共通のメカニズムを示唆する情報が多く得られている。

→評価対象物質の主要毒性は、溶血性貧血であり、用量25mg/kg/day未満で発現する可能性が高い（定性的な評価）。


Descriptors
Prediction
1.00E+3
9.00E+2
8.00E+2
7.00E+2
6.00E+2
5.00E+2
4.00E+2
3.00E+2
2.00E+2
1.00E+2
0.00E+0
LOEL (obs.), mg/kg/day
2.00
log Kow

Read across prediction of LOEL,
taking the average from the nearest 4 neighbours, based on 4 data points from 4 neighbour chemicals,
Observed target value: N/A, Predicted target value: 19.4 mg/kg/day

溶血性貧血に関するLOELの予測値
:19.4 mg/kg/day（詳細予測の結果）

Descriptor X: log Kow