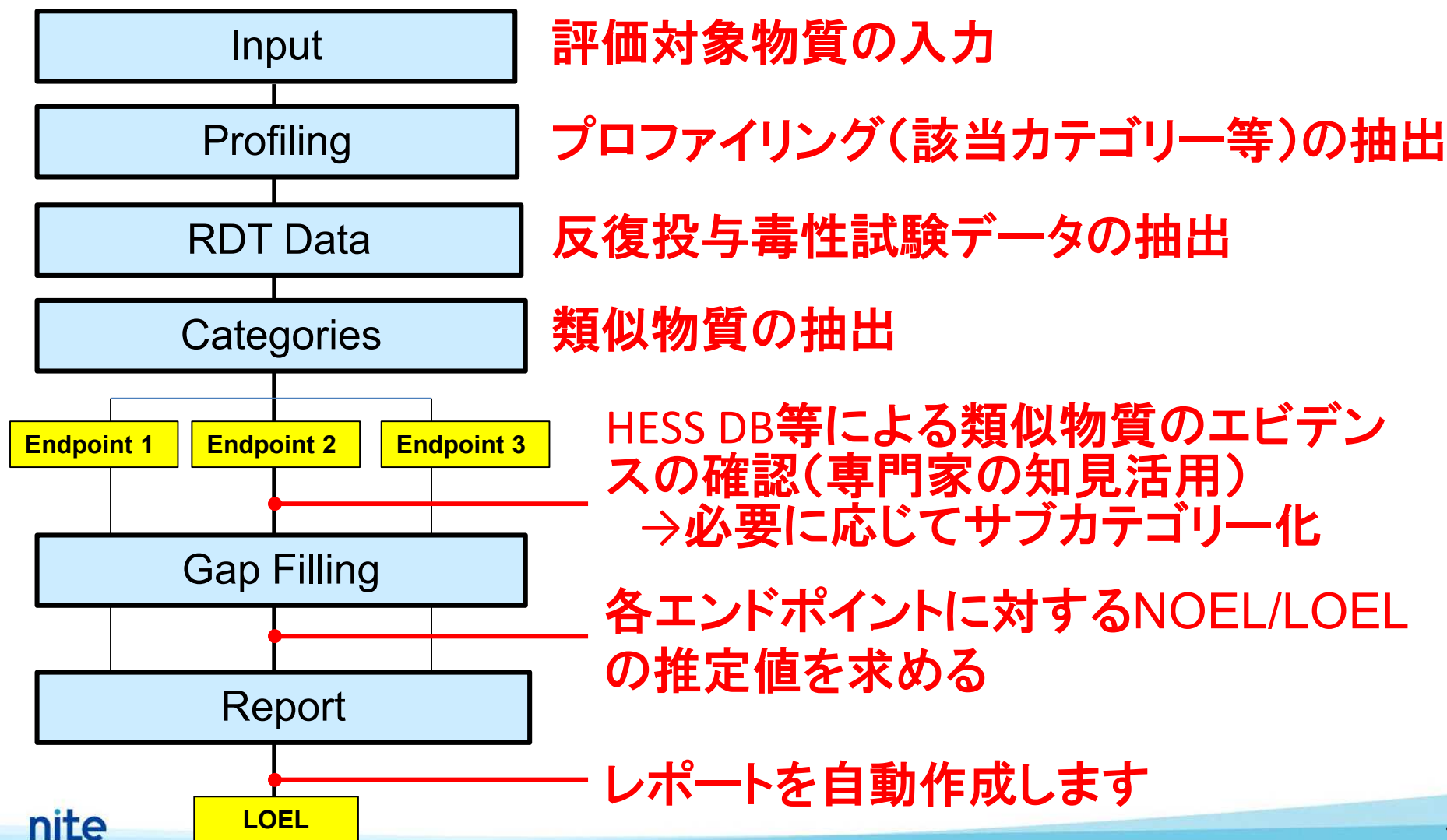



HESS の操作説明

Read-acrossによる反復投与毒性の予測

(独)製品評価技術基盤機構
化学物質管理センター
安全審査課

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





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

1

Input

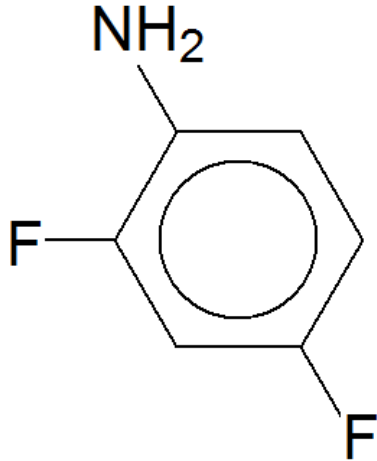
Chemical name: 2,4-difluoroaniline
CAS No 367-25-9
SMILES c1(N)c(F)cc(F)cc1

to data matrix -> metabolism mode...

