平成24年度第3回NITE QSAR講習会

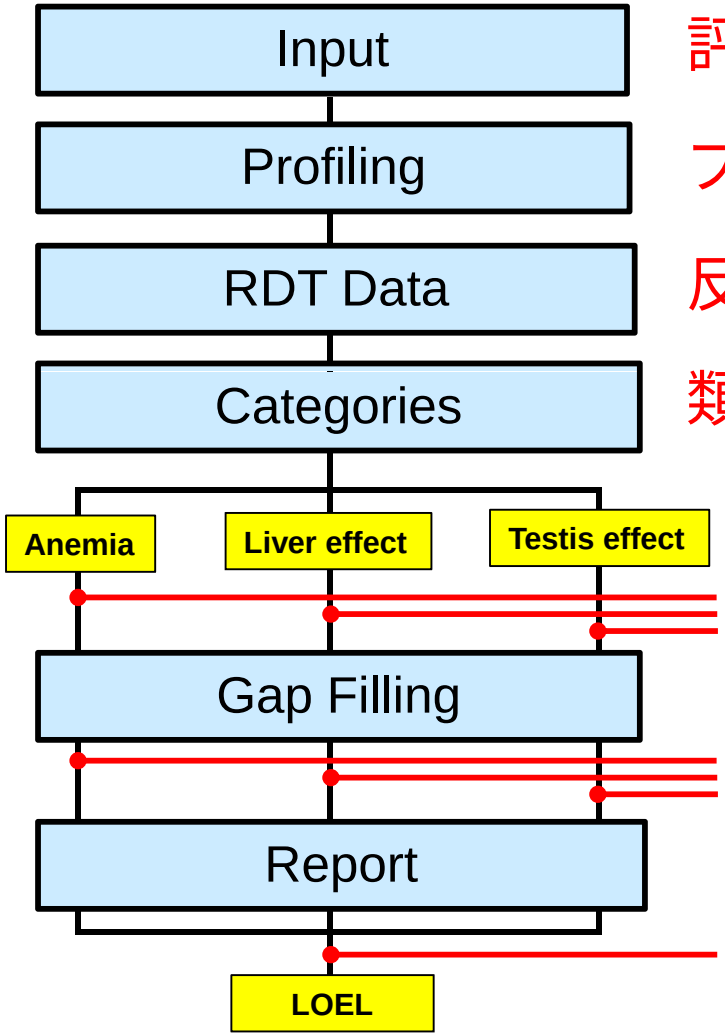
HESS 操作実習

Read-acrossによる反復投与毒性の予測

2012年11月26日(月)

㈱ 製品評価技術基盤機構
化学物質管理センター

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)



評価対象物質の入力

プロファイリング (該当カテゴリー等) の抽出

反復投与毒性試験データの抽出

類似物質の抽出

HESS DB等による類似物質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

各標的臓器等に対するLOELの推定値を求める

各標的臓器等に対するLOELの推定値の最少値を選択

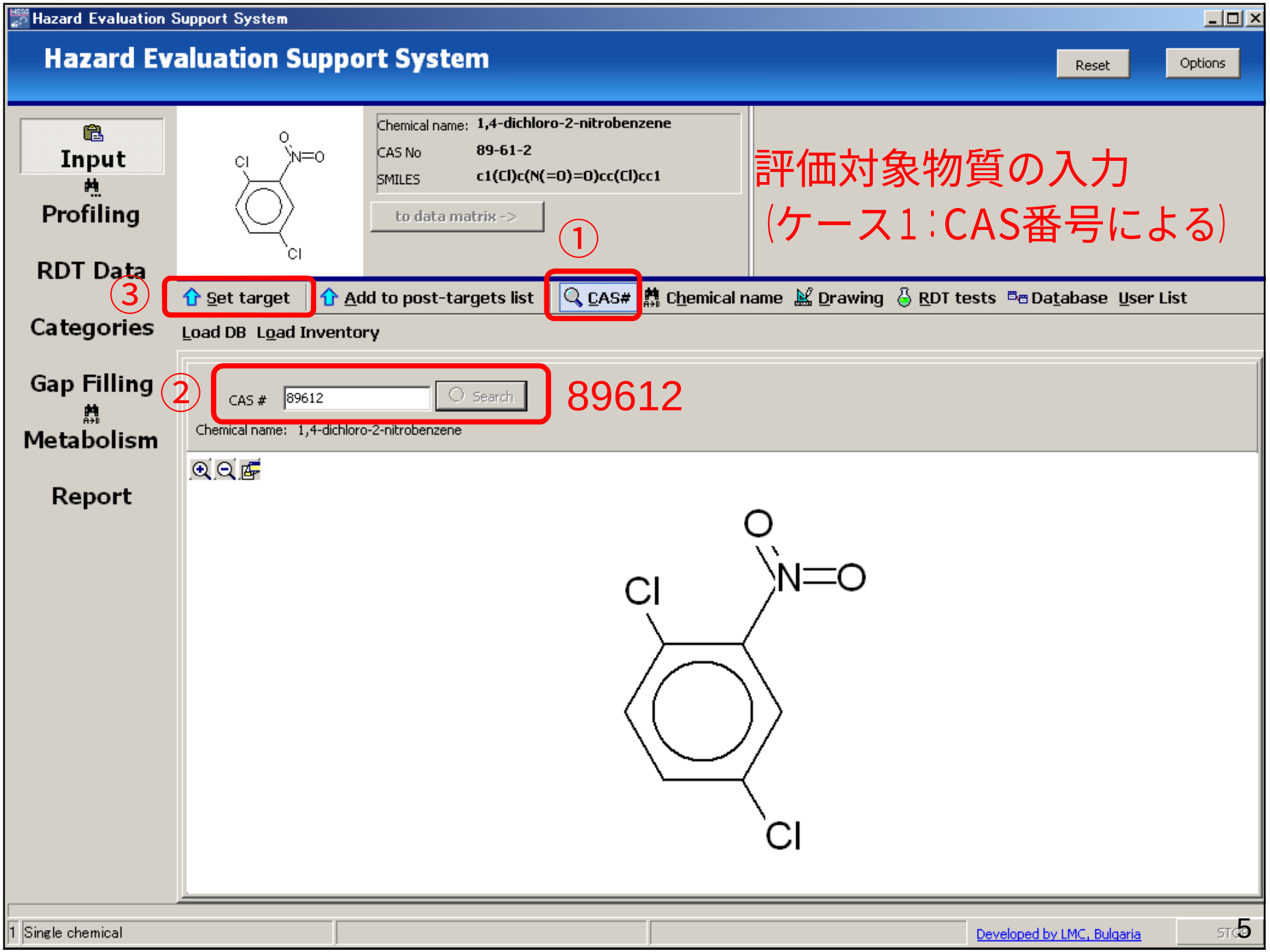
ケーススタディ:

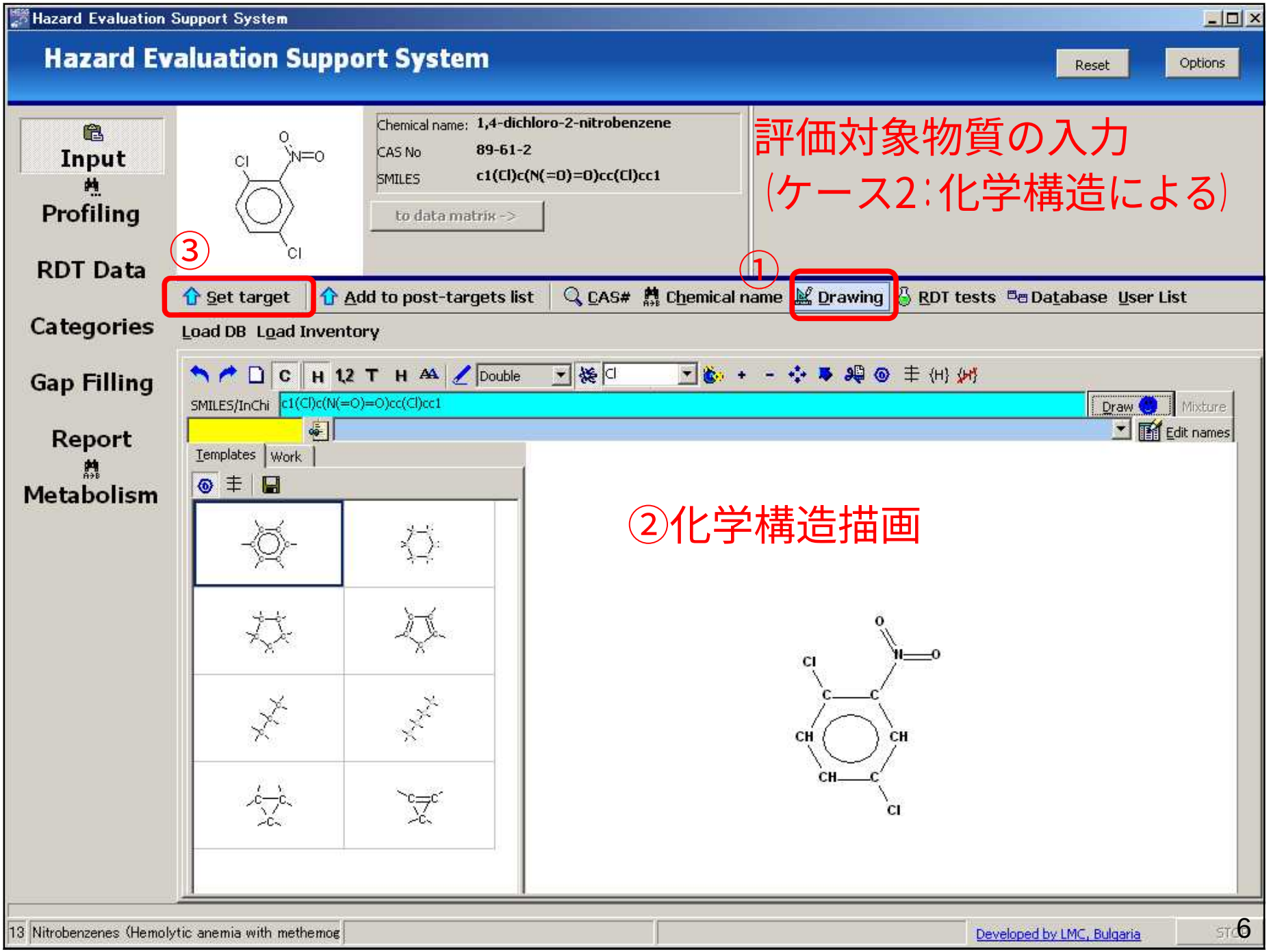
1,4-Dichloro-2-nitrobenzene

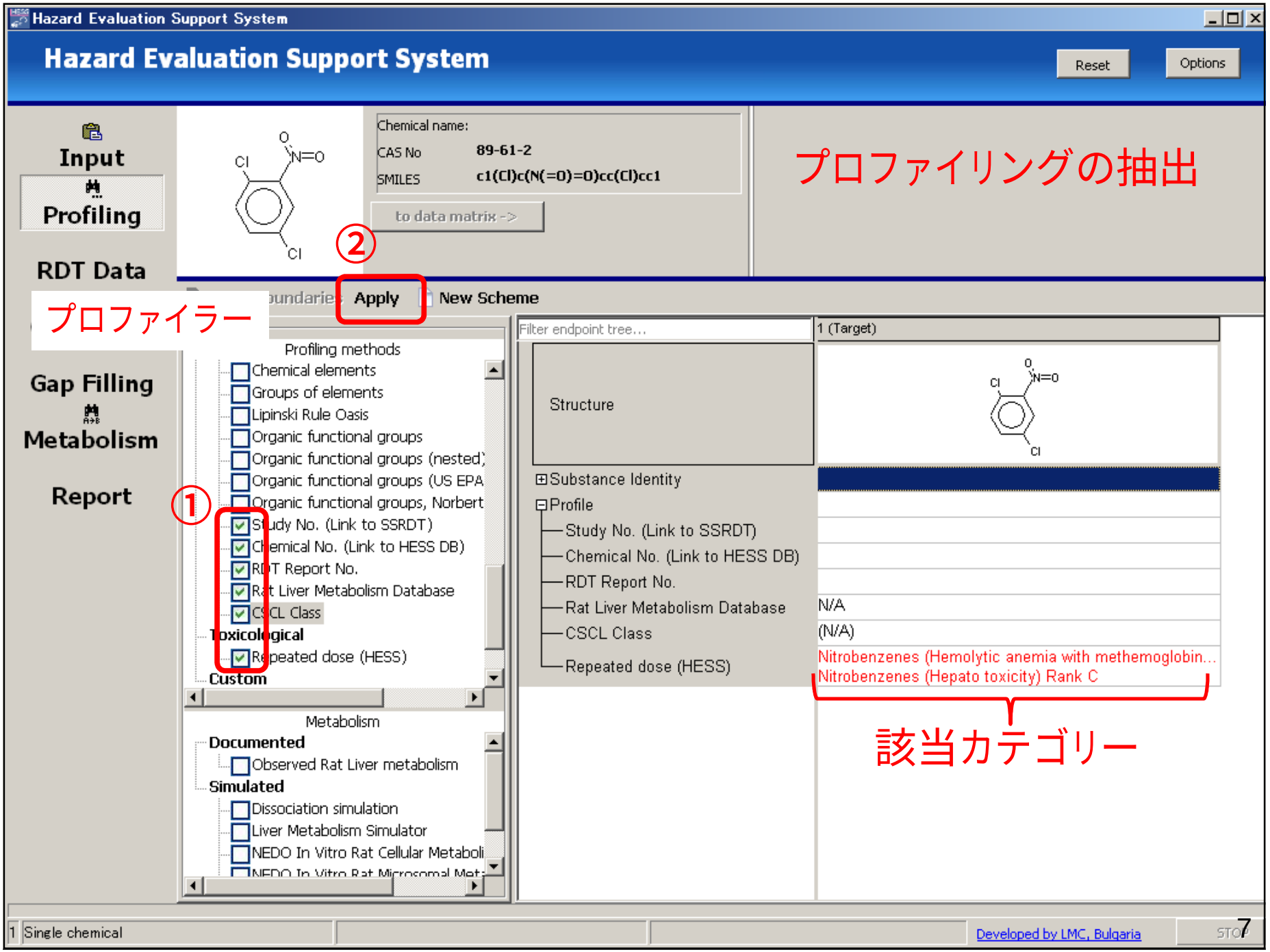
(89-61-2)

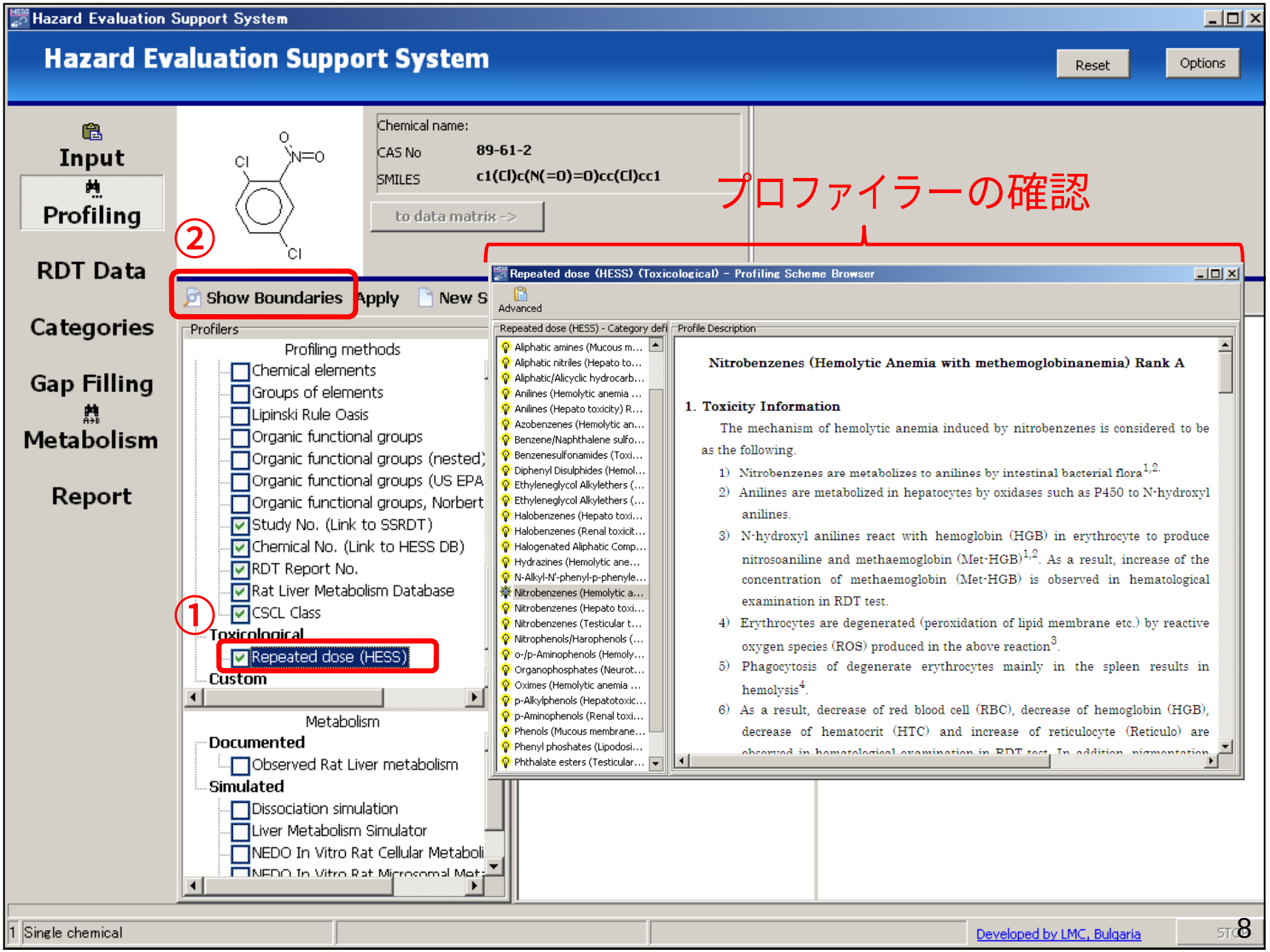
- 基本操作 -

評価対象物質の入力から
類似物質の抽出まで


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
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)
③
Set target
Add to post-targets list
CAS#
Chemical name
Drawing
RDT tests
Database
User List
Load DB
Load Inventory
②
CAS #
89612
Search
89612
Chemical name: 1,4-dichloro-2-nitrobenzene
Cl
N=O
Cl
1
Single chemical
Developed by LMC, Bulgaria


Hazard Evaluation Support System
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 ->
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
13 Nitrobenzenes (Hemolytic anemia with methemog
Developed by LMC, Bulgaria


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Gap Filling
Metabolism
Report
Chemical name:
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
②
プロファイリングの抽出
プロファイラー
Apply
New Scheme
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
①
Metabolism
Documented
Observed Rat Liver metabolism
Simulated
Dissociation simulation
Liver Metabolism Simulator
NEDO In Vitro Rat Cellular Metaboli
Filter endpoint tree...
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)
1 (Target)
N/A
(N/A)
Nitrobenzenes (Hemolytic anemia with methemoglobin...
Nitrobenzenes (Hepato toxicity) Rank C
該当カテゴリー
1 Single chemical
Developed by LMC, Bulgaria
STOP


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
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
①
Toxicological
Repeated dose (HESS)
Custom
Metabolism
Documented
Observed Rat Liver metabolism
Simulated
Dissociation simulation
Liver Metabolism Simulator
NEDO In Vitro Rat Cellular Metaboli
Repeated dose (HESS) (Toxicological) – Profiling Scheme Browser
Advanced
Repeated dose (HESS) - Category defi
Profile Description
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 phoshates (Lipodosi...
Phthalate esters (Testicular...
Nitrobenzenes (Hemolytic Anemia with methemoglobinanemia) Rank A
1. Toxicity Information
The mechanism of hemolytic anemia induced by nitrobenzenes is considered to be as the following.
1) Nitrobenzenes are metabolizes 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 reaction[3].
5) Phagocytosis of degenerate erythrocytes mainly in the spleen results in hemolysis[4].
6) As a result, decrease of red blood cell (RBC), decrease of hemoglobin (HGB), decrease of hematocrit (HTC) and increase of reticulocyte (Reticulo) are
1 Single chemical
Developed by LMC, Bulgaria

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

Advanced

カテゴリーの記述

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...
- Ethyleneglycol alkylethers (Hemolytic anemia) Rank A
- Ethyleneglycol 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 phoshates (Lipodosis of adrenocortial) Rank C
- Phthalate esters (Testicular toxicity) Rank C

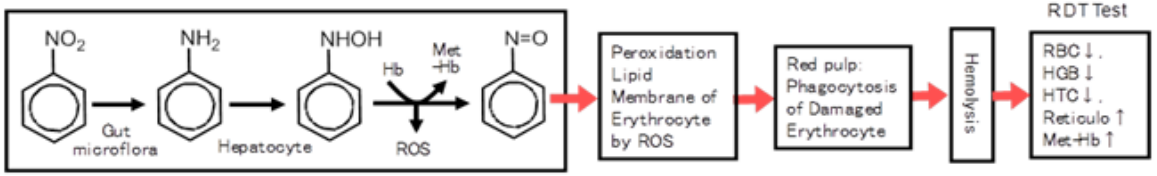
Profile Description

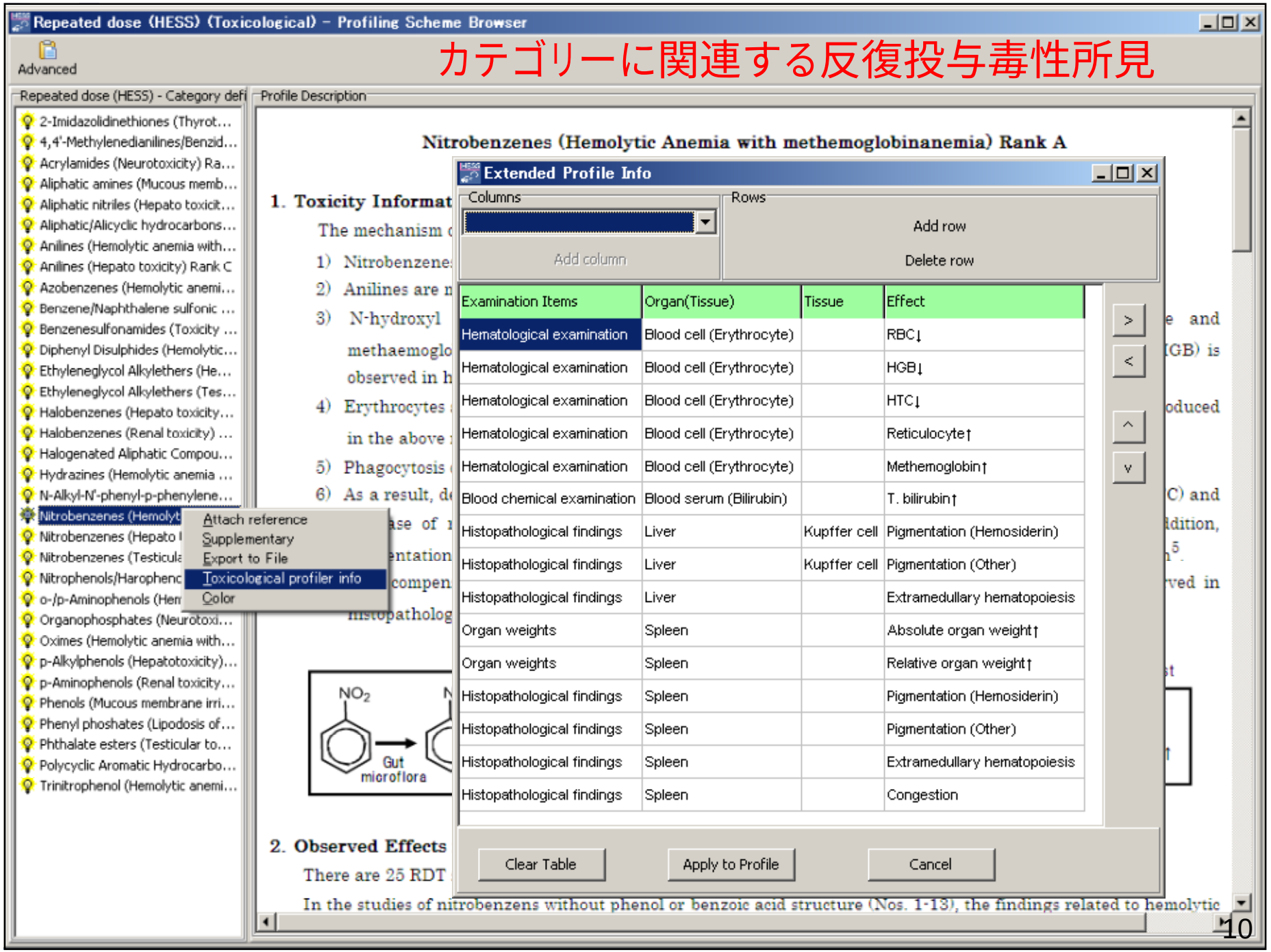
Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A