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

2 CAS # 367259 Search

Chemical name: 2,4-difluoroaniline



1 Single chemical

Developed by LMC, Bulgaria STOP

The screenshot shows the Hazard Evaluation Support System interface. A sidebar on the left contains navigation options: Input (highlighted with a blue box and number 1), Profiling, RDT Data, Categories (with a blue box and number 3), Gap Filling (with a blue box and number 2), Report, and Metabolism. The main window displays the chemical information for 2,4-difluoroaniline, including its name, CAS number (367-25-9), and SMILES string (c1(N)c(F)cc(F)cc1). A red box highlights the chemical name, CAS No, SMILES, and the chemical structure. Below this, a blue box highlights the 'Set target' button in the top navigation bar. Another blue box highlights the search input field in the 'Gap Filling' section, which contains the CAS number 367259. The main content area shows the chemical name and a large chemical structure of 2,4-difluoroaniline. At the bottom, there is a status bar with '1 Single chemical', 'Developed by LMC, Bulgaria', and a 'STOP' button.

Hazard Evaluation Support System

1

Input

Profiling

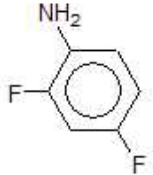
RDT Data

Categories

Gap Filling

Report

Metabolism



Chemical name: **2,4-difluoroaniline**

CAS No: **367-25-9**

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

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

2

Profilers

Profiling methods

- Bioaccumulation – metabolism half
- Biodegradation fragments (BioWIP)
- Carcinogenicity (genotox and non
- Eye irritation/corrosion Exclusion ru
- Eye irritation/corrosion Inclusion r
- in vitro mutagenicity (Ames test)
- in vivo mutagenicity (Micronucleus
- Oncologic Primary Classification
- Skin irritation/corrosion Exclusion r
- Skin irritation/corrosion Inclusion n

mpiric

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

oxicological

- Repeated dose (HESS)

Filter endpoint tree...

1 (Target)

About

Name
Repeated dose (HESS)

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

Disclaimer

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

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

Website

Details

| | |
|----------------------|-----|
| Version | 2.8 |
| Number of categories | 237 |
| Number of help files | 237 |

プロファイラ
の選択

Repeated dose (HESS) を選択して右クリック→
 About: プロファイラーの詳細を表示
 Show Boundaries: プロファイラーのカテゴリを表示
 ↓
 次のスライドへ

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

Advanced

Repeated dose (HESS) - Category definitions

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

Profile Description

Anilines (Hemolytic anemia with methemoglobinemia) Rank A

1. Toxicity Information

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

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

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

2. Observed Effects in the RDT DB

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

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

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

Advanced

Repeated dose (HESS) - Category definitions

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

Profile Description

ROS

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

2. Observed Effects in the RDT DB

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

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

o- and p- Aminophenols (Nos. 24-27) are thought to have a different mechanism for hemolytic anemia (See "o- and p-aminophenols" category).

m-Aminophenol (Nos. 23) and aminobenzene acids (Nos. 30-32) lack the potential to induce hemolytic anemia even at high dose levels. One reason is the reduction in their bioavailability due to their relatively high water solubility.

| No. | Chemical/Descriptor | | RDT Test data | | | | Category Boundary |
|-----|-------------------------------|------------------------------|---|-------------------------------|-----------------------------|---|-------------------|
| | Name (CAS) | Structure | MW log ₁₀ K _{ow} | Test Method | NOEL, LOEL*1 (mg/kg/day) | Observed effects related to the target endpoint*2 | |
| 1 | m-Toluidine (108-44-1) | <chem>Nc1ccc(C)cc1</chem> | 107 1.6 | OECD TG422 gavage S,201 | ♂:10, 50 | Hgb ↓ :250♂, RBC ↓ :250♂, Ret ↑ :250♂ Bil ↑ :>100♂ Spleen-abs wt ↑ :250♂, relat wt ↑ :250♂ extramedullary-hematopoiesis, erythrocytic; 250♂, congestion; 250♂, hemosiderin deposition; 250♂ | In |
| 2 | 2,3-Dimethylaniline (87-59-2) | <chem>Nc1c(C)c(C)ccc1</chem> | 121 2.2 | OECD TG407 gavage S,48 | ♂:12, 60 ♀:<12, 12 | RBC ↓ :>60♀, 300♂, Hgb ↓ :>60♀♂, Hct ↓ :>60♀, 300♂, Ret ↑ :300♀♂, Mat-Hb ↑ :>60♀, 300♂ T-Bil ↑ :300♀♂ Spleen-abs wt ↑ :300♂, relat wt ↑ :300♂ Spleen-red pulp-deposit, hemosiderin: >12♀, extramedullary-hematopoiesis: 300♀♂, congestion: 300♂ Liver-extramedullary-hematopoiesis: 300♀♂, deposit, hemosiderin, Kupffer's cell: 300♀♂ | In |
| 3 | 2,4-Dimethylaniline (95-68-1) | <chem>Nc1c(C)ccc(C)c1</chem> | 121 2.2 | OECD TG407 gavage S,156 | ♂:<2, 2 ♀:2, 10 | Hgb ↓ :>10♂, 50♀ Bil ↑ :>2♂, 50♀ | In |
| 4 | 2,6-Dimethylaniline (87-62-7) | <chem>Nc1c(C)cc(C)cc1</chem> | 121 ?? | OECD TG422 gavage | ♂:50, 250 | Hgb ↓ :250♂, RBC ↓ :250♂, Ret ↑ :250♂, Mat-HGB ↑ :250♂ Spleen-abs wt ↑ :250♂, relat wt ↑ :250♂ extramedullary-hematopoiesis: 250♂, extramedullary-hemosiderin | In |

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

Advanced

Repeated dose (HESS) - Category definitions

- [-] Repeated dose (HESS)
 - ... 2-Acetylaminofluorene (Hepatotoxicity) Alert
 - ... 3-Methylcholantrene (Hepatotoxicity) Alert
 - ... 4,4'-Diethylaminoethoxyhexestrol (Hepatotox
 - ... 4,4'-Methylenedianilines/benzidines (Hepatobi
 - ... 4-Aminopyrazolopyrimidine (Hepatotoxicity) A
 - ... Acetaminophen (Hepatotoxicity) Alert
 - ... Acrylamides (Neurotoxicity) Rank C
 - ... Aflatoxin B1 (Hepatotoxicity) Alert
 - ... Ajmaline (Hepatotoxicity) Alert
 - ... Aliphatic amines (Mucous membrane irritation)
 - ... Aliphatic nitriles (Hepatotoxicity) Rank B
 - ... Aliphatic/Alicyclic hydrocarbons (Alpha 2u-glot
 - ... Allopurinol (Hepatotoxicity) Alert
 - ... Allyl esters (Hepatotoxicity) Rank A
 - ... Alpha olefin (Less susceptible) No Rank
 - ... Alpha-Amanitin (Amatoxin) (Hepatotoxicity) A
 - ... Alpha-Naphthyl-isothiocyanate (Hepatotoxicit
 - ... Amine oxides (Less susceptible) No Rank
 - ... Amineptine (Hepatotoxicity) Alert
 - ... Amiodarone (Hepatotoxicity) Alert
 - ... Anilines (Hemolytic anemia with methemglobi
 - ... Anilines (Hepatotoxicity) Rank C
 - ... Aromatic hydrocarbons (Liver enzyme inductio
 - ... Azithromycin (Hepatotoxicity) Alert
 - ... Azobenzenes (Hemolytic anemia with methem
 - ... Benzene/ Naphthalene sulfonic acids (Less sus
 - ... Benzenesulfonamides (Toxicity to urinary syst
 - ... Beta-Naphthylisothiocyanate (Hepatotoxicity)
 - ... Bosentan (Hepatotoxicity) Alert
 - ... Bromfenac (Hepatotoxicity) Alert
 - ... Carbamazepine (Hepatotoxicity) Alert
 - ... Carbon Disulfide (Hepatotoxicity) Alert
 - ... Carboxylic acids (Hepatotoxicity) No rank
 - ... Chloramphenicol (Hepatotoxicity) Alert
 - ... Chloroquine (Hepatotoxicity) Alert
 - ... Chlorphentermine (Hepatotoxicity) Alert
 - ... Chlorpromazine (Hepatotoxicity) Alert
 - ... Cisplatin (Hepatotoxicity) Alert
 - ... Clindamycin (Hepatotoxicity) Alert
 - ... Clofibrate (Hepatotoxicity) Alert
 - ... Coumarin (Hepatotoxicity) Alert
 - ... Cuprizone (Hepatotoxicity) Alert
 - ... Cycloheximide (Hepatotoxicity) Alert

Profile Description

3. Category Boundary in the Profiler

The following structure is defined as the structural boundary of the category.