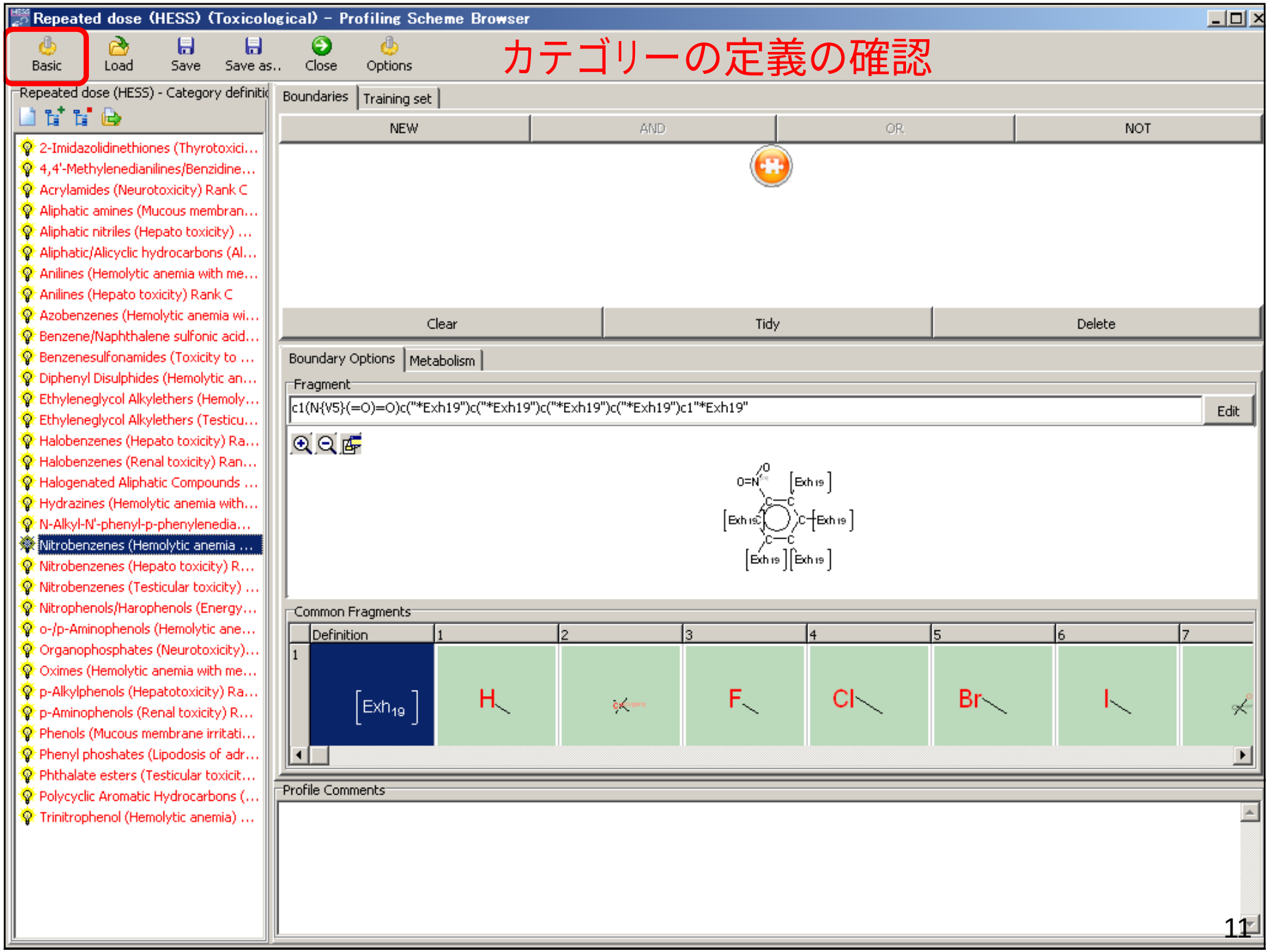
1. Toxicity Information

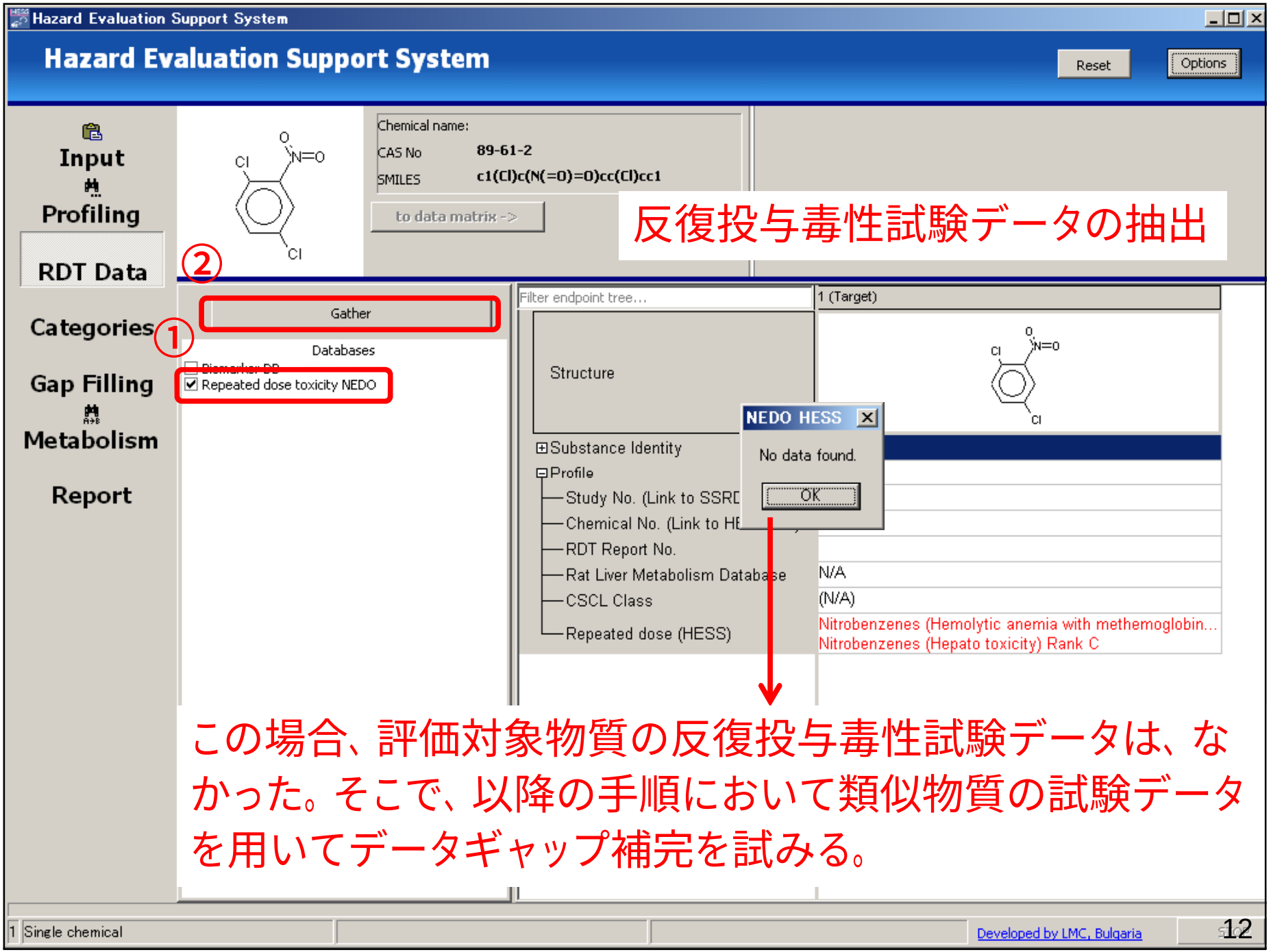
The mechanism of hemolytic anemia induced by nitrobenzenes is considered to be the following.

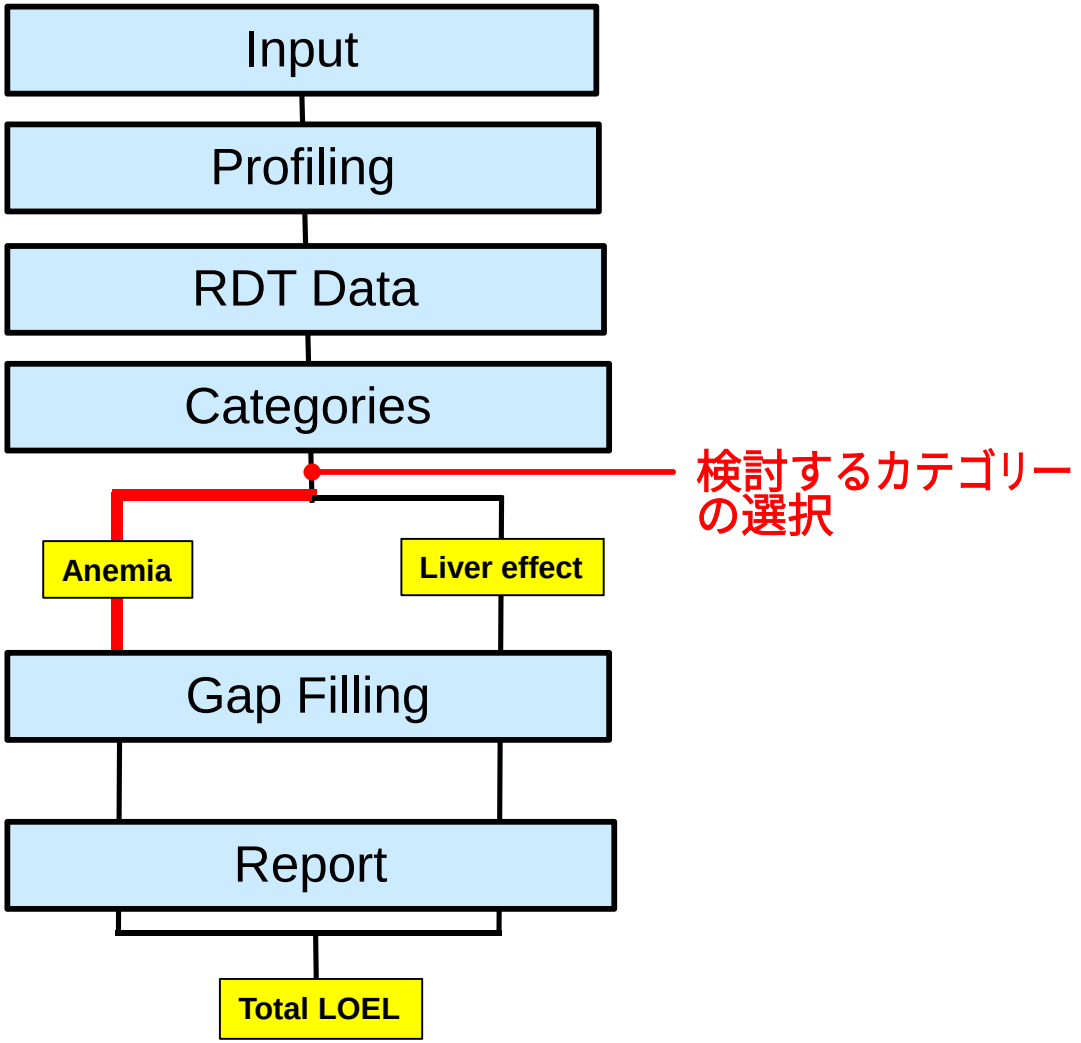
1) Nitrobenzenes are metabolized to anilines by intestinal bacterial flora[1,2].
2) Anilines are metabolized in hepatocytes by oxidases such as P450 to N-hydroxyl anilines.
3) N-hydroxyl anilines react with hemoglobin (Hgb) in erythrocytes to produce nitrosoaniline and methemoglobin (Met-Hgb)[1,2]. As 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 reaction[3].
5) Phagocytosis of degenerate erythrocytes, mainly in the spleen, results in hemolysis[4].
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 examination[5].
7) As a compensatory response of anemia, extramedullary hematopoiesis, mainly in the spleen, is observed upon histopathological examination[4].

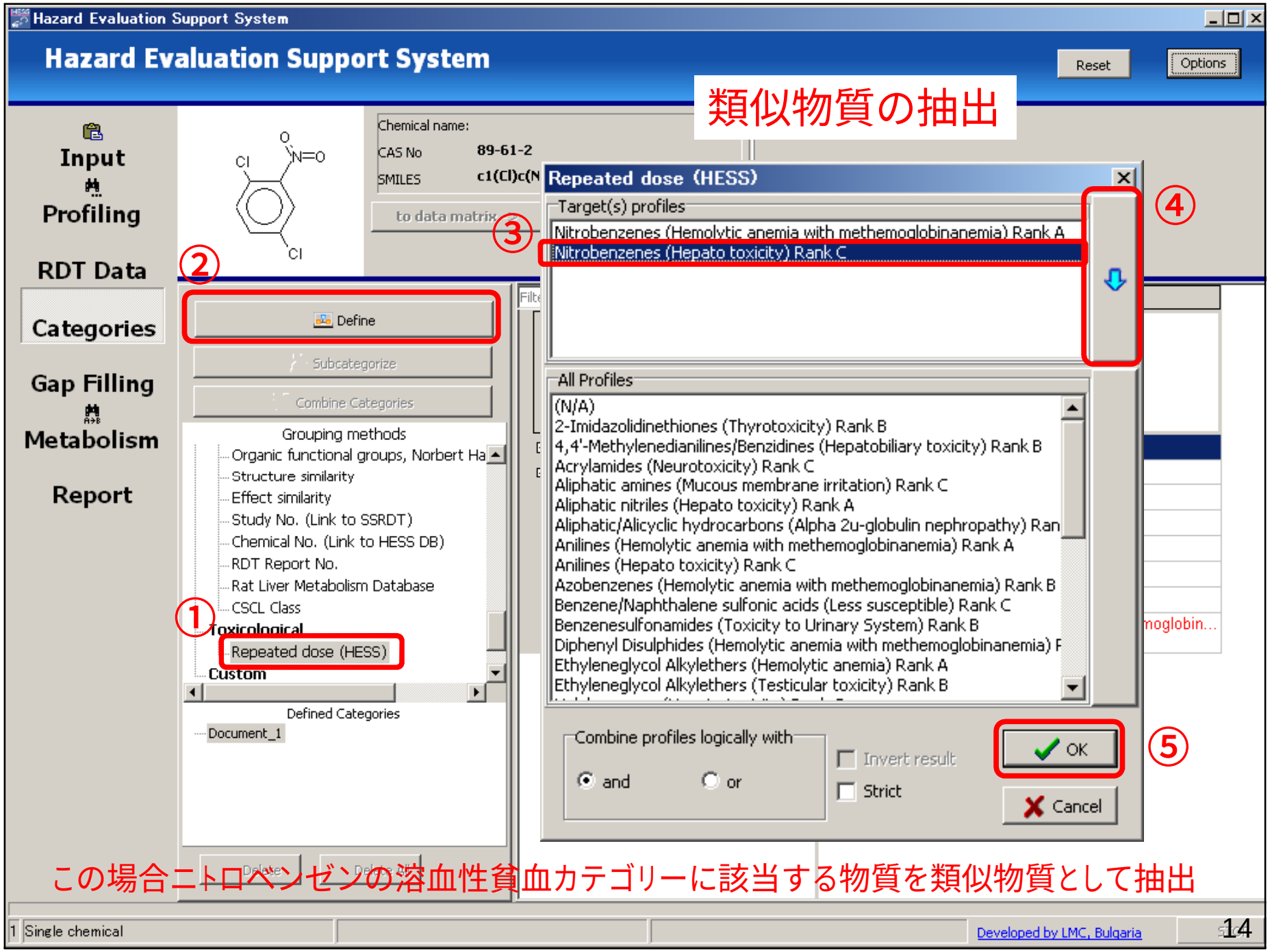


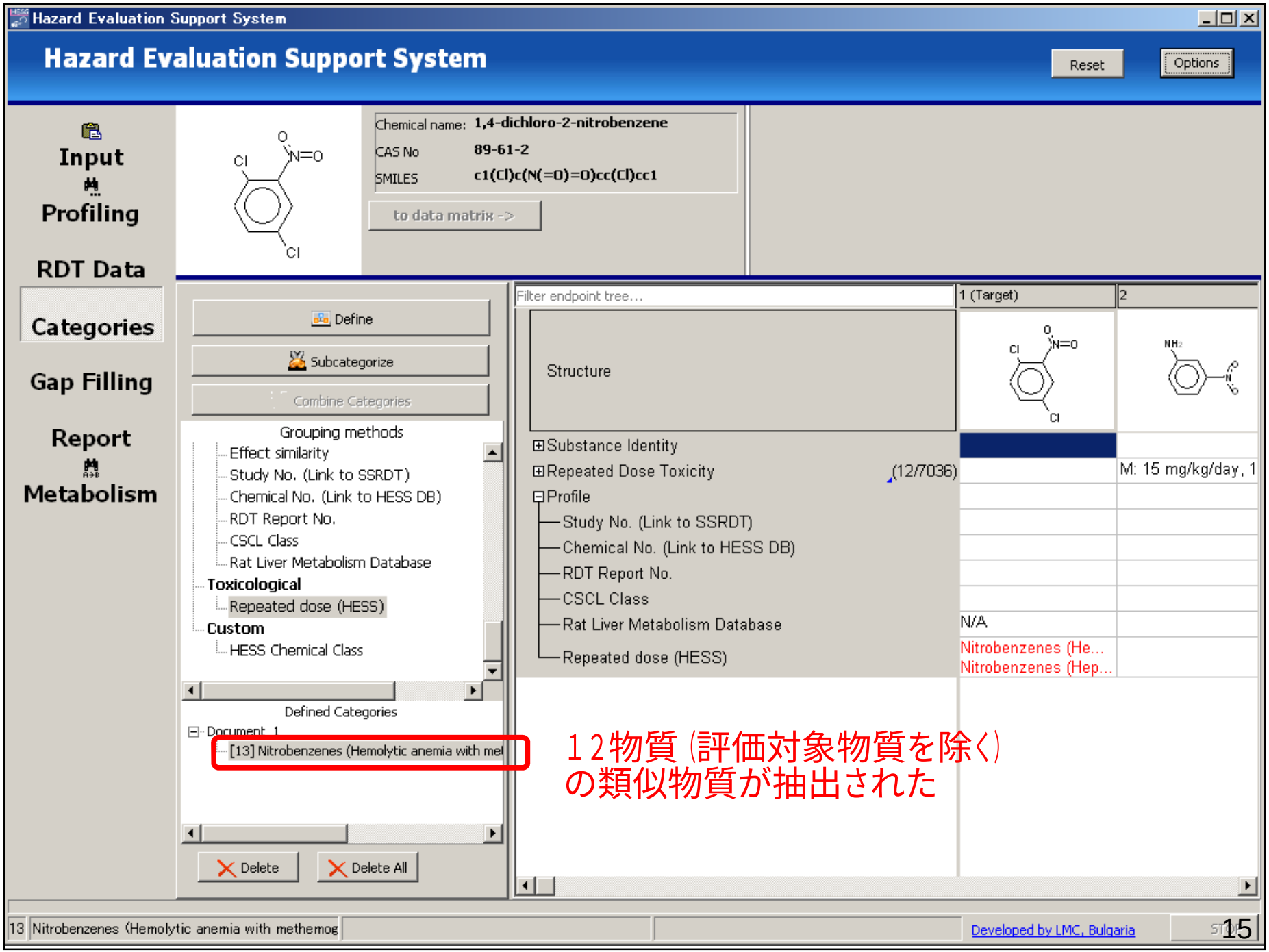

Repeated dose (HESS) (Toxicological) – Profiling Scheme Browser
Advanced
カテゴリーに関連する反復投与毒性所見
Repeated dose (HESS) - Category defi
Profile Description
2-Imidazolidinethiones (Thyrot...
4,4'-Methylenedianilines/Benzid...
Acrylamides (Neurotoxicity) Ra...
Aliphatic amines (Mucous memb...
Aliphatic nitriles (Hepato toxicit...
Aliphatic/Alicyclic hydrocarbons...
Anilines (Hemolytic anemia with...
Anilines (Hepato toxicity) Rank C
Azobenzenes (Hemolytic anemi...
Benzene/Naphthalene sulfonic ...
Benzenesulfonamides (Toxicity ...
Diphenyl Disulphides (Hemolytic...
Ethyleneglycol Alkylethers (He...
Ethyleneglycol Alkylethers (Tes...
Halobenzenes (Hepato toxicity...
Halobenzenes (Renal toxicity) ...
Halogenated Aliphatic Compou...
Hydrazines (Hemolytic anemia ...
N-Alkyl-N'-phenyl-p-phenylene...
Nitrobenzenes (Hemolyt
Nitrobenzenes (Hepato
Nitrobenzenes (Testicula
Nitrophenols/Harophenc
o-/p-Aminophenols (Her
Organophosphates (Neurotoxi...
Oximes (Hemolytic anemia with...
p-Alkylphenols (Hepatotoxicity)...
p-Aminophenols (Renal toxicity...
Phenols (Mucous membrane irri...
Phenyl phoshates (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 methemoglobinanemia) Rank A
1. Toxicity Informat
The mechanism
1) Nitrobenzene
2) Anilines are
3) N-hydroxyl
methaemoglo
observed in h
4) Erythrocytes
in the above
5) Phagocytosis
6) As a result, d
ase of
entation
compen
histopatholog
NO2
Gut microflora
2. Observed Effects
There are 25 RDT
In the studies of nitrobenzens without phenol or benzoic acid structure (Nos. 1-13), the findings related to hemolytic
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
Clear Table
Apply to Profile
Cancel