$R_1, R_2 = \text{H, methyl or ethyl. } R_3 \sim R_7 = \text{H, alkyl, halo, alkoxy, NO}_2, \text{NH}_2.$

4. Rank of reliability of the categories in the profiler

| *Rank of reliability | A | B | C |
|----------------------|--|---|--|
| Toxicity Mechanism | Well known | Well known | Not well known |
| Category Boundaries | Validated by the RDT test data for enough number of compounds. | Not validated by the RDT test data. (RDT data for enough number of compound doses not available). But, estimated by the test data other than RDT test such as SDT and in vitro. | Experientially defined by using the RDT test data. |

*Rank of reliability for each category is marked in the name of the category

1 **Profiling**

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

2 **Profiling methods**

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

3 **Apply**

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

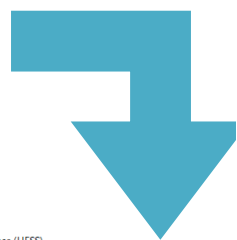
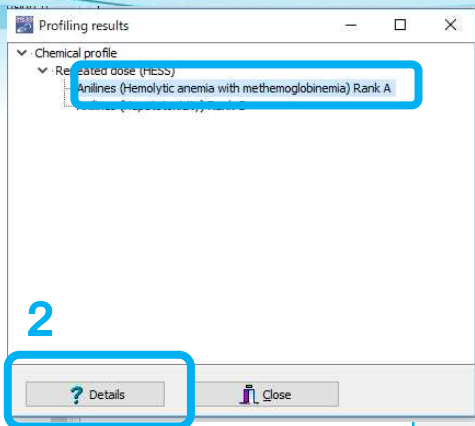
Root of map No. 901

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

4 **ダブルクリックでカテゴリレポートへリンク**

プロファイルの選択

Target Chemical のプロファイリング



1) Hemolytic anemia with methemoglobinemia for Anilines の構造領域

1) Hemolytic anemia with methemoglobinemia for AnilinesのAOPに基づく毒性カテゴリー情報

Anilines (Hemolytic anemia with methemoglobinemia) Rank A

Target

Target

Boundaries Training set Options

Boundary Options Metabolism

Fragment

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

Common Fragments

| Definition | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------------|---------|---|---|---|---|---|---|---|---|
| 1 | [Exh13] | H | | | | | | | |

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.

Target Chemical のRDT dataの収集

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

to data matrix -> metabolism mode...

1 RDT Data 3 Gather

2 Report 4 NITE HESS

Filter endpoint tree... 1 (Target)

Structure

Substance Identity

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

Root of map No. 901

Anilines (Hemolytic...)

Anilines (Hepatotox...)

Developed by LMC, Bulgaria STOP

データベース
にチェック

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

The HESS (Hazard Evaluation Support System) Repeated Dose Toxicity database contains repeated dose toxicity test data of 696 industrial chemicals (745 studies) conducted under the following test condition.

- GLP test
- Test animal: Rat
- Administration period: 28 day - 17 week
- Administration route: Oral (gavage, feed, drinking water)

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

- MHLW/NHHS safety examination of existing chemicals under Chemical Substances Control Law in Japan: 269 studies

Donators

The database was developed by National Institute of Technology and Evaluation (NITE) in the contract research project "Development of Hazard Assessment Techniques by using Structure-activity Method (FY2007-FY2011)" by New Energy and Industrial Technology Development Organization (NEDO) and Ministry of Economy, Trade and Industry (METI) in Japan (Project Leader: Dr. Makoto Hayashi, Biosafety Research Center, Foods, Drugs and Pesticides, Director General)

Disclaimer

Copyrights of the database are to be owned by NITE. Users are requested to comply with international conventions and rules related to copyrights. The commercial use of the database is prohibited. For example, it is prohibited to extract data into another system or database, such as data.

| | |
|----------------------|------------|
| Number of chemicals | 700 |
| Number of data | 6962 |
| Number of endpoints | 2 |
| Name of endpoints | NOEL, LOEL |
| Version | |
| Adopted | Undefined |
| QA Chemical identity | |
| QA Data | |

OK

選択した
DBからは
データは
みつから
なかった

Target Chemicalの類似物質検索 (1)

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

1 Categories

2 HESSのプロファイルを選択

3 Define

4 Hepatotoxicityを選択して除外する

5

6

17 Anilines (Hemolytic anemia with methemoglot

12

Target Chemicalの類似物質検索(2)

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

Hazard Evaluation Support System

Hazard Evaluation Support System

Input Profiling RDT Data Categories Gap Filling Report Metabolism

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

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

Define Subcategorize Combine Categories

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

Toxicological
 Repeated dose (HESS)
 Custom
 HESS Chemical Class

Defined Categories
 [28] Anilines (Hemolytic anemia with methemo...)

Structure

Filter endpoint tree...
 Substance Identity
 Repeated Dose Toxicity
 LOEL (12/19)
 Blood Chemical Examination (25/147)
 Hematological Examination (23/158)
 Histopathological Findings (18/56)
 Organ Weights (27/630)
 NOEL
 Profile
 Study No. (Link to SSRDT)
 Chemical No. (Link to HESS DB)
 RDT Report No.
 Rat Liver Metabolism Database
 Repeated dose (HESS)

| | 1 (Target) | 2 | 3 | 4 | 5 | 6 |
|--|--|--|--|---|---|------------------|
| Min | | M: 20 mg/kg/day | M: 10 mg/kg/day | M: 5 mg/kg/day | M: 15 mg/kg/day | |
| | | M: 20 mg/kg/day, ... | M: 10 mg/kg/day, ... | M: 5 mg/kg/day, 5 ... | M: 15 mg/kg/day, ... | |
| | | M: 80 mg/kg/day, ... | M: 10 mg/kg/day, ... | M: 10 mg/kg/day, ... | M: 15 mg/kg/day, ... | |
| | | M: 40 mg/kg/day, ... | M: 20 mg/kg/day, ... | M: 10 mg/kg/day, ... | M: 15 mg/kg/day, ... | |
| | | M: 10 mg/kg/day, ... | M: 10 mg/kg/day, ... | M: 10 mg/kg/day, ... | M: 15 mg/kg/day, ... | M: 100 mg/kg/day |
| | 312 | 313 | 950 | 5 | 701 | |
| | 301 | 302 | 781 | 5 | 564 | |
| | 301 | 301 | 806 | 5 | 591 | |
| Root of map No. 901 | Root of map No. 248 | Root of map No. 249 | Root of map No. 250 | Root of map No. 6 | N/A | |
| Metabolite in map ... | Metabolite in map ... | Metabolite in map ... | Metabolite in map ... | Metabolite in map ... | | |
| Anilines (Hemolytic anemia with methemoglobinemia) | Anilines (Hemolytic anemia with methemoglobinemia) | Anilines (Hemolytic anemia with methemoglobinemia) | Anilines (Hemolytic anemia with methemoglobinemia) | Anilines (Hemolytic anemia with methemoglobinemia) | Anilines (Hemolytic anemia with methemoglobinemia) | |
| Anilines (Hepatotoxicity) | Anilines (Hepatotoxicity) | Anilines (Hepatotoxicity) | Anilines (Hepatotoxicity) | Anilines (Hepatotoxicity) | Anilines (Hepatotoxicity) | |
| | Styrene (Renal Toxicity) | | Chlorphentermine (Hepatotoxicity) | Nitrobenzenes (Hemolytic anemia with methemoglobinemia) | Nitrobenzenes (Hemolytic anemia with methemoglobinemia) | |
| | Toluene (Renal Toxicity) | | Clofibrate (Hepatotoxicity) | Nitrobenzenes (Hemolytic anemia with methemoglobinemia) | Nitrobenzenes (Hemolytic anemia with methemoglobinemia) | |

類似物質のLOELs/NOELs

類似物質のRDT data

エンドポイント

| Endpoint | Count | Chemical 1 | Chemical 2 | Chemical 3 | Chemical 4 | Chemical 5 | Chemical 6 | Chemical 7 | Chemical 8 | Chemical 9 |
|----------------------------|----------|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|-----------------------|-------------|------------|
| Blood Chemical Examination | (16/112) | M: 40 mg/kg/day, 1... | M: 160 mg/kg/day, ... | M: 100 mg/kg/day, ... | M: 12.5 mg/kg/day, ... | M: 60 mg/kg/day, 3... | M: 40 mg/kg/day, 1... | M: 50 mg/kg/day, 2... | M: 50 mg/kg | |
| FOB | (1/2) | | | | | | M: 250 mg/kg/day, ... | | | |
| General Signs | (14/78) | M: 20 mg/kg/day, 4... | M: 80 mg/kg/day, 8... | M: 100 mg/kg/day, ... | | M: 300 mg/kg/day, ... | M: 50 mg/kg/day, 5... | | M: 50 mg/kg | |
| Blood Cell | (5/9) | | | | | | | | | |
| Blood Cell (Coagulation) | (4/5) | | | | | | | | | |
| Blood Cell (Erythrocyte) | | | | | | | | | | |
| Undefined Tissue | | | | | | | | | | |
| RBC↓ | (15/25) | M: 20 mg/kg/day, 6... | M: 20 mg/kg/day, 1... | M: 100 mg/kg/day | M: 50 mg/kg/day | M: 60 mg/kg/day | M: 250 mg/kg/day, ... | M: 250 mg/kg/day, ... | | |
| HGB↓ | (14/25) | M: 20 mg/kg/day, 4... | M: 10 mg/kg/day, 1... | M: 100 mg/kg/day | M: 50 mg/kg/day | M: 60 mg/kg/day | M: 160 mg/kg/day | M: 250 mg/kg/day | M: 50 mg/kg | |
| MCV↑ | (9/15) | | | | M: 50 mg/kg/day | | M: 250 mg/kg/day | | | |
| MCV↓ | (1/1) | | | | | | | | M: 50 mg/kg | |