Repeated dose (HESS) (Toxicological) – Profiling Scheme Browser
Basic
Load
Save
Save as..
Close
Options
カテゴリーの定義の確認
Repeated dose (HESS) - Category definiti
2-Imidazolidinethiones (Thyrotoxici...
4,4'-Methylenedianilines/Benzidine...
Acrylamides (Neurotoxicity) Rank C
Aliphatic amines (Mucous membran...
Aliphatic nitriles (Hepato toxicity) ...
Aliphatic/Alicyclic hydrocarbons (Al...
Anilines (Hemolytic anemia with me...
Anilines (Hepato toxicity) Rank C
Azobenzenes (Hemolytic anemia wi...
Benzene/Naphthalene sulfonic acid...
Benzenesulfonamides (Toxicity to ...
Diphenyl Disulphides (Hemolytic an...
Ethyleneglycol Alkylethers (Hemoly...
Ethyleneglycol Alkylethers (Testicu...
Halobenzenes (Hepato toxicity) Ra...
Halobenzenes (Renal toxicity) Ran...
Halogenated Aliphatic Compounds ...
Hydrazines (Hemolytic anemia with...
N-Alkyl-N'-phenyl-p-phenylenedia...
Nitrobenzenes (Hemolytic anemia ...
Nitrobenzenes (Hepato toxicity) R...
Nitrobenzenes (Testicular toxicity) ...
Nitrophenols/Harophenols (Energy...
o-/p-Aminophenols (Hemolytic ane...
Organophosphates (Neurotoxicity)...
Oximes (Hemolytic anemia with me...
p-Alkylphenols (Hepatotoxicity) Ra...
p-Aminophenols (Renal toxicity) R...
Phenols (Mucous membrane irritati...
Phenyl phoshates (Lipodosis of adr...
Phthalate esters (Testicular toxicit...
Polycyclic Aromatic Hydrocarbons (...
Trinitrophenol (Hemolytic anemia) ...
Boundaries
Training set
NEW
AND
OR
NOT
Clear
Tidy
Delete
Boundary Options
Metabolism
Fragment
c1(N(V5)(=O)=O)c("*Exh19")c("*Exh19")c("*Exh19")c("*Exh19")c1"*Exh19"
Edit
Common Fragments
Definition
1
2
3
4
5
6
7
Exh19
H
F
Cl
Br
I
Profile Comments


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
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 ->
反復投与毒性試験データの抽出
②
Gather
①
Databases
Repeated dose toxicity NEDO
Filter endpoint tree...
1 (Target)
Structure
Substance Identity
Profile
Study No. (Link to SSRD
Chemical No. (Link to HE
RDT Report No.
Rat Liver Metabolism Database
CSCL Class
Repeated dose (HESS)
NEDO HESS
No data found.
OK
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。
1 Single chemical
Developed by LMC, Bulgaria


Input
Profiling
RDT Data
Categories
検討するカテゴリーの選択
Anemia
Liver effect
Gap Filling
Report
Total LOEL

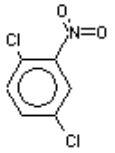
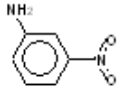
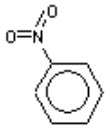
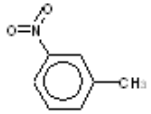
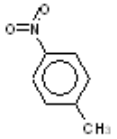

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
類似物質の抽出
Input
Profiling
RDT Data
Categories
Gap Filling
Metabolism
Report
Chemical name:
CAS No 89-61-2
SMILES c1(Cl)c(N
to data matrix
②
Define
Subcategorize
Combine Categories
Grouping methods
Organic functional groups, Norbert Ha
Structure similarity
Effect similarity
Study No. (Link to SSRDT)
Chemical No. (Link to HESS DB)
RDT Report No.
Rat Liver Metabolism Database
CSCL Class
Toxicological
Repeated dose (HESS)
Custom
①
Defined Categories
Document_1
③
Repeated dose (HESS)
Target(s) profiles
Nitrobenzenes (Hemolytic anemia with methemoglobinanemia) Rank A
Nitrobenzenes (Hepato toxicity) Rank C
④
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) Ran
Anilines (Hemolytic anemia with methemoglobinanemia) Rank A
Anilines (Hepato toxicity) Rank C
Azobenzenes (Hemolytic anemia with methemoglobinanemia) Rank B
Benzene/Naphthalene sulfonic acids (Less susceptible) Rank C
Benzenesulfonamides (Toxicity to Urinary System) Rank B
Diphenyl Disulphides (Hemolytic anemia with methemoglobinanemia) F
Ethyleneglycol Alkylethers (Hemolytic anemia) Rank A
Ethyleneglycol Alkylethers (Testicular toxicity) Rank B
Combine profiles logically with
and
or
Invert result
Strict
OK
⑤
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
1 Single chemical
Developed by LMC, Bulgaria


Hazard Evaluation Support System
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 met
Delete
Delete All
Filter endpoint tree...
Structure
1 (Target)
2
Substance Identity
Repeated Dose Toxicity (12/7036)
M: 15 mg/kg/day, 1
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
13 Nitrobenzenes (Hemolytic anemia with methemog
Developed by LMC, Bulgaria

類似物質の
毒性試験データの確認

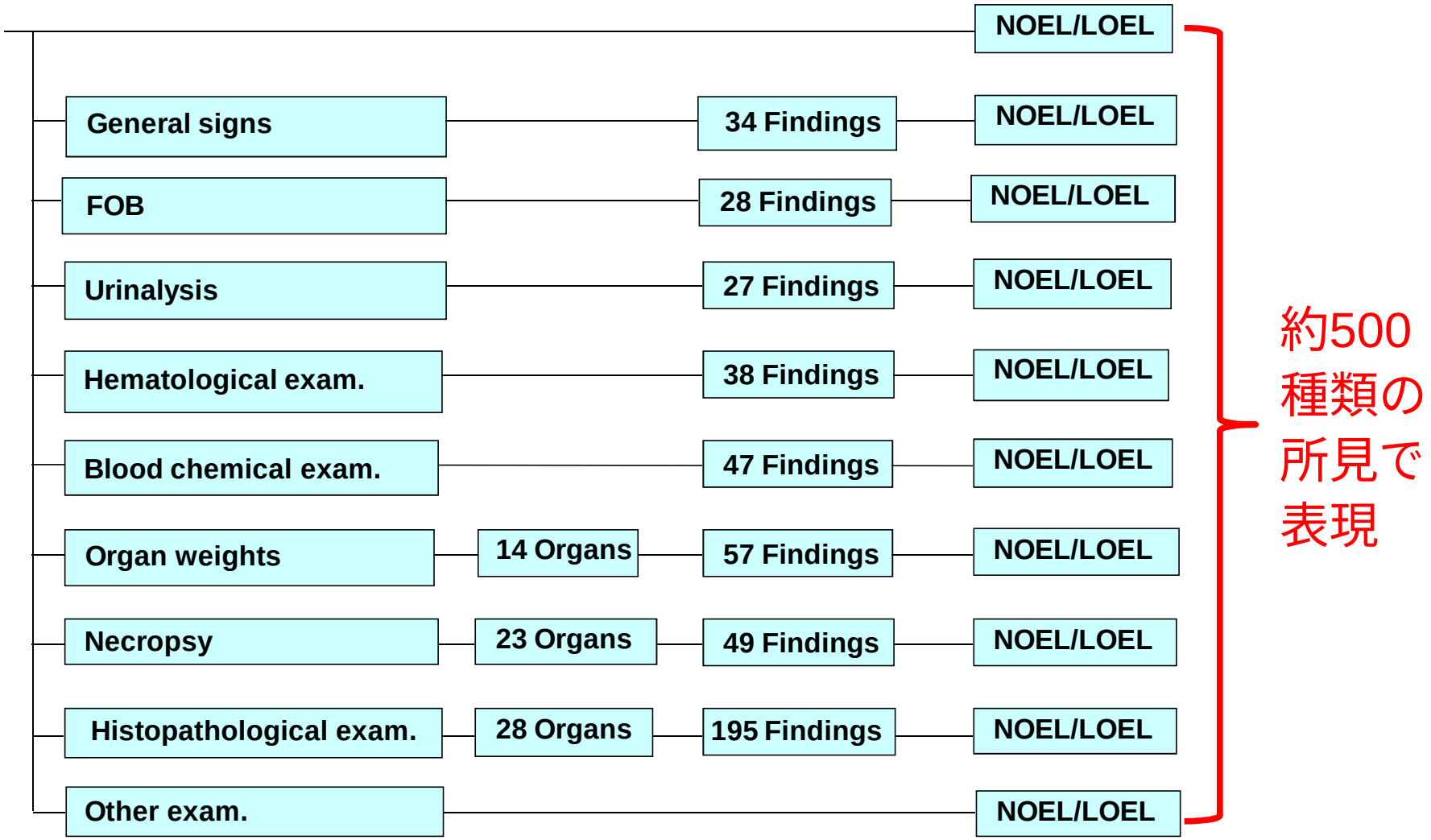
類似物質の反復投与毒性試験データの確認

類似物質

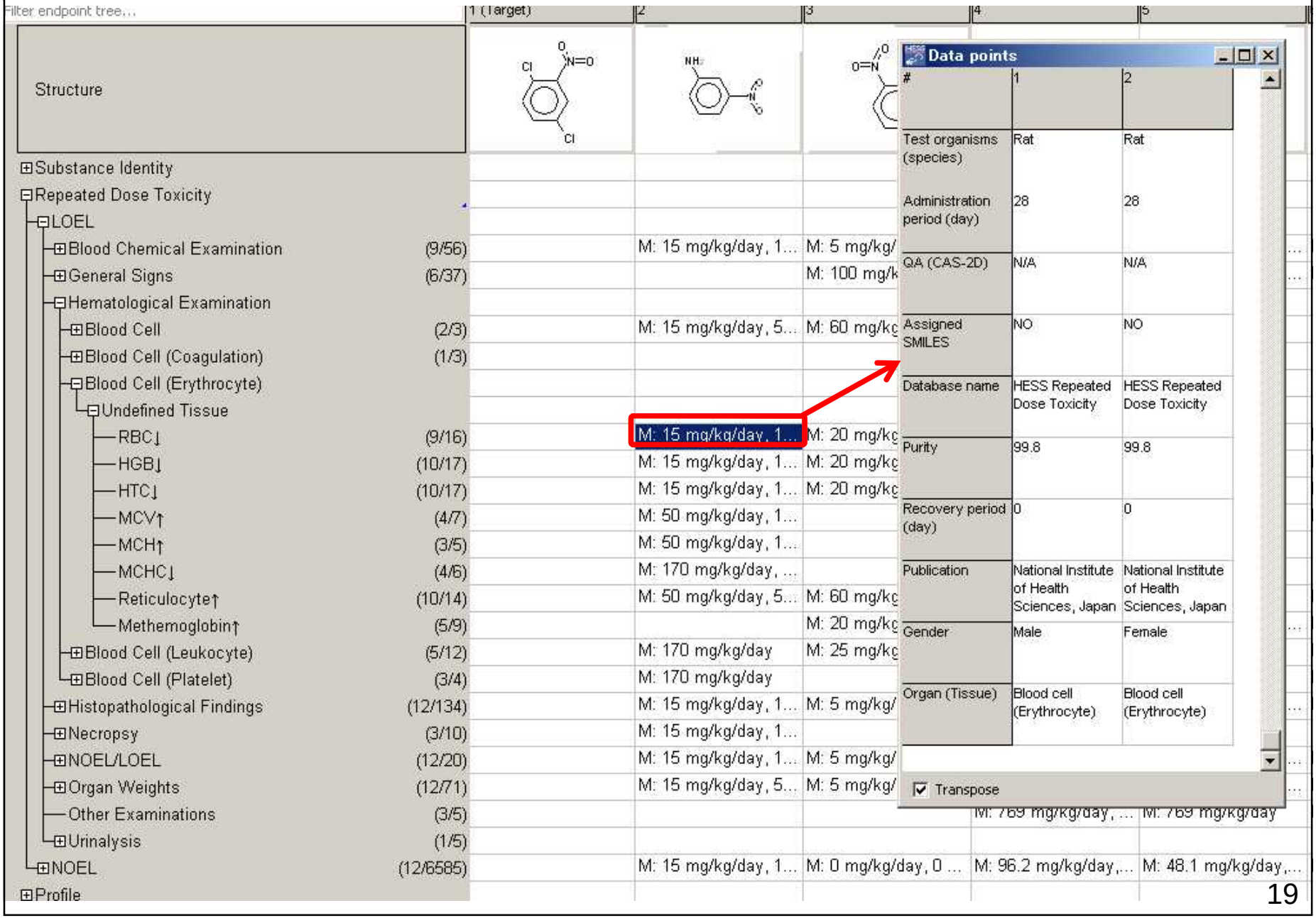
Filter endpoint tree...		1 (Target)	2	3	4	5
Structure						
⊞Substance Identity						
⊟Repeated Dose Toxicity						
⊟LOEL	(物質数/試験数)					
⊞Blood Chemical Examination	(9/56)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 mg/kg/day,...
⊞General Signs	(6/37)			M: 100 mg/kg/day, ...	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						

各所見に対するLOELを物質間で横並びに比較

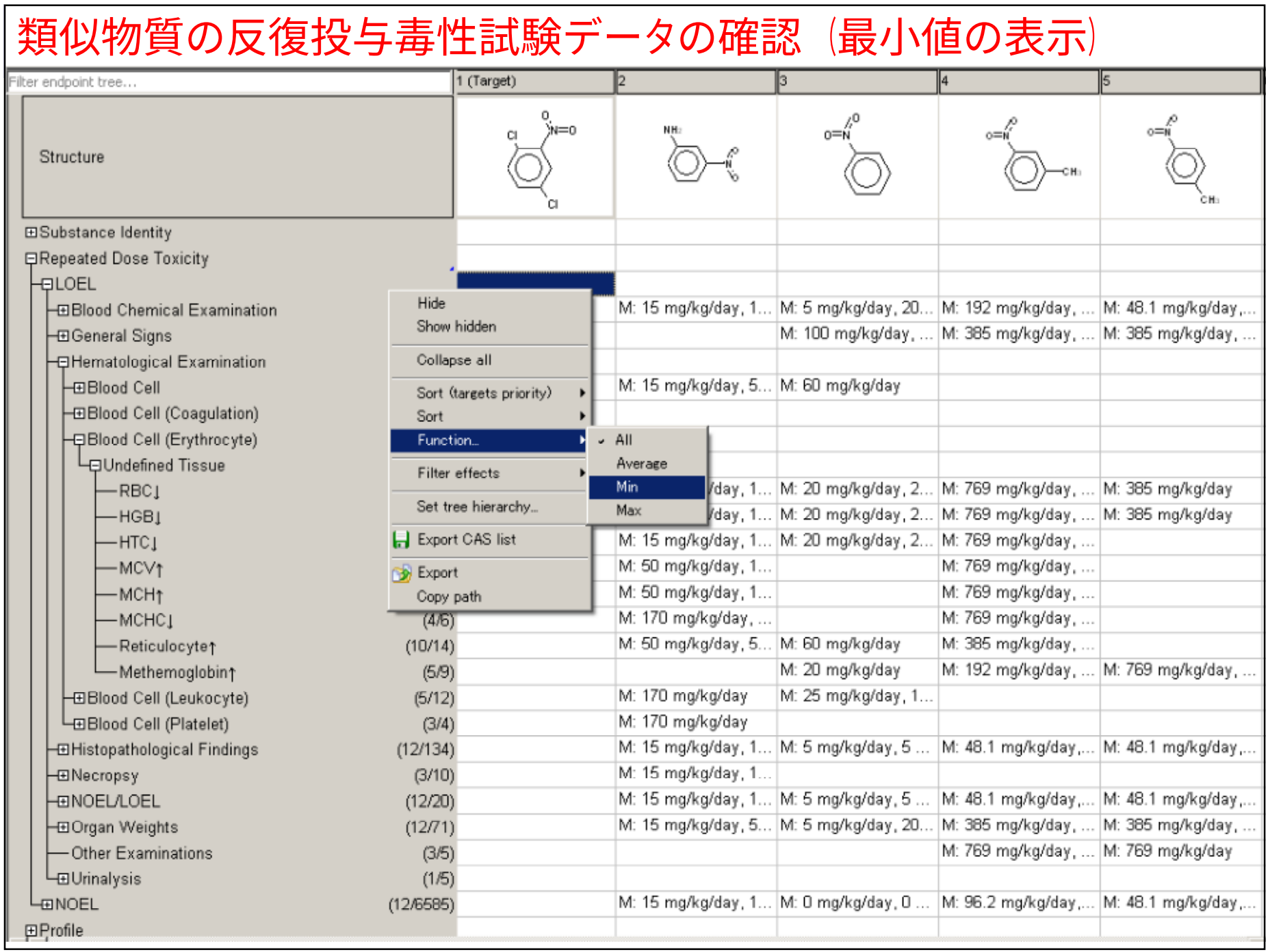
HESSにおける反復投与毒性試験データのデータストラクチャー



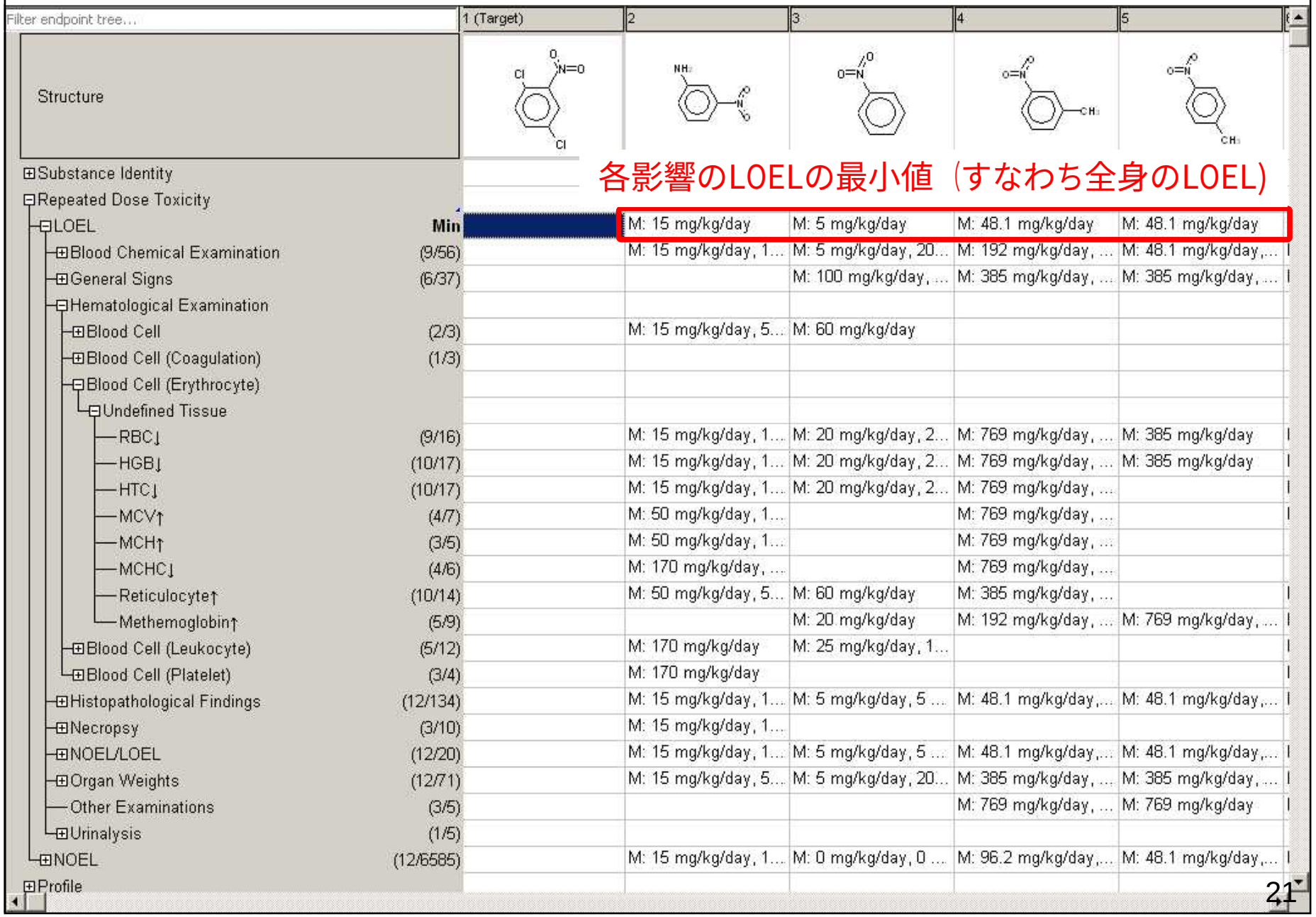
類似物質の反復投与毒性試験データの確認（試験条件の確認）



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）



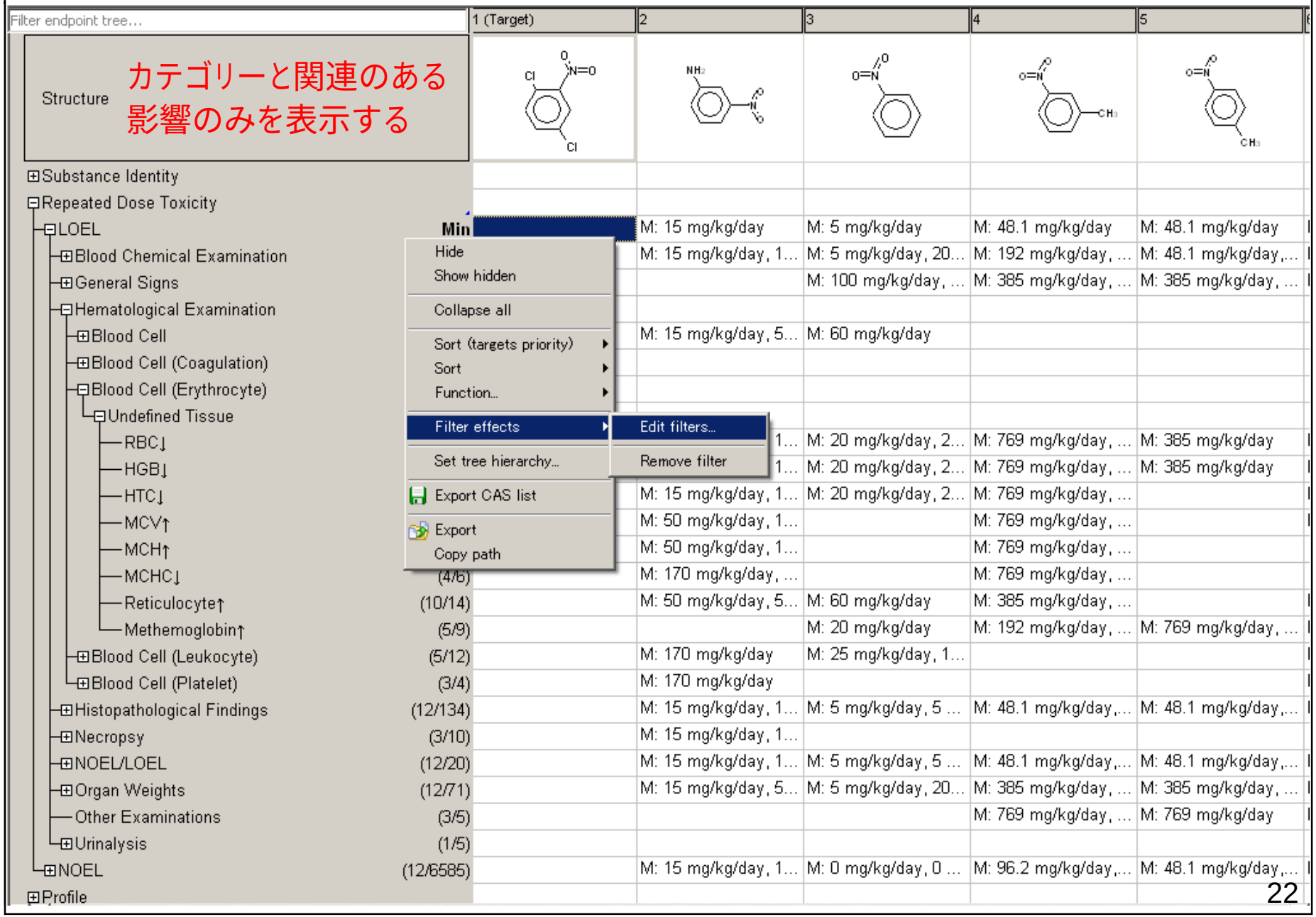
類似物質の反復投与毒性試験データの確認（最小値の表示）



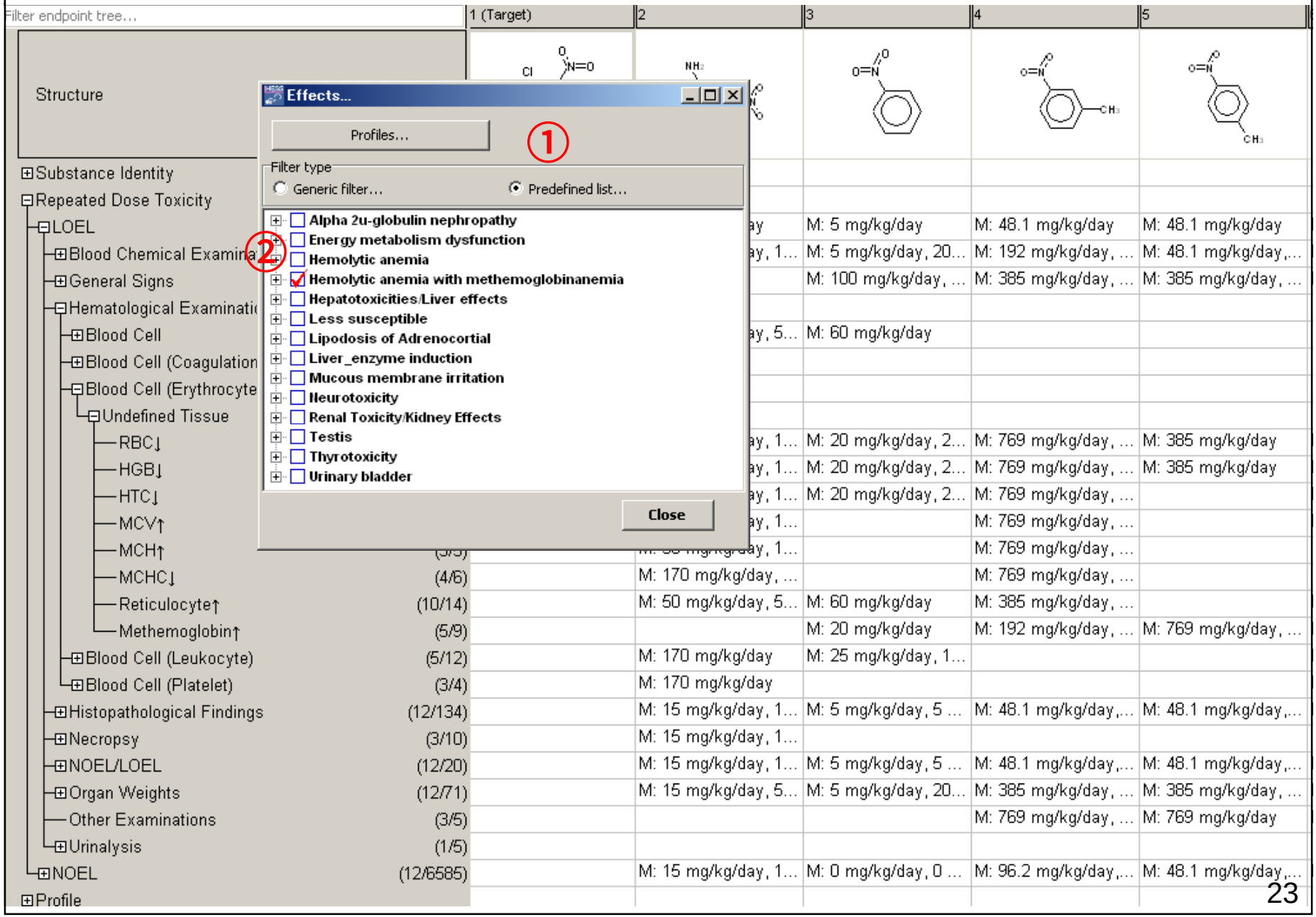
Filter endpoint tree...		1 (Target)	2	3	4	5
Structure						
⊞Substance Identity						
⊟Repeated Dose Toxicity						
⊟LOEL	Min		M: 15 mg/kg/day	M: 5 mg/kg/day	M: 48.1 mg/kg/day	M: 48.1 mg/kg/day
⊞Blood Chemical Examination	(9/56)		M: 15 mg/kg/day, 1...	M: 5 mg/kg/day, 20...	M: 192 mg/kg/day, ...	M: 48.1 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)	(1/3)					
⊟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						

各影響のLOELの最小値（すなわち全身のLOEL)