類似物質

red blood cells (RBC)の減少に関するLOELs

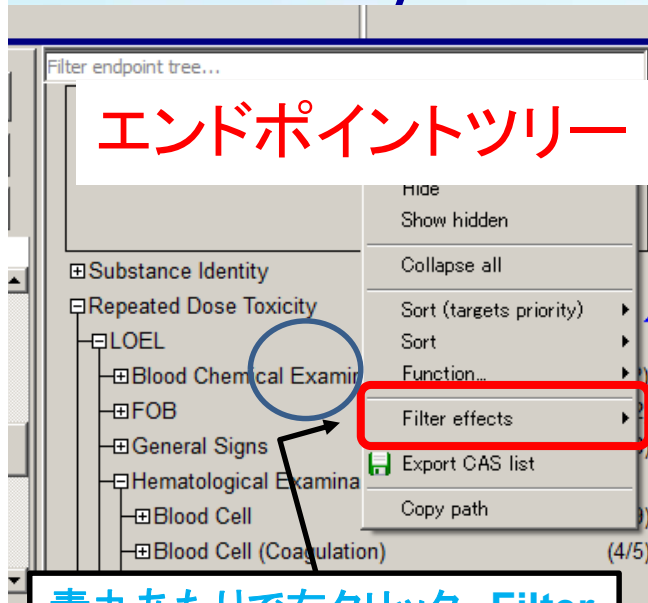
(# of chemicals / # of data points)

セルをダブルクリックで試験データ詳細が表示

| Endpoint | Value | Original value | Route | Strain | Examination items | Effect | |
|----------|-------|----------------|--------------|---------------|-------------------|---------------------------|------|
| 1 | LOEL | 20 mg/kg/day | 20 mg/kg/day | Oral (Gavage) | F344 | Hematological examination | RBC↓ |
| 2 | LOEL | 80 mg/kg/day | 80 mg/kg/day | Oral (Gavage) | F344 | Hematological | RBC↓ |

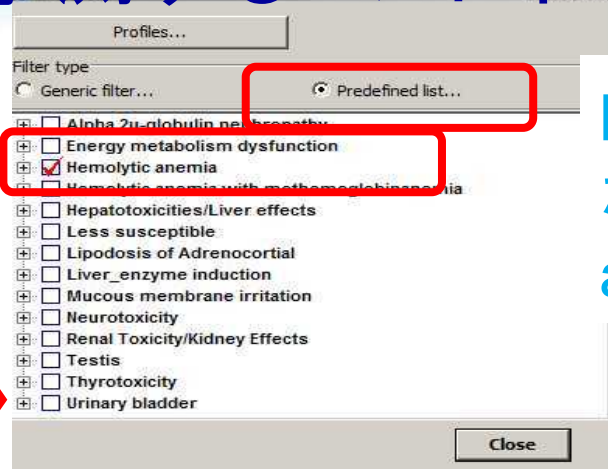
Categories

LOELs/NOELsを予測するエンドポイントの選択(1)

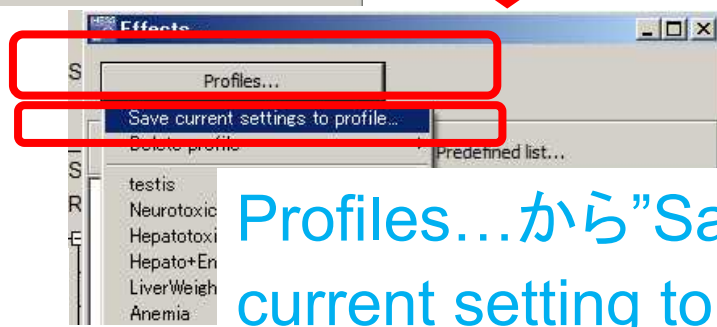


エンドポイントツリー

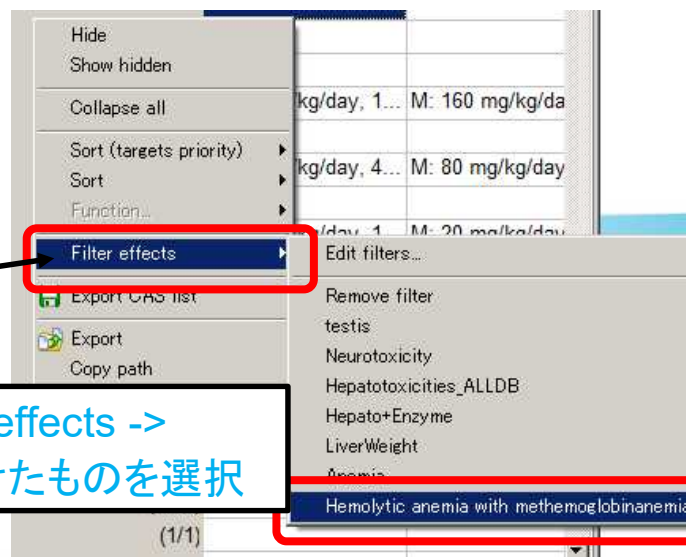
青丸あたりで右クリック Filter effects -> edit filters



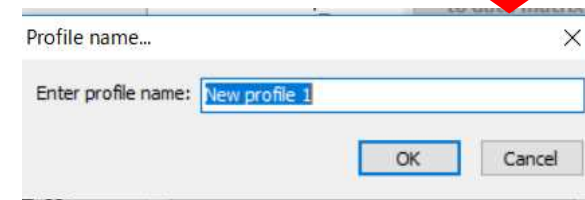
predefined list から“Hemolytic anemia”を選択



Profiles...から“Save current setting to profiles ...”を選択



右クリック Filter effects -> 自分で名前をつけたものを選択



名前をつけたら、OKを押してClose

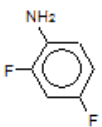
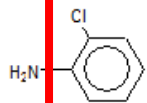
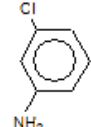
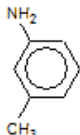
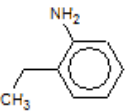

LOELs/NOELsを予測するエンドポイントの選択 (2)

| | | | |
|------------------------|-----------------------|-----------------------|-----------------------|
| Min | M: 20 mg/kg/day | M: 10 mg/kg/day | M: 30 mg/kg/day |
| (9/14) | | | M: 100 mg/kg/day |
| Hemolytic anemiaのLOELs | | | |
| (15/25) | M: 20 mg/kg/day, 8... | M: 20 mg/kg/day, 1... | M: 100 mg/kg/day |
| (11/25) | M: 20 mg/kg/day, 4... | M: 10 mg/kg/day, 1... | M: 100 mg/kg/day |
| | M: 20 mg/kg/day, 4... | M: 10 mg/kg/day, 1... | |
| | M: 80 mg/kg/day, 8... | M: 20 mg/kg/day, 1... | M: 100 mg/kg/day |
| | M: 80 mg/kg/day, 8... | M: 20 mg/kg/day, 4... | M: 30 mg/kg/day, 3... |
| | M: 40 mg/kg/day, 4... | M: 20 mg/kg/day, 2... | |
| (15/27) | M: 160 mg/kg/day, ... | M: 160 mg/kg/day, ... | M: 30 mg/kg/day |

Hemolytic anemia
に関連した所見の
みを表示

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

Chemical Structure

| Enter endpoint tree... | 1 (Target) | 2 | 3 | 4 | 5 | 6 |
|--------------------------------|---|---|---|---|---|---|
| Structure |  |  |  |  |  |  |
| RDT Data (LOELs/NOELs) | Min (9/14) | M: 10 mg/kg/day | M: 10 mg/kg/day | M: 30 mg/kg/day M: 100 mg/kg/day | M: 12.5 mg/kg/day M: 50 mg/kg/day | M: 2.4 mg/l M: 60 mg/l |
| LOEL | | | | | | |
| Blood Chemical Examination | | | | | | |
| Hematological Examination | | | | | | |
| Blood Cell (Erythrocyte) | | | | | | |
| Undefined Tissue | | | | | | |
| RBC↓ | (15/25) | M: 20 mg/kg/day, 8... | M: 20 mg/kg/day, 1... | M: 100 mg/kg/day | M: 50 mg/kg/day | M: 60 mg/l |
| HGB↓ | (14/25) | M: 20 mg/kg/day, 4... | M: 10 mg/kg/day, 1... | M: 100 mg/kg/day | M: 50 mg/kg/day | M: 60 mg/l |
| Reticulocyte↑ | (12/20) | M: 20 mg/kg/day, 4... | M: 10 mg/kg/day, 1... | | M: 50 mg/kg/day | M: 300 mg |
| Methemoglobin↑ | (8/14) | M: 10 mg/kg/day, 1... | M: 10 mg/kg/day, 1... | | | |
| HCT↓ | (13/22) | M: 80 mg/kg/day, 8... | M: 20 mg/kg/day, 1... | M: 100 mg/kg/day | | M: 60 mg/l |
| Histopathological Findings | | | | | | |
| Liver | (12/32) | M: 160 mg/kg/day, ... | M: 40 mg/kg/day, 4... | M: 100 mg/kg/day | | |
| Spleen | | | | | | |
| Undefined Tissue | (13/55) | M: 80 mg/kg/day, 8... | M: 20 mg/kg/day, 4... | | | |
| Organ Weights | | | | | | |
| Spleen | (10/31) | M: 40 mg/kg/day, 4... | M: 20 mg/kg/day, 2... | | | |
| 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...) | | | | |