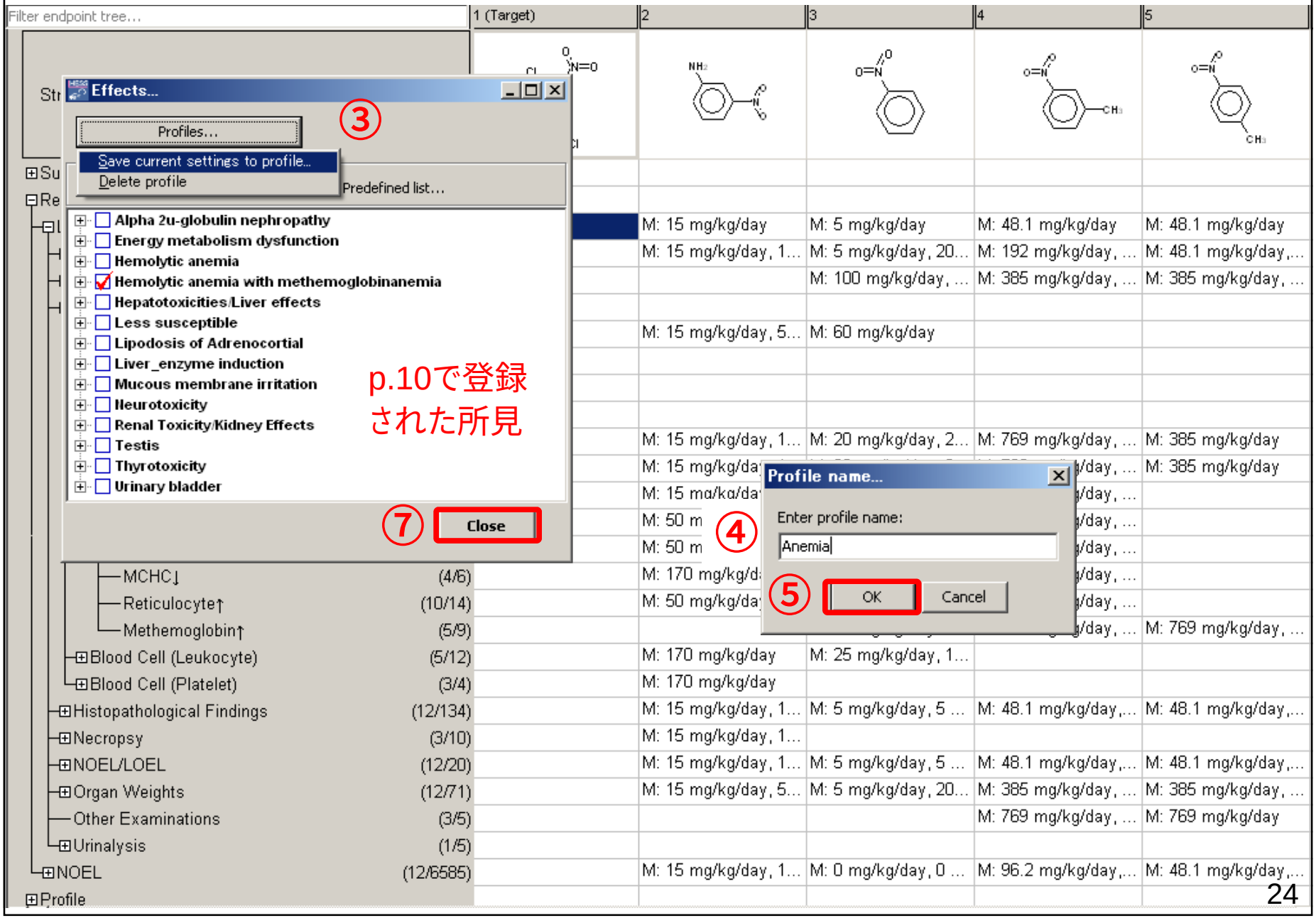
類似物質の反復投与毒性試験データの確認（影響フィルター）



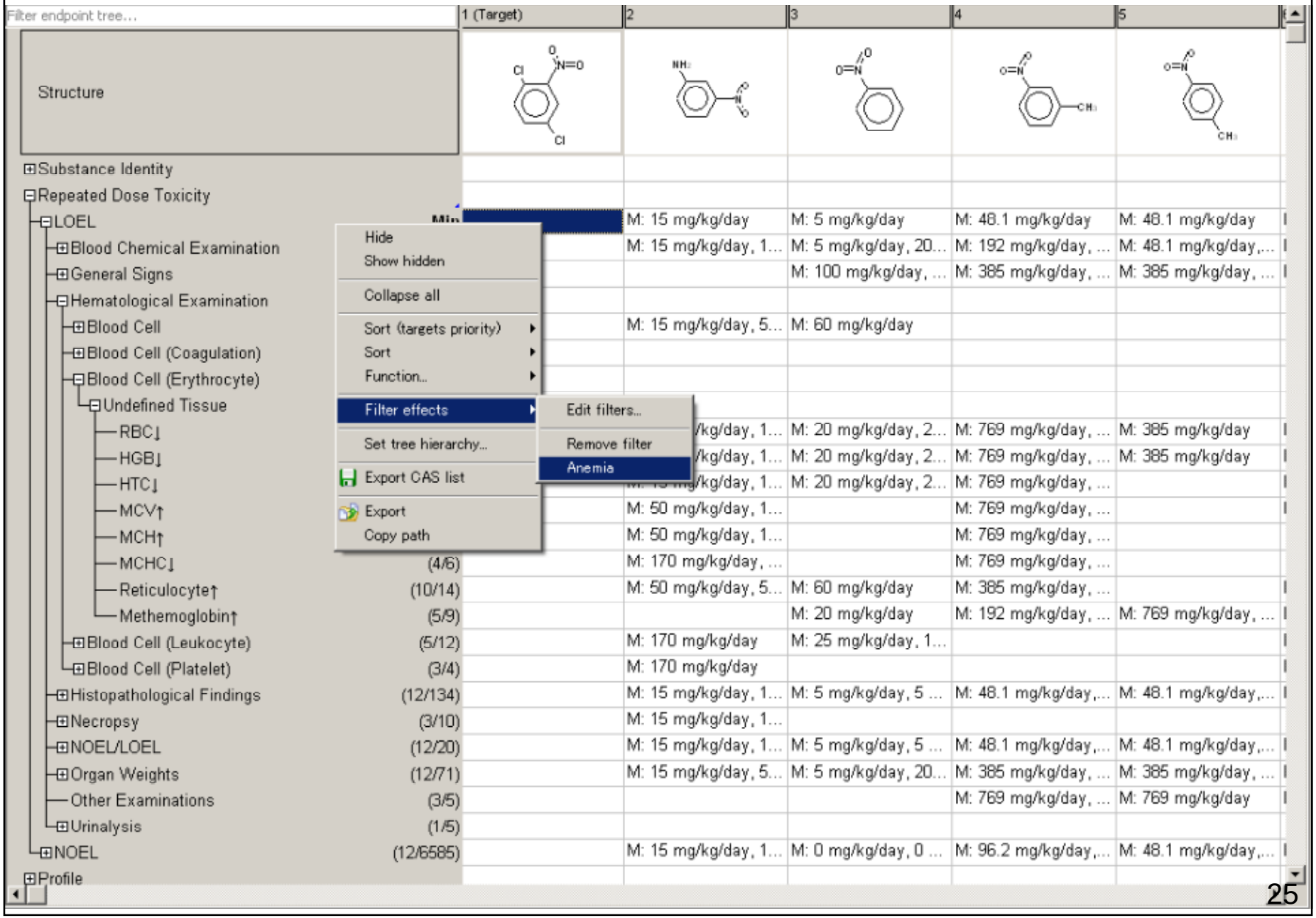
類似物質の反復投与毒性試験データの確認（影響フィルター）



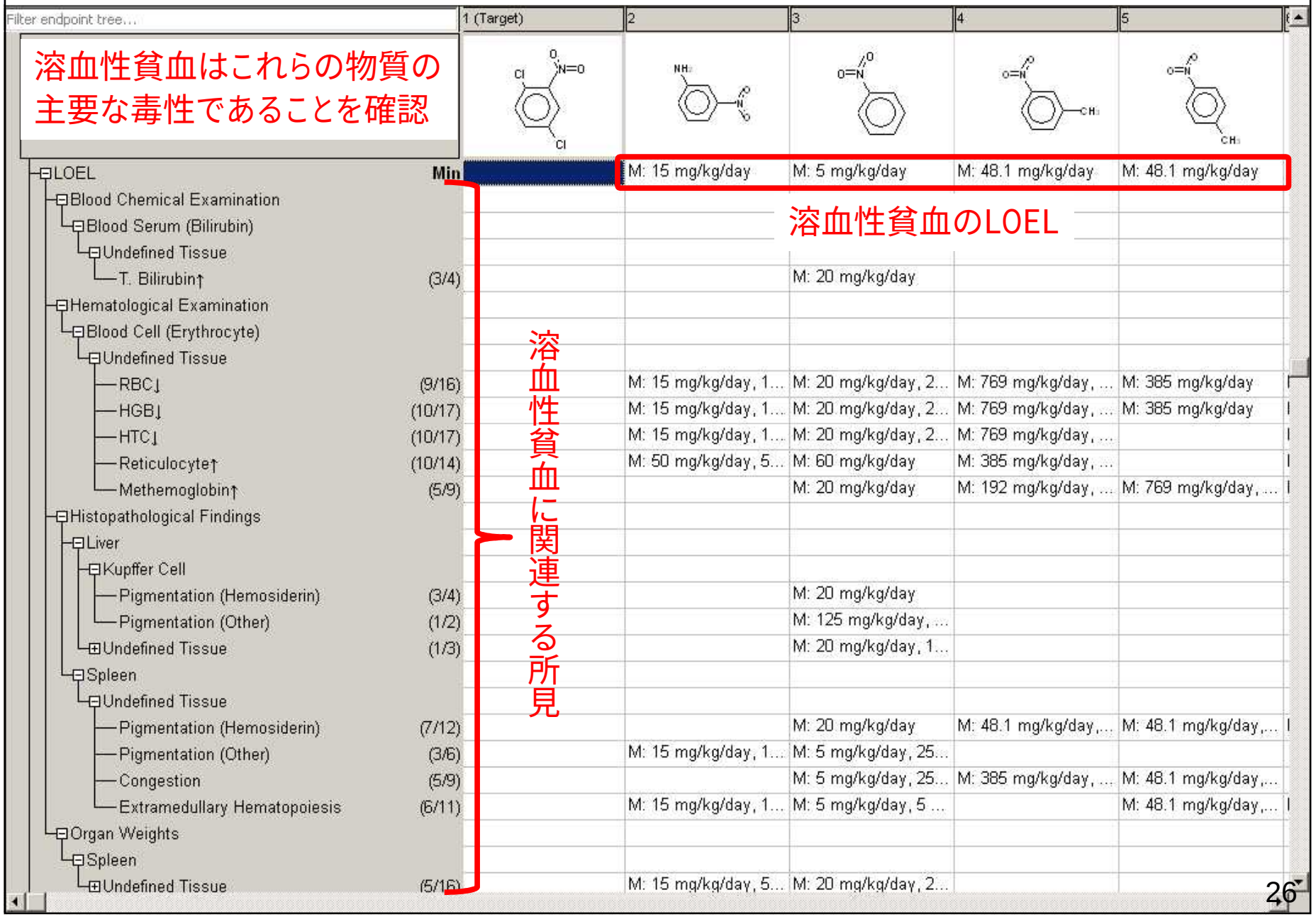
類似物質の反復投与毒性試験データの確認（影響フィルター）



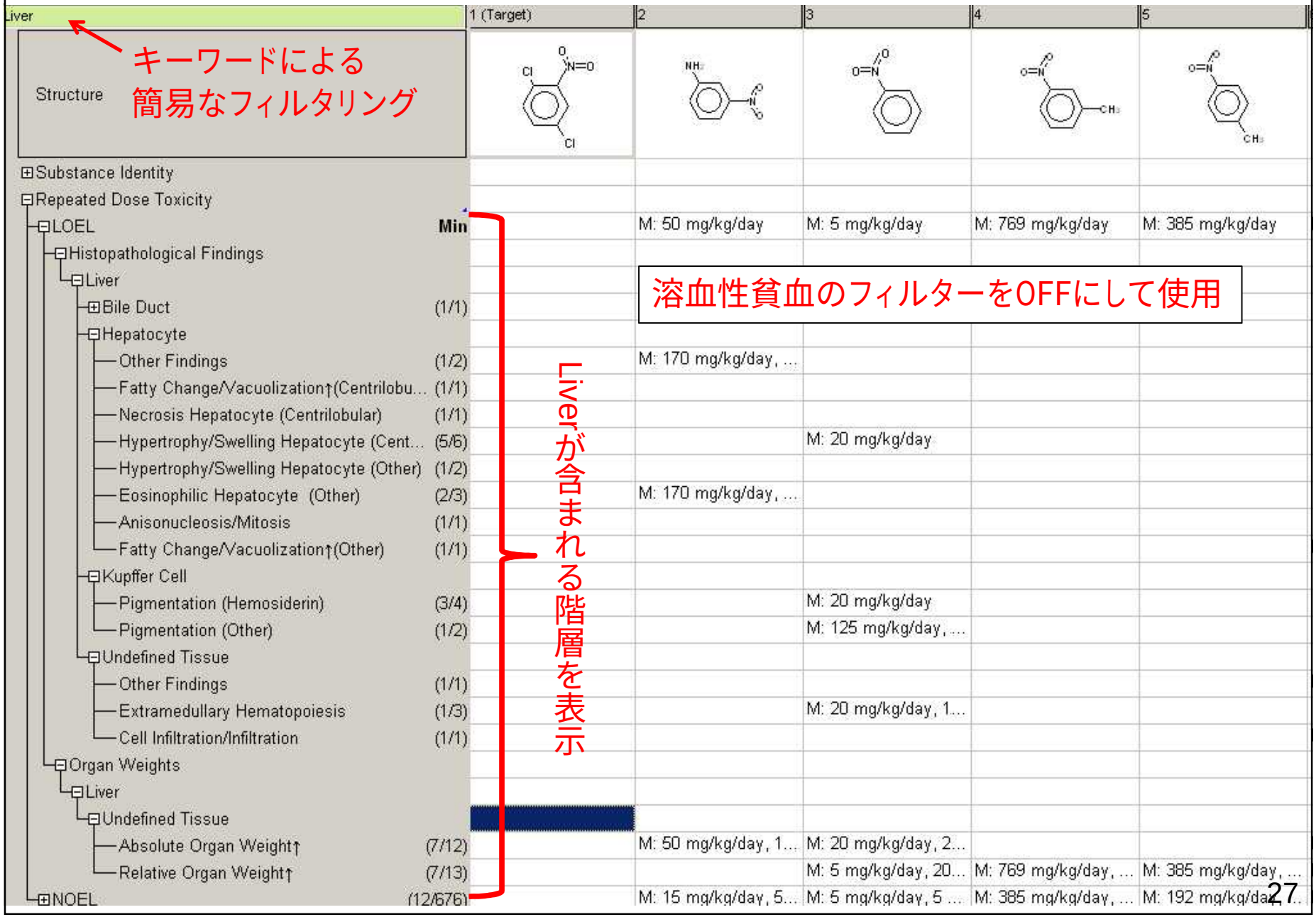
類似物質の反復投与毒性試験データの確認（影響フィルター）



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）

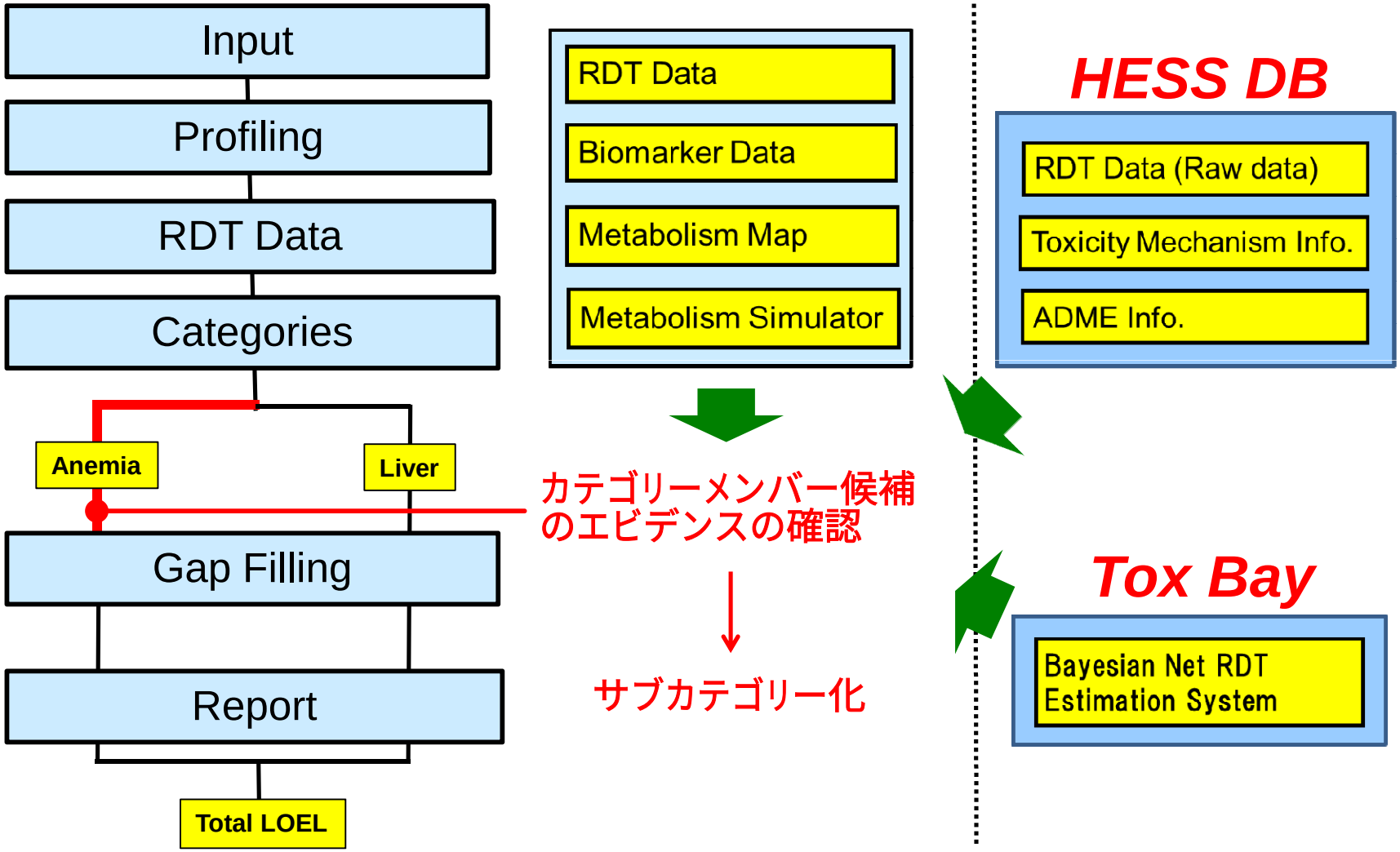


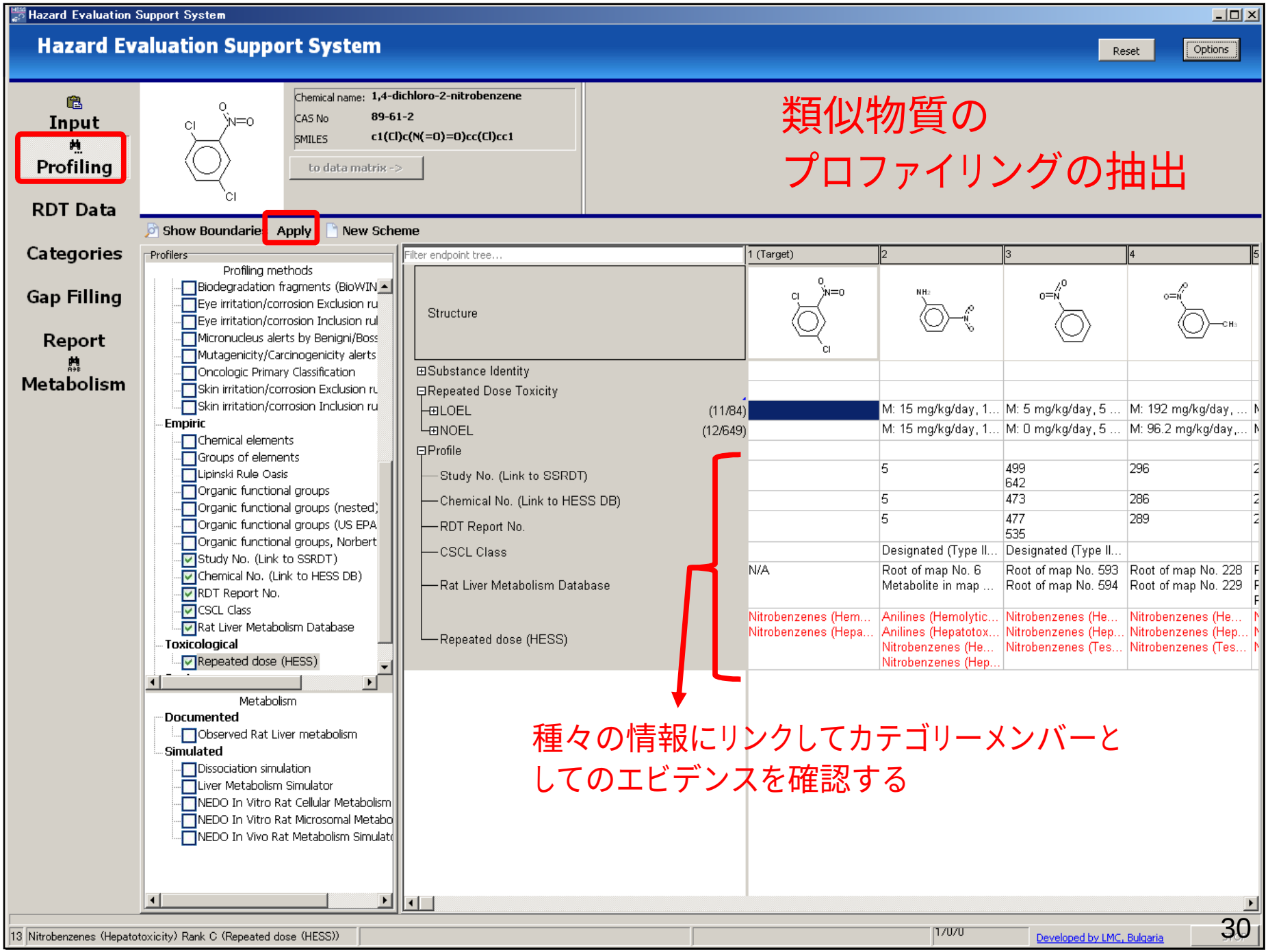
類似物質の反復投与毒性試験データの確認（影響フィルター）

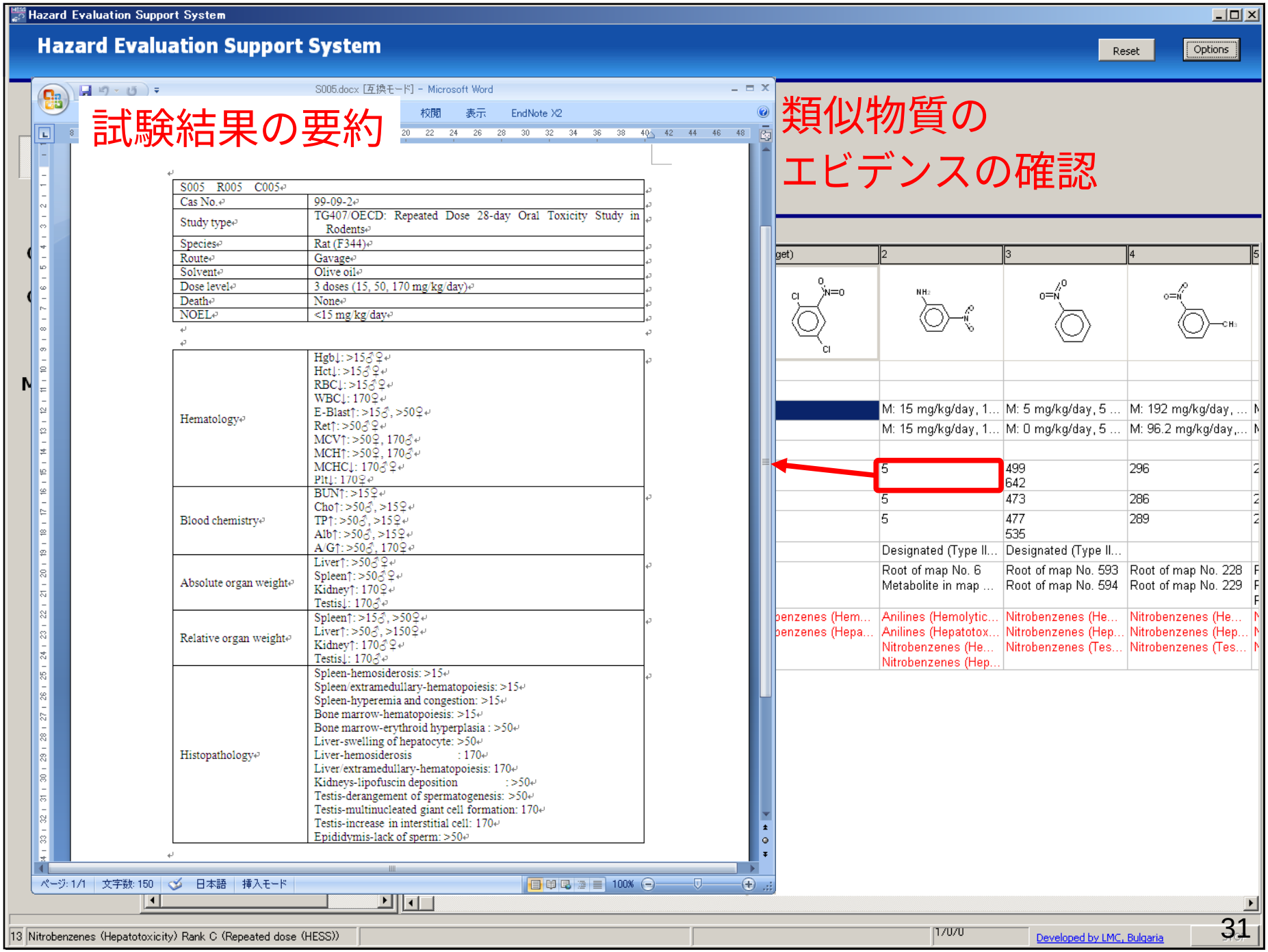


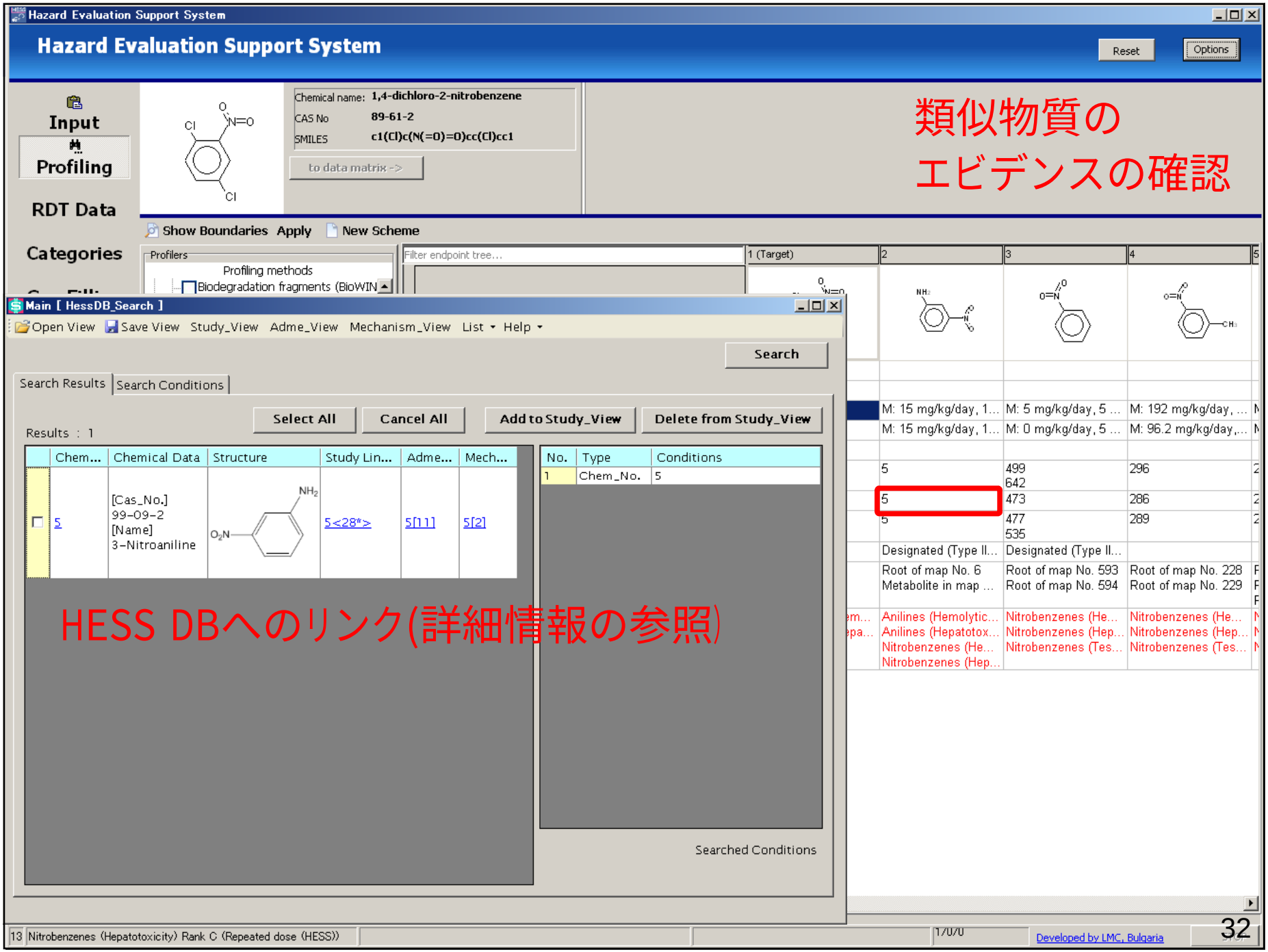
カテゴリーメンバーとしての
エビデンスの確認
⑷詳細情報へのリンク⑵

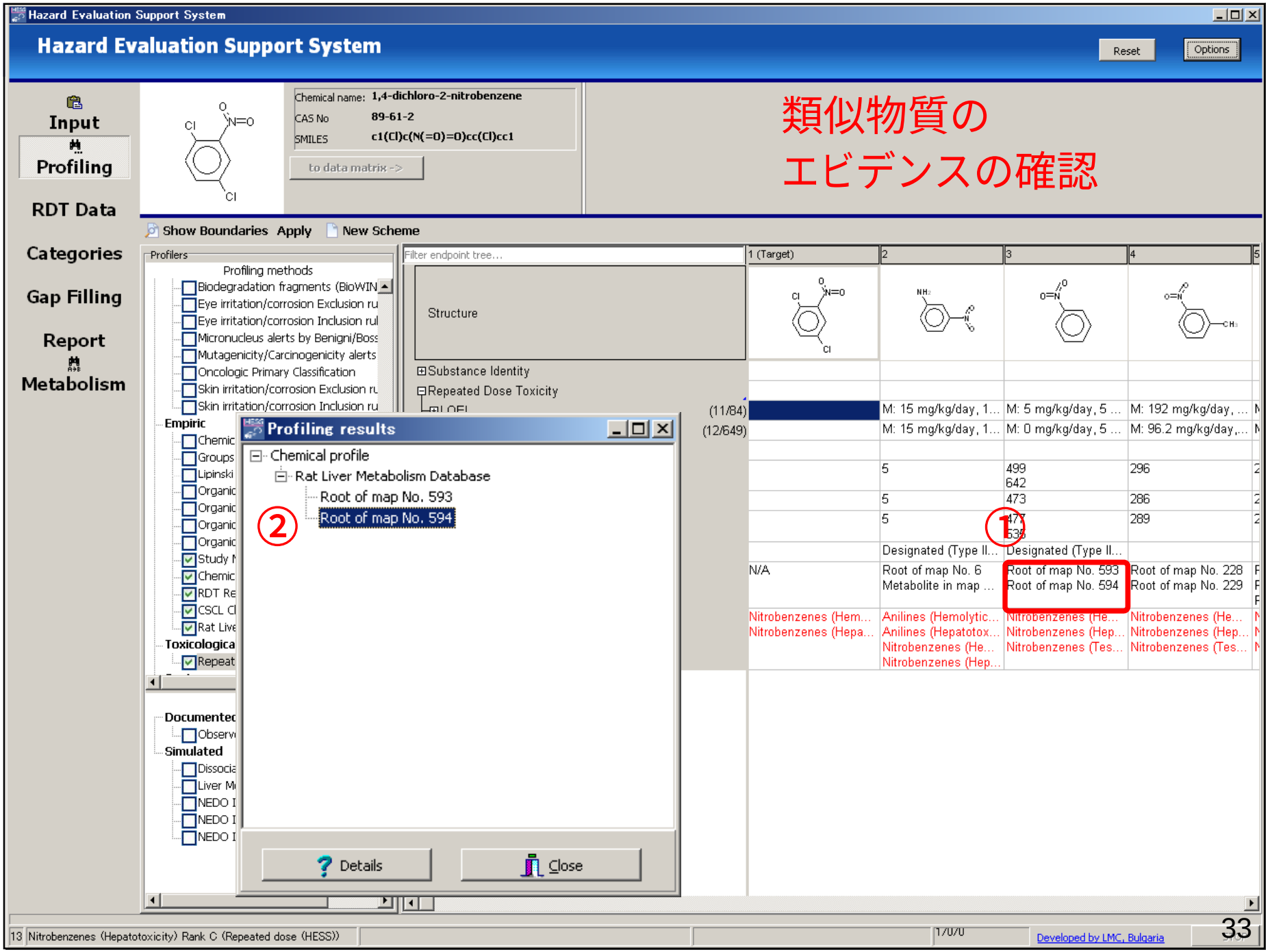
HESS

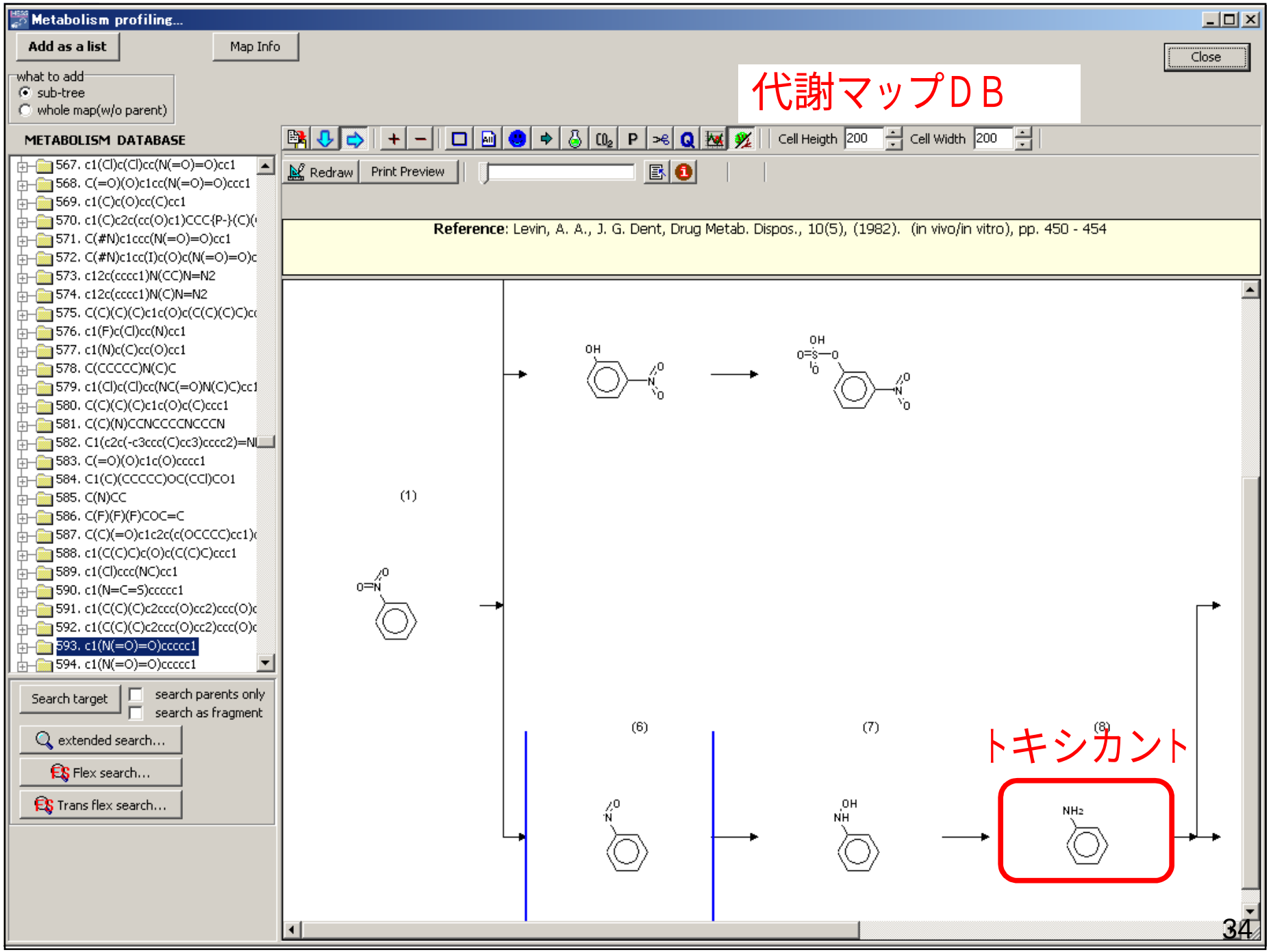

Input
Profiling
RDT Data
Categories
Anemia
Liver
Gap Filling
Report
Total LOEL
RDT Data
Biomarker Data
Metabolism Map
Metabolism Simulator
カテゴリーメンバー候補
のエビデンスの確認
サブカテゴリー化
HESS DB
RDT Data (Raw data)
Toxicity Mechanism Info.
ADME Info.
Tox Bay
Bayesian Net RDT
Estimation System