HESS-DBへのリンク
(toxicity test report,
MOE, ADME)
Rat Liver
Metabolism

詳細情報
へのリンク

Hazard Evaluation Support System

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

to data matrix ->

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)

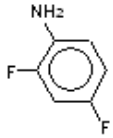
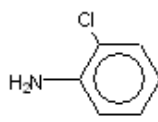
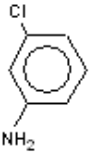
1 Profiling methods

- Empiric
 - Chemical
 - Groups of
 - Lipinski Ru
 - Organic f
 - Organic f
 - Organic f
 - Organic f
 - Study No
 - Chemical
 - RDT Rep
 - CSCL Clas
 - Rat Liver
- Toxicological
 - Repeated
- Metabolism
 - Documented
 - Observed
 - Simulated
 - Dissociatic
 - Liver Met
 - NEDO In
 - NEDO In

2 Apply

Structure

Substance Identity
 Repeated Dose Toxicity
 Profile
 Study No. (Link to SSRDT)
 Chemical No. (Link to HESS DB)
 RDT Report No.
 Rat Liver Metabolism Database
 Repeated dose (HESS)

| Filter endpoint tree... | 1 (Target) | 2 |
|---|---|---|
|  |  |  |
| | M: 10 mg/kg/day, 1... | M: 10 mg/kg/day, 1... |
| | 312 | 313 |
| | 301 | 302 |
| | 301 | 301 |
| Root of map No. 001 | Root of map No. 248 Metabolite in map ... | Root of map No. 249 Metabolite in map ... |
| Anilines (Hemolytic... Anilines (Hepatotox... | Anilines (Hemolytic... Anilines (Hepatotox... | Anilines (Hemolytic... Anilines (Hepatotox... |

試験データの要約 (SSRDT) へリンク

ラット代謝マップDB 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

16 Anilines (Hemolytic anemia with methemoglobin) Developed by LMC, Bulgaria 18

類似物質の溶血性貧血LOELから、
対象物質の溶血性貧血LOELを予測

“Read across”を選択し、Apply。

Scaleから“mg/L”のチェックを外し、OK。

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

Possible data inconsistency

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

Selected [1066/1157] points

LOELの予測

溶血性貧血のLOEL予測値:

38.0 mg/kg/day

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

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

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

類似物質のプロットをダブルクリックすると、データの詳細が表示される

データギャップ方法のオプション

- : Target chemical
- : 予測に使用した類似物質
- : 予測に使用していない類似物質

The screenshot displays the Hazard Evaluation Support System (HESS) interface. The main window title is "Hazard Evaluation Support System". The interface is divided into several sections:

- Header:** "Hazard Evaluation Support System" with "Reset", "Options", and "Help" buttons.
- Left Sidebar:** A vertical menu with icons and labels: "Input", "Profiling", "RDT Data", "Categories", "Gap Filling", "Report" (highlighted), and "Metabolism".
- Chemical Information:** A box containing the chemical name "2,4-difluoroaniline", CAS No "367-25-9", and SMILES "c1(N)c(F)cc(F)cc1". Below this are buttons for "to data matrix ->" and "metabolism mode...".
- Chemical Structure:** A 2D chemical structure of 2,4-difluoroaniline is shown.
- Reports Panel:** A list of actions: "Create", "Save as PDF", "Print", "Save as HTML", "Close", "Save as RTF". Below this is a "Repository" section with "Available data to report" including "Predictions" (with "[1] NITE HESS prediction for LOEL" selected), "(Q)SARs", and "Categories".
- Prediction Window:** A large window titled "Prediction [1]" showing the text "Prediction of LOEL for 2,4-difluoroaniline" and "1 / 25". The main content area displays "**NITE HESS prediction based on read-across**" and "Prediction of LOEL for 2,4-difluoroaniline".
- Footer:** A status bar at the bottom shows "17 Anilines (Hemolytic anemia with methemoglobinemia) Ra", "Developed by LMC, Bulgaria", and a "STOP" button.