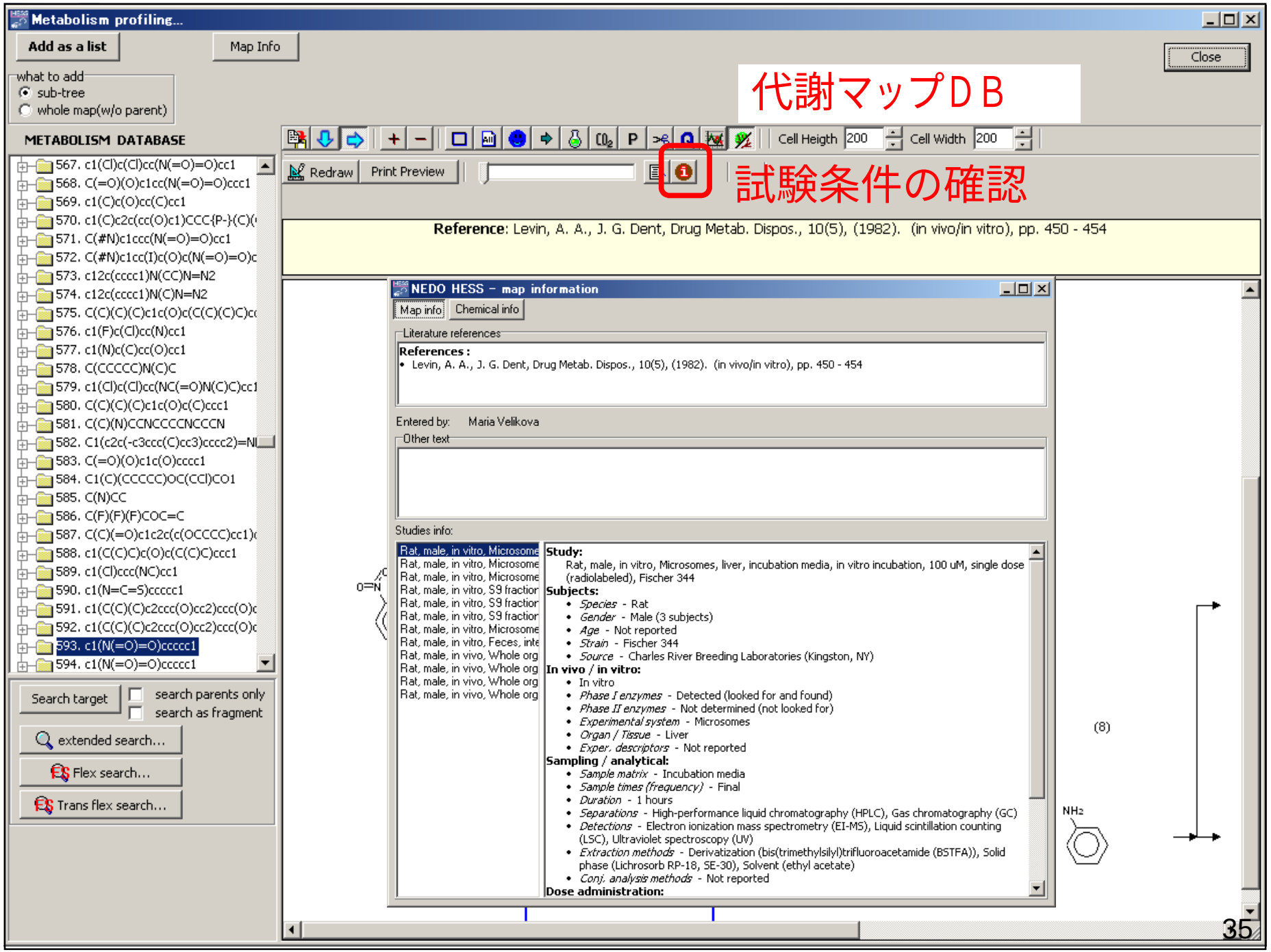

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
類似物質の
プロファイリングの抽出
Show Boundarie
Apply
New Scheme
Profilers
Profiling methods
Biodegradation fragments (BioWIN
Eye irritation/corrosion Exclusion ru
Eye irritation/corrosion Inclusion rul
Micronucleus alerts by Benigni/Boss
Mutagenicity/Carcinogenicity alerts
Oncologic Primary Classification
Skin irritation/corrosion Exclusion ru
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)
Metabolism
Documented
Observed Rat Liver metabolism
Simulated
Dissociation simulation
Liver Metabolism Simulator
NEDO In Vitro Rat Cellular Metabolism
NEDO In Vitro Rat Microsomal Metabo
NEDO In Vivo Rat Metabolism Simulat
Filter endpoint tree...
Structure
Substance Identity
Repeated Dose Toxicity
LOEL (11/84)
NOEL (12/649)
Profile
Study No. (Link to SSRDT)
Chemical No. (Link to HESS DB)
RDT Report No.
CSCL Class
Rat Liver Metabolism Database
Repeated dose (HESS)
1 (Target)
2
3
4
M: 15 mg/kg/day, 1...
M: 5 mg/kg/day, 5 ...
M: 192 mg/kg/day, ...
M: 15 mg/kg/day, 1...
M: 0 mg/kg/day, 5 ...
M: 96.2 mg/kg/day,...
5
499
642
296
5
473
286
5
477
535
289
Designated (Type II...
Designated (Type II...
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
Nitrobenzenes (Hem...
Nitrobenzenes (Hepa...
Anilines (Hemolytic...
Anilines (Hepatotox...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (Tes...
Nitrobenzenes (Tes...
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
13 Nitrobenzenes (Hepatotoxicity) Rank C (Repeated dose (HESS))
Developed by LMC, Bulgaria


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
S005.docx [互換モード] - Microsoft Word
校閲
表示
EndNote X2
試験結果の要約
類似物質の
エビデンスの確認
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♂♀
Plt↓: 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
get)
2
3
4
M: 15 mg/kg/day, 1...
M: 5 mg/kg/day, 5 ...
M: 192 mg/kg/day, ...
M: 15 mg/kg/day, 1...
M: 0 mg/kg/day, 5 ...
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
benzenes (Hem...
benzenes (Hepa...
Anilines (Hemolytic...
Anilines (Hepatotox...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (Tes...
Nitrobenzenes (Tes...
13 Nitrobenzenes (Hepatotoxicity) Rank C (Repeated dose (HESS))
Developed by LMC, Bulgaria

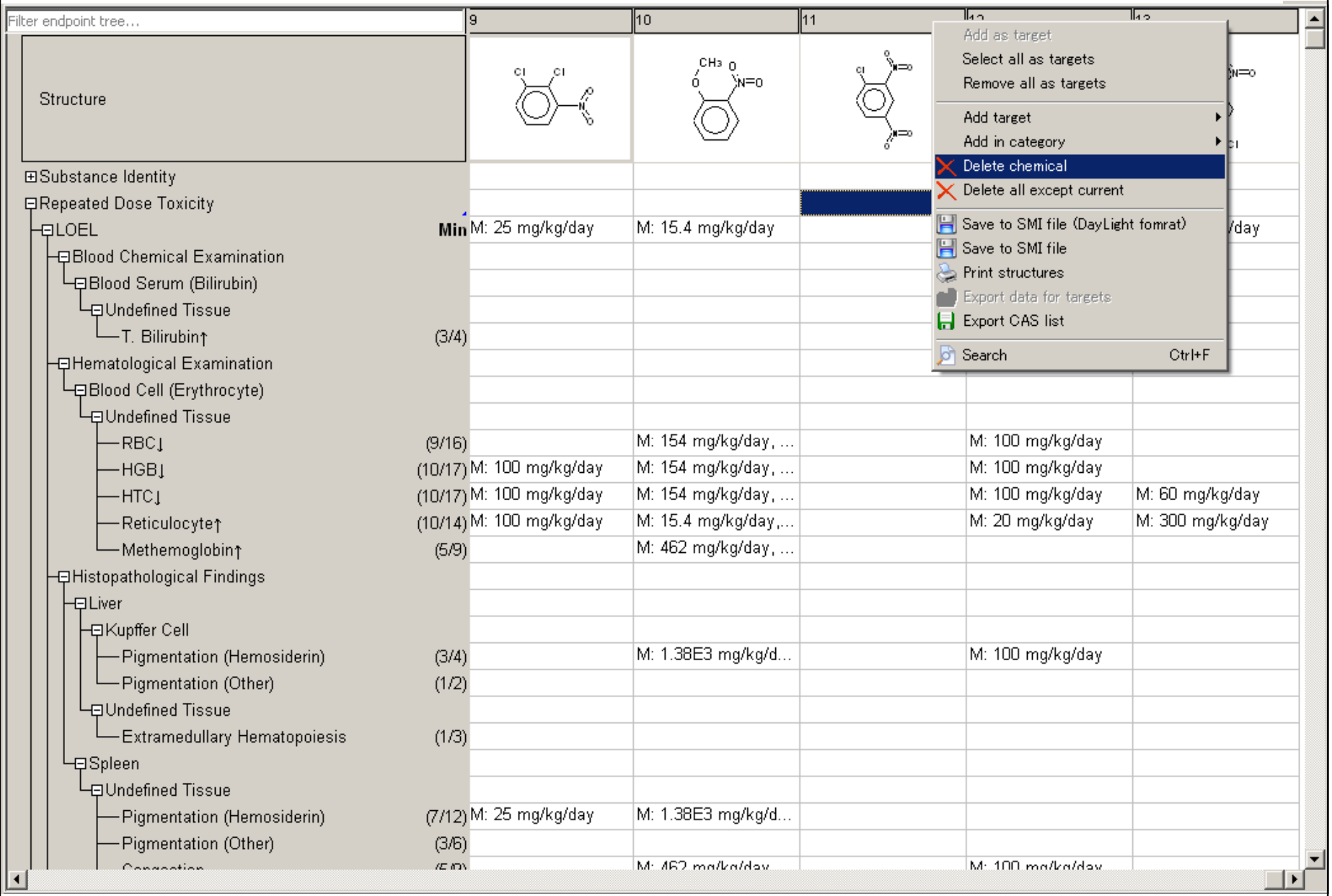

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
類似物質の
エビデンスの確認
Show Boundaries Apply New Scheme
Profilers
Profiling methods
Biodegradation fragments (BioWIN
Filter endpoint tree...
1 (Target)
2
3
4
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...
5
[Cas_No.]
99-09-2
[Name]
3-Nitroaniline
5<28*>
5[11]
5[2]
No.
Type
Conditions
1
Chem_No.
5
HESS DBへのリンク(詳細情報の参照)
Searched Conditions
M: 15 mg/kg/day, 1...
M: 5 mg/kg/day, 5 ...
M: 192 mg/kg/day, ...
M: 15 mg/kg/day, 1...
M: 0 mg/kg/day, 5 ...
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
Anilines (Hemolytic...
Anilines (Hepatotox...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (Tes...
Nitrobenzenes (Tes...
13 Nitrobenzenes (Hepatotoxicity) Rank C (Repeated dose (HESS))
Developed by LMC, Bulgaria


Hazard Evaluation Support System
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 ->
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 rul
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
Toxicologica
Repeat
Documented
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
②
Details
Close
Filter endpoint tree...
Structure
Substance Identity
Repeated Dose Toxicity
1 (Target)
2
3
4
5
(11/84)
(12/649)
M: 15 mg/kg/day, 1...
M: 5 mg/kg/day, 5 ...
M: 192 mg/kg/day, ...
M: 15 mg/kg/day, 1...
M: 0 mg/kg/day, 5 ...
M: 96.2 mg/kg/day,...
5
499
642
296
5
473
286
5
289
①
Designated (Type II...
Designated (Type II...
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
Nitrobenzenes (Hem...
Nitrobenzenes (Hepa...
Anilines (Hemolytic...
Anilines (Hepatotox...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (Tes...
Nitrobenzenes (He...
Nitrobenzenes (Hep...
Nitrobenzenes (Tes...
13 Nitrobenzenes (Hepatotoxicity) Rank C (Repeated dose (HESS))
Developed by LMC, Bulgaria
33

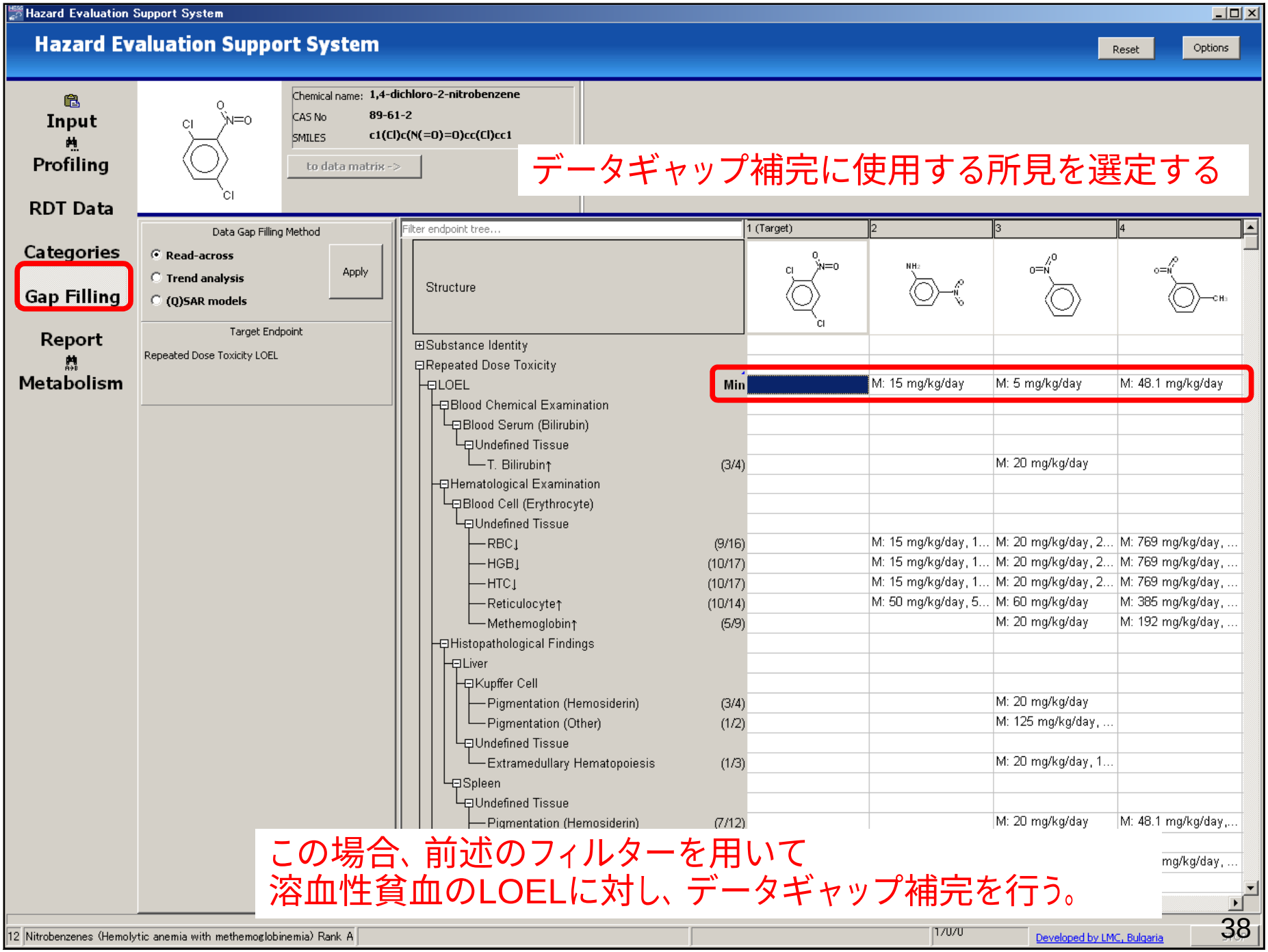

Metabolism profiling...
Add as a list
Map Info
Close
what to add
sub-tree
whole map(w/o parent)
代謝マップＤＢ
METABOLISM DATABASE
Cell Heigth 200
Cell Width 200
Redraw
Print Preview
Reference: Levin, A. A., J. G. Dent, Drug Metab. Dispos., 10(5), (1982). (in vivo/in vitro), pp. 450 - 454
567. c1(Cl)c(Cl)cc(N(=O)=O)cc1
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)c
576. c1(F)c(Cl)cc(N)cc1
577. c1(N)c(C)cc(O)cc1
578. C(CCCCC)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)CCNCCCCNCCCN
582. C1(c2c(-c3ccc(C)cc3)cccc2)=N
583. C(=O)(O)c1c(O)cccc1
584. C1(C)(CCCCC)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)ccccc1
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)ccccc1
594. c1(N(=O)=O)ccccc1
Search target
search parents only
search as fragment
extended search...
Flex search...
Trans flex search...
(1)
(6)
(7)
(8)
トキシカント

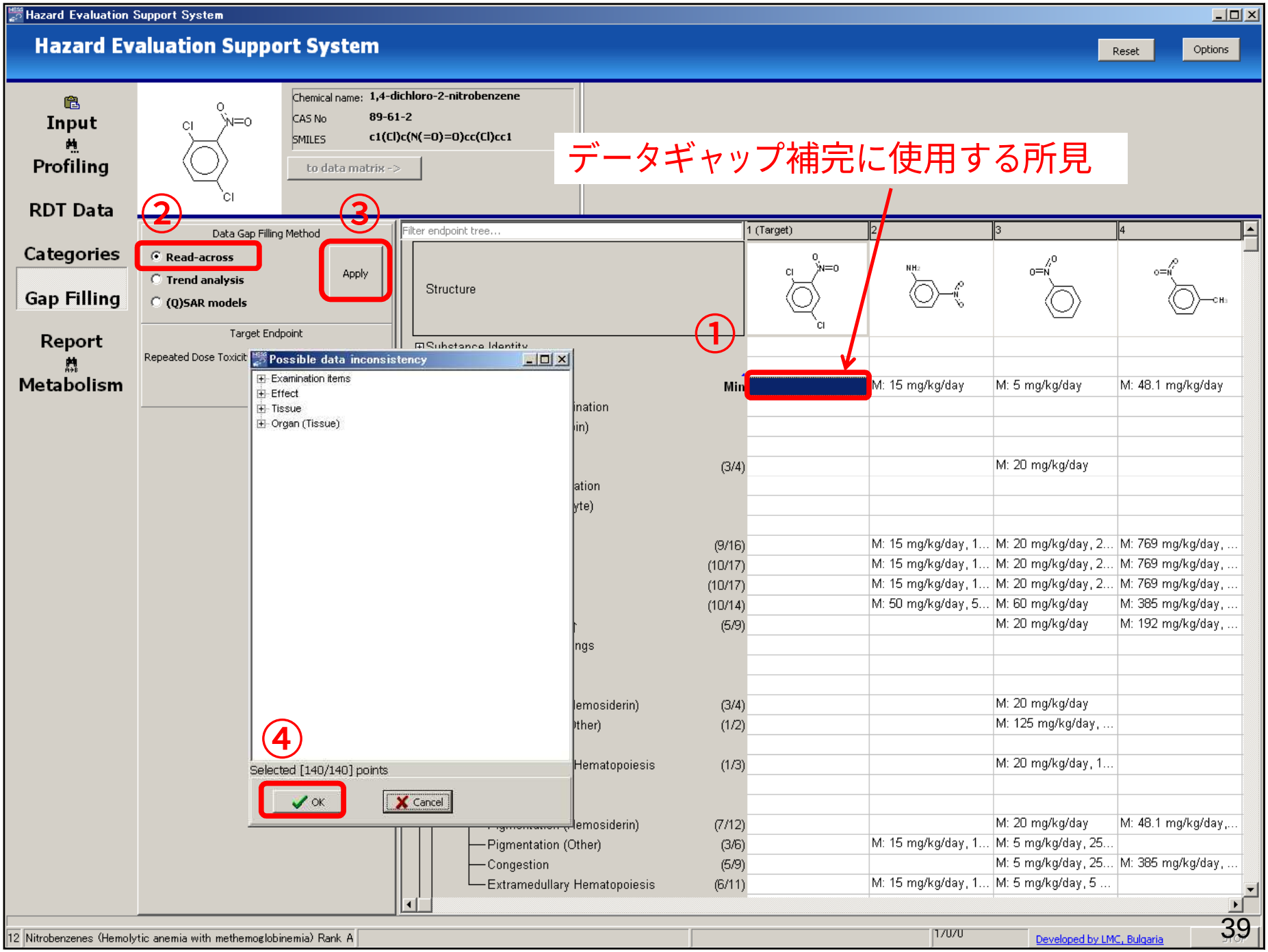

Metabolism profiling...
Add as a list
Map Info
Close
what to add
sub-tree
whole map(w/o parent)
代謝マップＤＢ
METABOLISM DATABASE
Cell Heigth 200
Cell Width 200
Redraw
Print Preview
試験条件の確認
Reference: Levin, A. A., J. G. Dent, Drug Metab. Dispos., 10(5), (1982). (in vivo/in vitro), pp. 450 - 454
NEDO HESS - 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:
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:
Search target
search parents only
search as fragment
extended search...
Flex search...
Trans flex search...
(8)
NH2

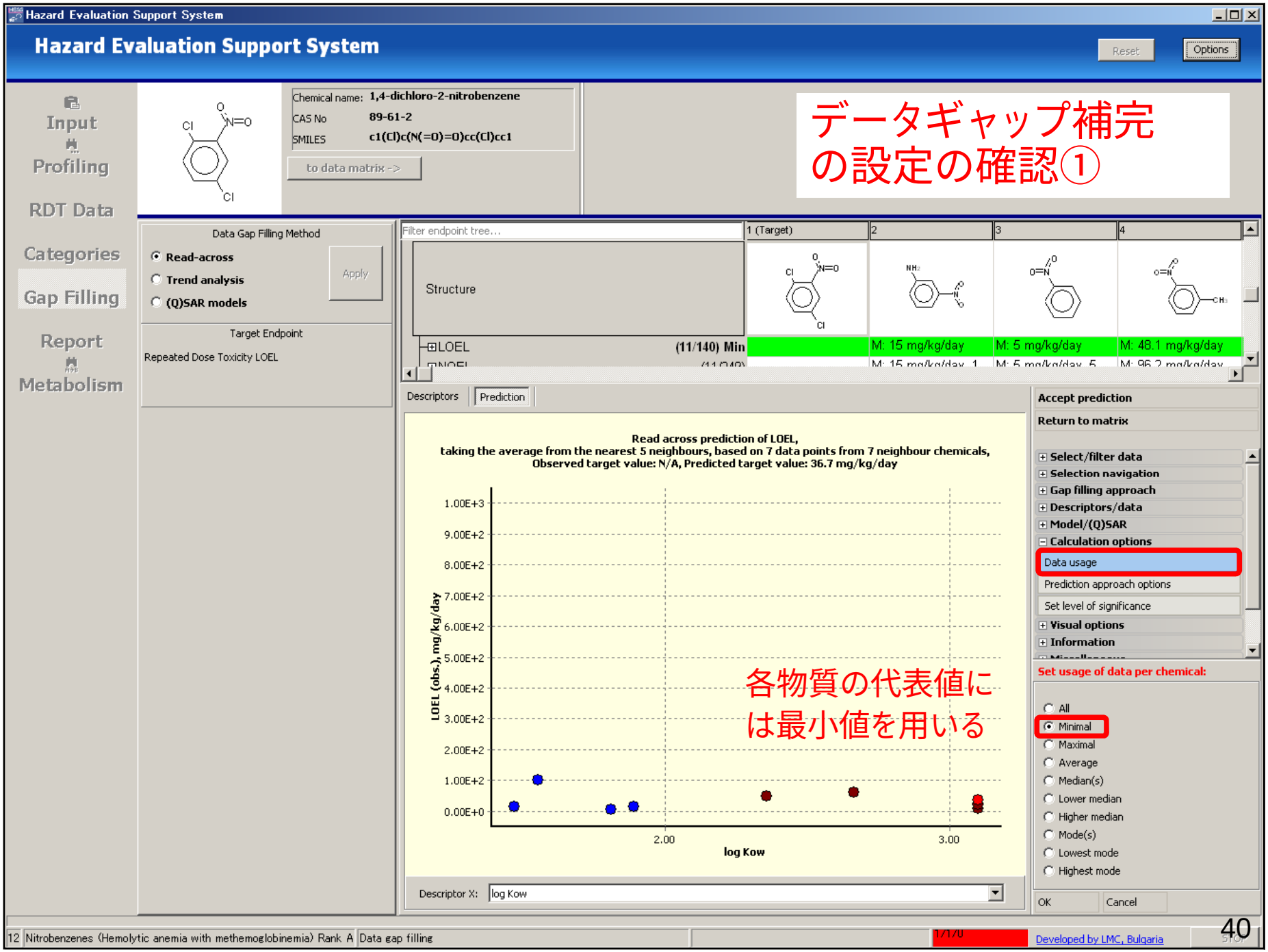
カテゴリーとして不適切と思われる物質を除外する方法

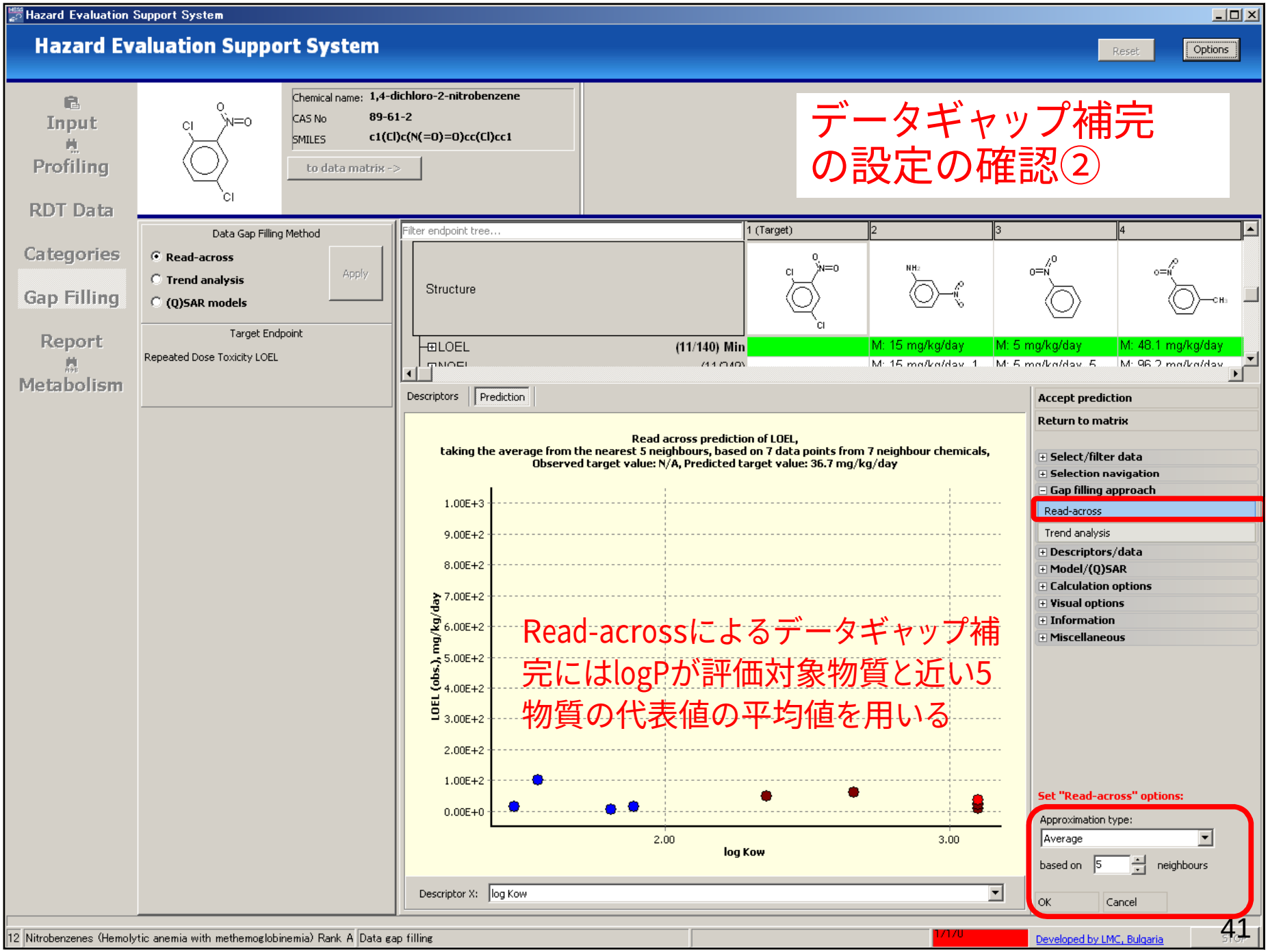


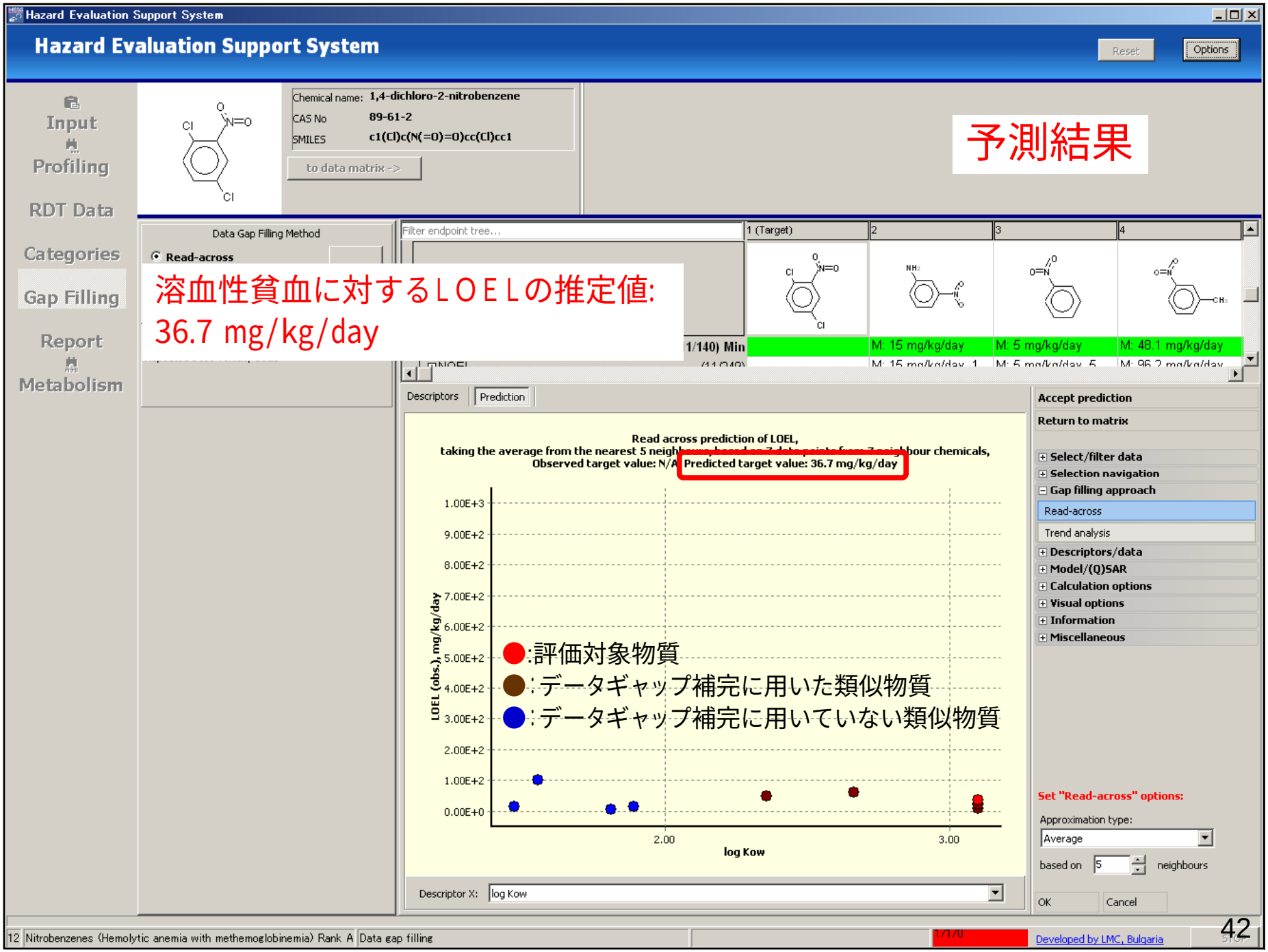
リードアクロスによる
データギャップ補完

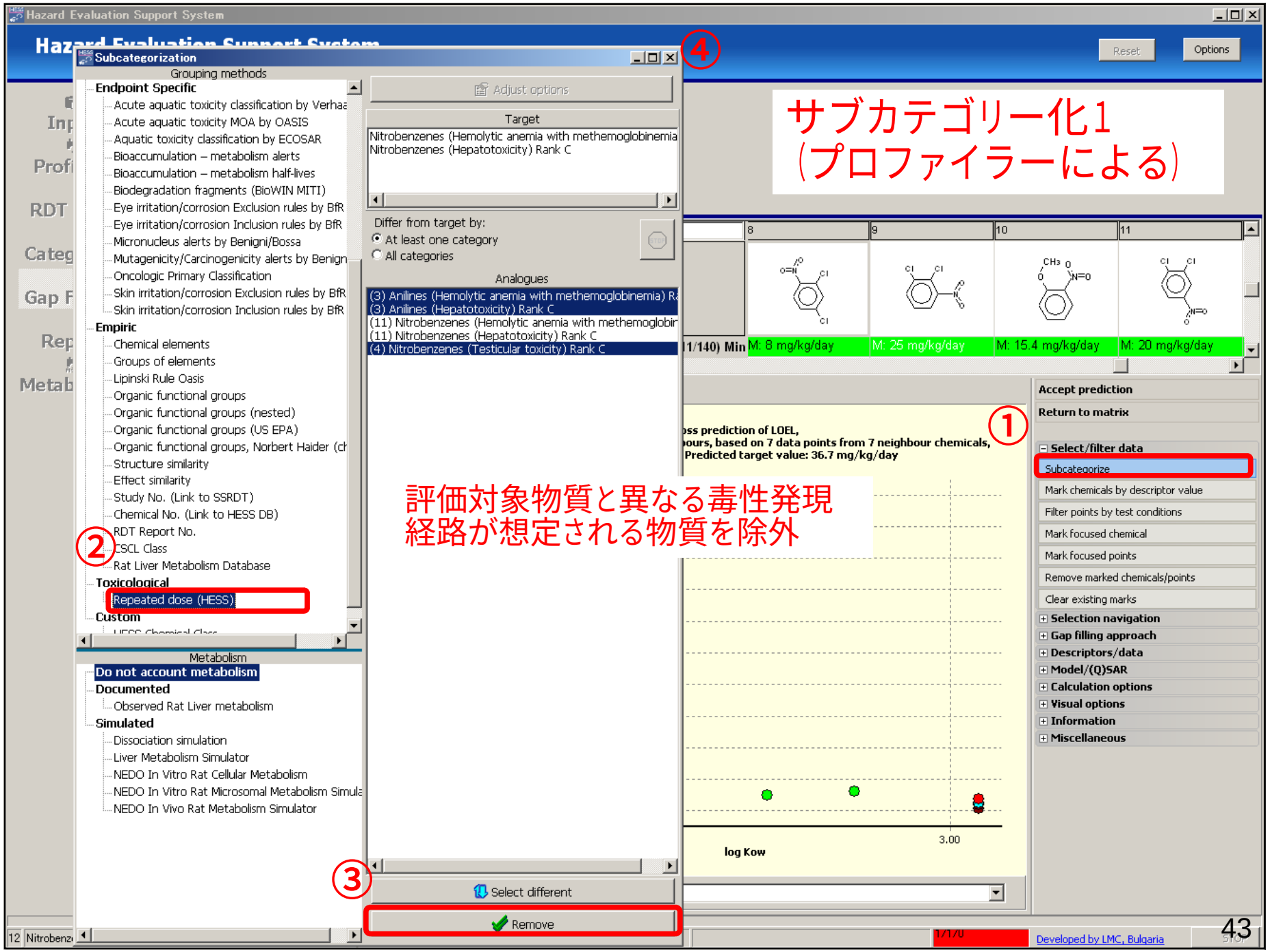

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
データギャップ補完に使用する所見を選定する
Data Gap Filling Method
Read-across
Trend analysis
(Q)SAR models
Apply
Target Endpoint
Repeated Dose Toxicity LOEL
Filter endpoint tree...
Structure
1 (Target)
2
3
4
Substance Identity
Repeated Dose Toxicity
LOEL
Min
M: 15 mg/kg/day
M: 5 mg/kg/day
M: 48.1 mg/kg/day
Blood Chemical Examination
Blood Serum (Bilirubin)
Undefined Tissue
T. Bilirubin↑ (3/4)
M: 20 mg/kg/day
Hematological Examination
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, ...
HGB↓ (10/17)
M: 15 mg/kg/day, 1...
M: 20 mg/kg/day, 2...
M: 769 mg/kg/day, ...
HTC↓ (10/17)
M: 15 mg/kg/day, 1...
M: 20 mg/kg/day, 2...
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, ...
Histopathological Findings
Liver
Kupffer Cell
Pigmentation (Hemosiderin) (3/4)
M: 20 mg/kg/day
Pigmentation (Other) (1/2)
M: 125 mg/kg/day, ...
Undefined Tissue
Extramedullary Hematopoiesis (1/3)
M: 20 mg/kg/day, 1...
Spleen
Undefined Tissue
Pigmentation (Hemosiderin) (7/12)
M: 20 mg/kg/day
M: 48.1 mg/kg/day,...
mg/kg/day, ...
この場合、前述のフィルターを用いて
溶血性貧血のLOELに対し、データギャップ補完を行う。
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
Developed by LMC, Bulgaria

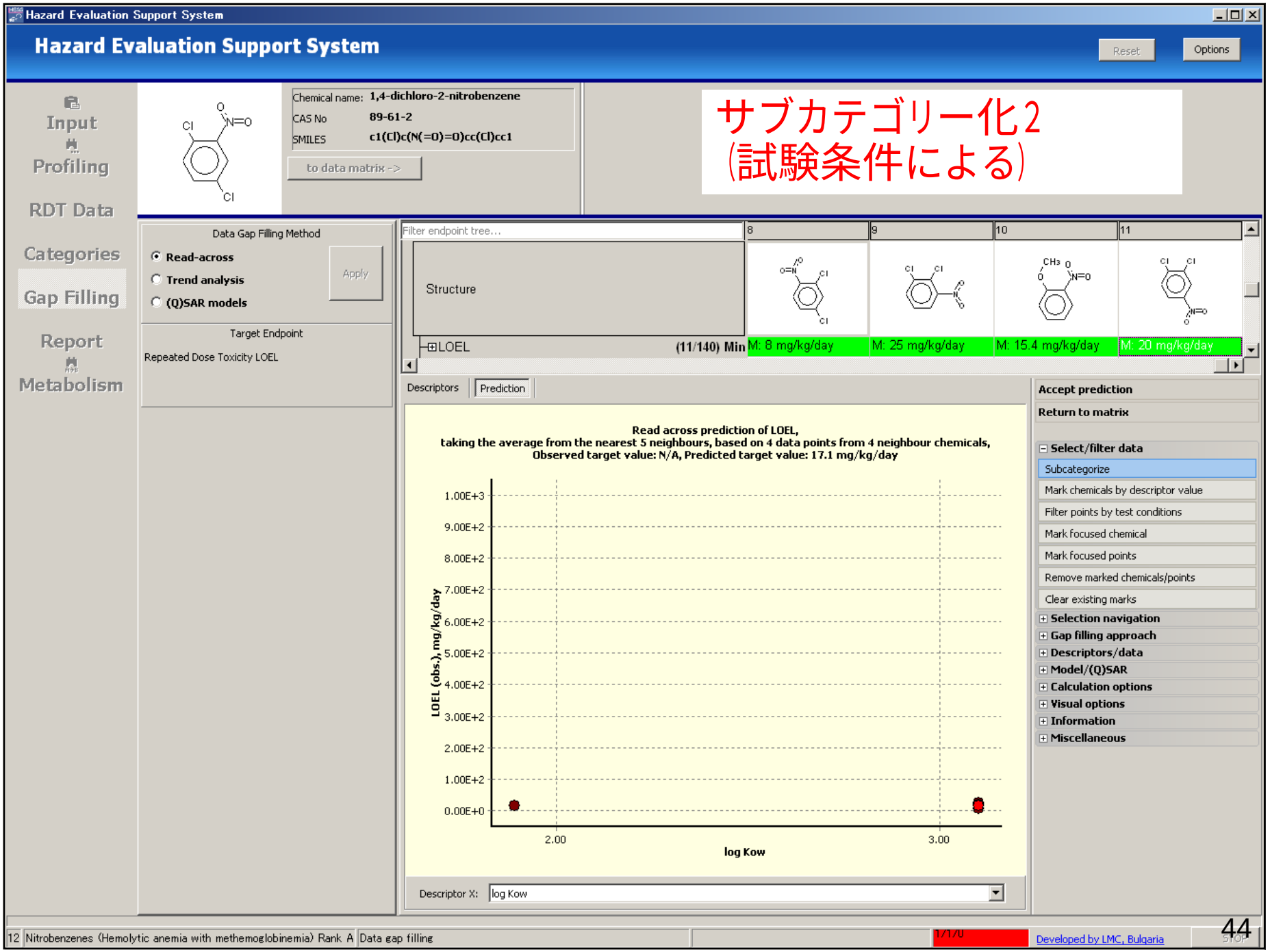

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
データギャップ補完に使用する所見
②
③
Data Gap Filling Method
Read-across
Trend analysis
(Q)SAR models
Apply
Target Endpoint
Repeated Dose Toxicit
Filter endpoint tree...
Structure
①
1 (Target)
2
3
4
Possible data inconsistency
Examination items
Effect
Tissue
Organ (Tissue)
④
Selected [140/140] points
OK
Cancel
M: 15 mg/kg/day
M: 5 mg/kg/day
M: 48.1 mg/kg/day
(3/4)
M: 20 mg/kg/day
(9/16)
M: 15 mg/kg/day, 1...
M: 20 mg/kg/day, 2...
M: 769 mg/kg/day, ...
(10/17)
M: 15 mg/kg/day, 1...
M: 20 mg/kg/day, 2...
M: 769 mg/kg/day, ...
(10/17)
M: 15 mg/kg/day, 1...
M: 20 mg/kg/day, 2...
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, ...
(3/4)
M: 20 mg/kg/day
(1/2)
M: 125 mg/kg/day, ...
(1/3)
M: 20 mg/kg/day, 1...
(7/12)
M: 20 mg/kg/day
M: 48.1 mg/kg/day,...
Pigmentation (Other)
(3/6)
M: 15 mg/kg/day, 1...
M: 5 mg/kg/day, 25...
Congestion
(5/9)
M: 5 mg/kg/day, 25...
M: 385 mg/kg/day, ...
Extramedullary Hematopoiesis
(6/11)
M: 15 mg/kg/day, 1...
M: 5 mg/kg/day, 5 ...
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
Developed by LMC, Bulgaria

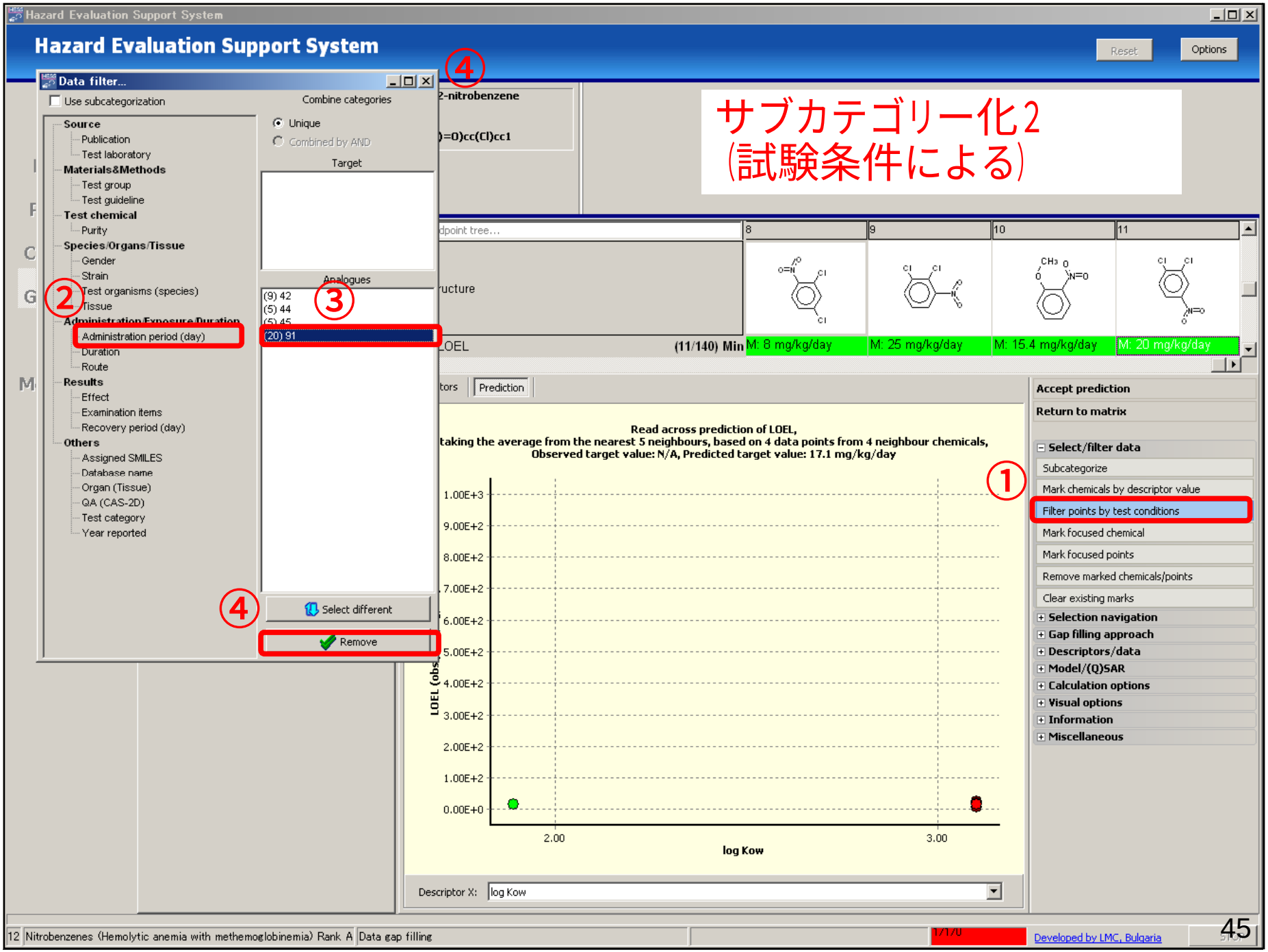

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
データギャップ補完の設定の確認①
Data Gap Filling Method
Read-across
Trend analysis
(Q)SAR models
Apply
Target Endpoint
Repeated Dose Toxicity LOEL
Filter endpoint tree...
Structure
1 (Target)
2
3
4
LOEL (11/140) Min
M: 15 mg/kg/day
M: 5 mg/kg/day
M: 48.1 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
LOEL (obs.), mg/kg/day
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
2.00
3.00
log Kow
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
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A Data gap filling
Developed by LMC, Bulgaria

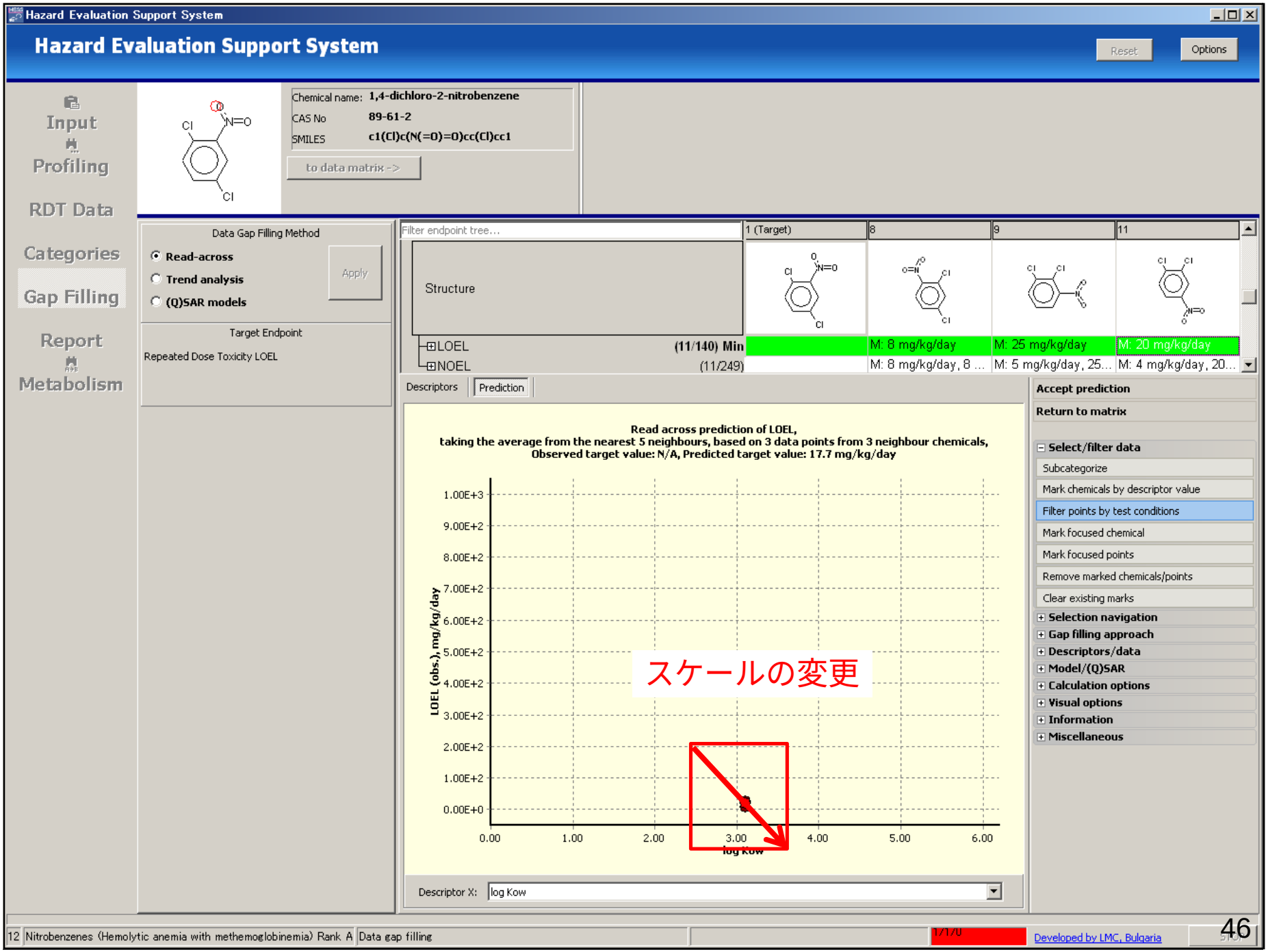

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
データギャップ補完の設定の確認②
Data Gap Filling Method
Read-across
Trend analysis
(Q)SAR models
Apply
Target Endpoint
Repeated Dose Toxicity LOEL
Filter endpoint tree...
1 (Target)
2
3
4
Structure
LOEL (11/140) Min
M: 15 mg/kg/day
M: 5 mg/kg/day
M: 48.1 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
LOEL (obs.), mg/kg/day
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
2.00
3.00
log Kow
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
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A Data gap filling
Developed by LMC, Bulgaria
STOP


Hazard Evaluation Support System
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 ->
予測結果
Data Gap Filling Method
Read-across
溶血性貧血に対するＬＯＥＬの推定値:
36.7 mg/kg/day
Filter endpoint tree...
1 (Target)
2
3
4
M: 15 mg/kg/day
M: 5 mg/kg/day
M: 48.1 mg/kg/day
Descriptors
Prediction
Read across prediction of LOEL,
Observed target value: N/A
Predicted target value: 36.7 mg/kg/day
LOEL (obs.), mg/kg/day
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
2.00
3.00
log Kow
●:評価対象物質
●:データギャップ補完に用いた類似物質
●:データギャップ補完に用いていない類似物質
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
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
Data gap filling
Developed by LMC, Bulgaria
STOP

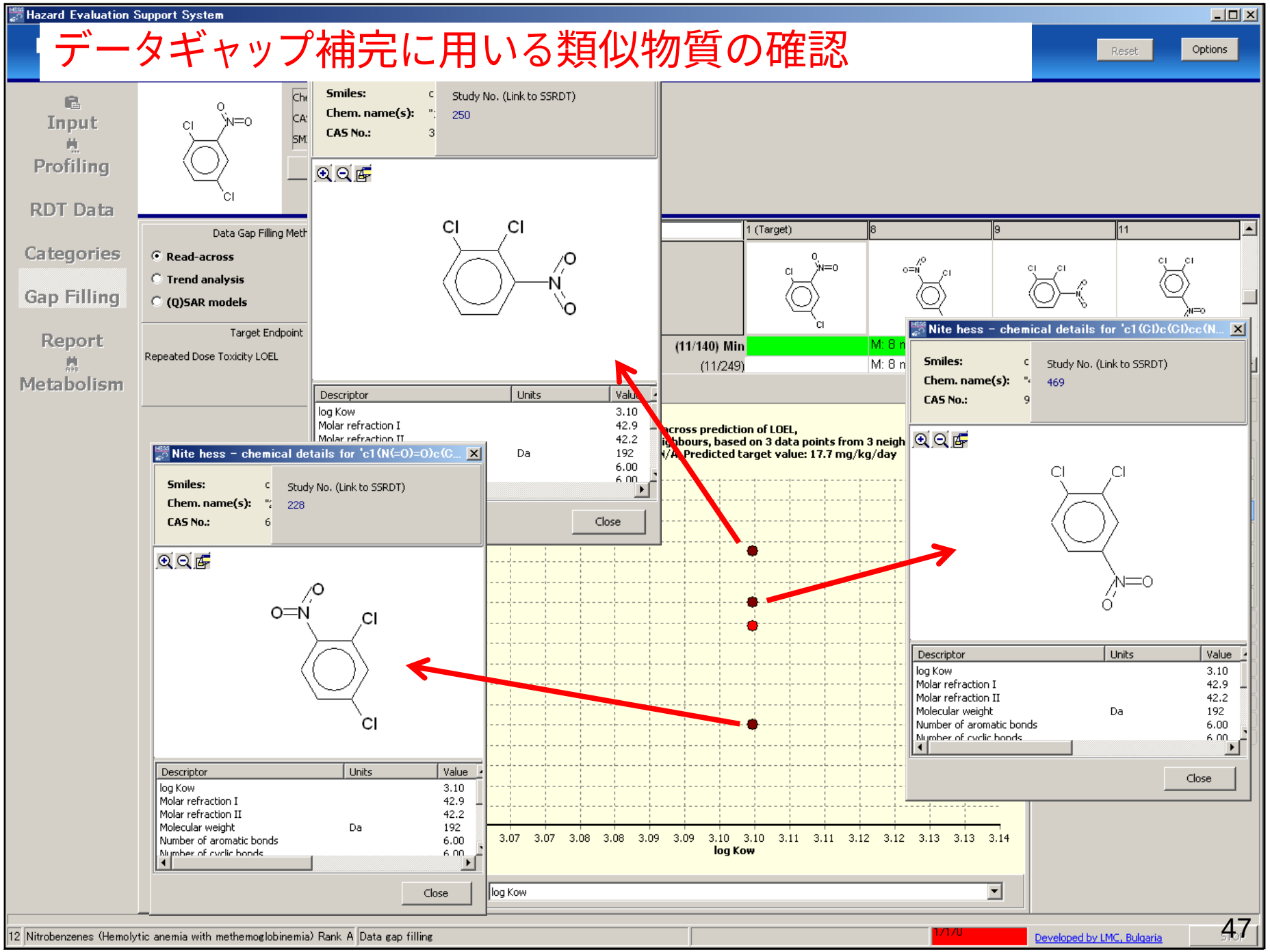

Hazard Evaluation Support System
Subcategorization
Grouping methods
Endpoint Specific
Acute aquatic toxicity classification by Verhaa
Acute aquatic toxicity MOA by OASIS
Aquatic toxicity classification by ECOSAR
Bioaccumulation – metabolism alerts
Bioaccumulation – metabolism half-lives
Biodegradation fragments (BioWIN MITI)
Eye irritation/corrosion Exclusion rules by BfR
Eye irritation/corrosion Inclusion rules by BfR
Micronucleus alerts by Benigni/Bossa
Mutagenicity/Carcinogenicity alerts by Benign
Oncologic Primary Classification
Skin irritation/corrosion Exclusion rules by BfR
Skin irritation/corrosion Inclusion rules by BfR
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 Haider (cl
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
Metabolism
Do not account metabolism
Documented
Observed Rat Liver metabolism
Simulated
Dissociation simulation
Liver Metabolism Simulator
NEDO In Vitro Rat Cellular Metabolism
NEDO In Vitro Rat Microsomal Metabolism Simula
NEDO In Vivo Rat Metabolism Simulator
Adjust options
Target
Nitrobenzenes (Hemolytic anemia with methemoglobinemia
Nitrobenzenes (Hepatotoxicity) Rank C
Differ from target by:
At least one category
All categories
Analogues
(3) Anilines (Hemolytic anemia with methemoglobinemia) Ra
(3) Anilines (Hepatotoxicity) Rank C
(11) Nitrobenzenes (Hemolytic anemia with methemoglobir
(11) Nitrobenzenes (Hepatotoxicity) Rank C
(4) Nitrobenzenes (Testicular toxicity) Rank C
Select different
Remove
Reset
Options
サブカテゴリー化1
（プロファイラーによる）
8
9
10
11
M: 8 mg/kg/day
M: 25 mg/kg/day
M: 15.4 mg/kg/day
M: 20 mg/kg/day
評価対象物質と異なる毒性発現
経路が想定される物質を除外
Accept prediction
Return to matrix
Select/filter data
Subcategorize
Mark chemicals by descriptor value
Filter points by test conditions
Mark focused chemical
Mark focused points
Remove marked chemicals/points
Clear existing marks
Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR
Calculation options
Visual options
Information
Miscellaneous
Predicted target value: 36.7 mg/kg/day
3.00
log Kow
Developed by LMC, Bulgaria
①
②
③
④

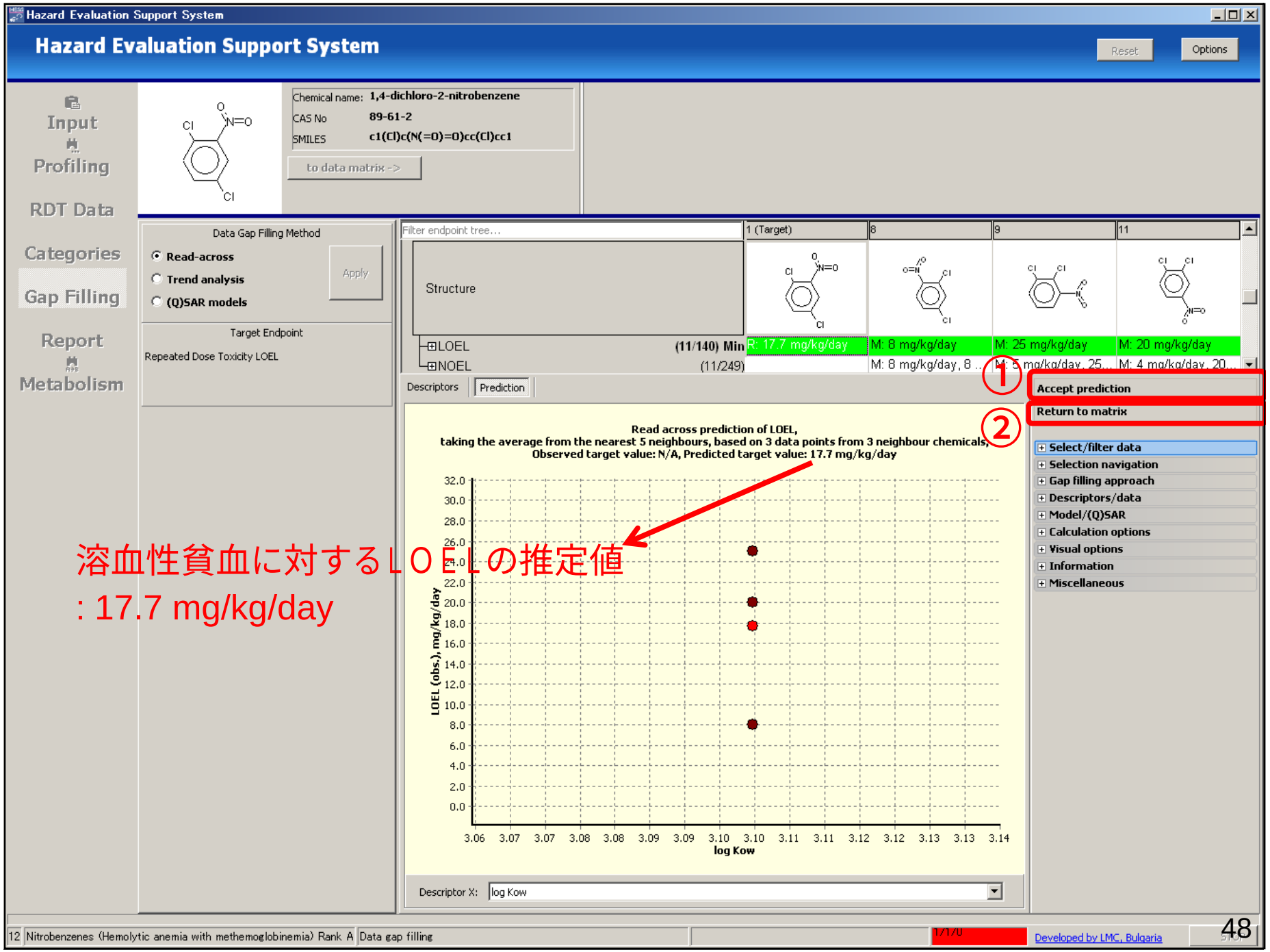

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
サブカテゴリー化2
(試験条件による)
Data Gap Filling Method
Read-across
Trend analysis
(Q)SAR models
Apply
Target Endpoint
Repeated Dose Toxicity LOEL
Filter endpoint tree...
Structure
LOEL
(11/140) Min
8
9
10
11
M: 8 mg/kg/day
M: 25 mg/kg/day
M: 15.4 mg/kg/day
M: 20 mg/kg/day
Descriptors
Prediction
Read across prediction of LOEL,
taking the average from the nearest 5 neighbours, based on 4 data points from 4 neighbour chemicals,
Observed target value: N/A, Predicted target value: 17.1 mg/kg/day
LOEL (obs.), mg/kg/day
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
2.00
3.00
log Kow
Descriptor X: log Kow
Accept prediction
Return to matrix
Select/filter data
Subcategorize
Mark chemicals by descriptor value
Filter points by test conditions
Mark focused chemical
Mark focused points
Remove marked chemicals/points
Clear existing marks
Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR
Calculation options
Visual options
Information
Miscellaneous
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A Data gap filling
Developed by LMC, Bulgaria
STOP


Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Data filter...
Use subcategorization
Combine categories
Unique
Combined by AND
Target
Analogues
Source
Publication
Test laboratory
Materials&Methods
Test group
Test guideline
Test chemical
Purity
Species/Organs/Tissue
Gender
Strain
Test organisms (species)
Tissue
Administration/Exposure/Duration
Administration period (day)
Duration
Route
Results
Effect
Examination items
Recovery period (day)
Others
Assigned SMILES
Database name
Organ (Tissue)
QA (CAS-2D)
Test category
Year reported
(9) 42
(5) 44
(20) 91
Select different
Remove
2-nitrobenzene
)=O)cc(Cl)cc1
ucture
LOEL
(11/140) Min
M: 8 mg/kg/day
M: 25 mg/kg/day
M: 15.4 mg/kg/day
M: 20 mg/kg/day
Prediction
Read across prediction of LOEL,
taking the average from the nearest 5 neighbours, based on 4 data points from 4 neighbour chemicals,
Observed target value: N/A, Predicted target value: 17.1 mg/kg/day
LOEL (obs)
log Kow
Descriptor X:
Accept prediction
Return to matrix
Select/filter data
Subcategorize
Mark chemicals by descriptor value
Filter points by test conditions
Mark focused chemical
Mark focused points
Remove marked chemicals/points
Clear existing marks
Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR
Calculation options
Visual options
Information
Miscellaneous
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
Data gap filling
Developed by LMC, Bulgaria
サブカテゴリー化2
(試験条件による)
①
②
③
④

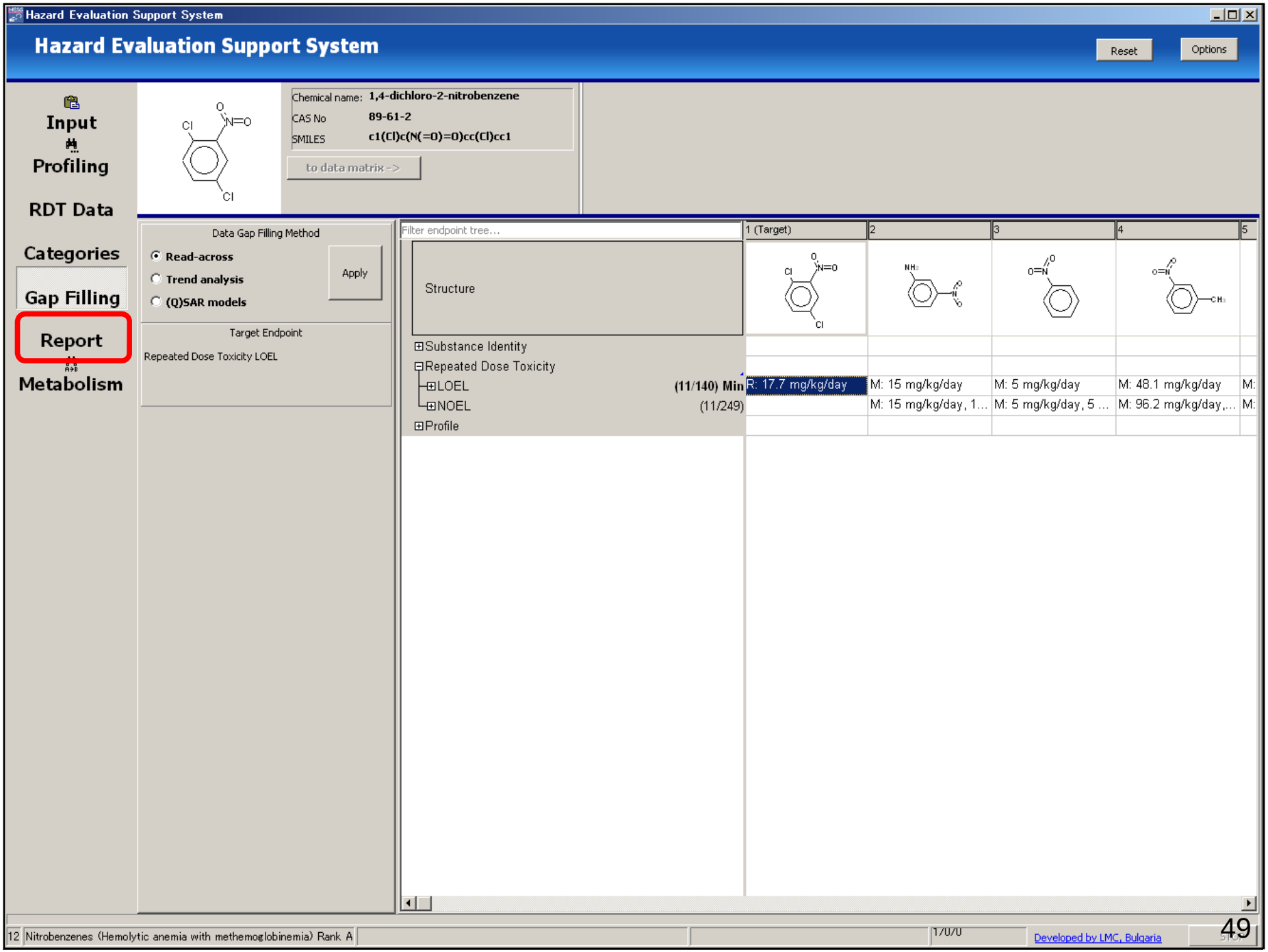

Hazard Evaluation Support System
Hazard Evaluation Support System
Reset
Options
Input
Profiling
RDT Data
Categories
Gap Filling
Report
Metabolism
Chemical name: 1,4-dichloro-2-nitrobenzene
CAS No 89-61-2
SMILES c1(Cl)c(N(=O)=O)cc(Cl)cc1
to data matrix ->
Data Gap Filling Method
Read-across
Trend analysis
(Q)SAR models
Apply
Target Endpoint
Repeated Dose Toxicity LOEL
Filter endpoint tree...
1 (Target)
8
9
11
Structure
LOEL (11/140) Min
M: 8 mg/kg/day
M: 25 mg/kg/day
M: 20 mg/kg/day
NOEL (11/249)
M: 8 mg/kg/day, 8 ...
M: 5 mg/kg/day, 25...
M: 4 mg/kg/day, 20...
Descriptors
Prediction
Read across prediction of LOEL,
taking the average from the nearest 5 neighbours, based on 3 data points from 3 neighbour chemicals,
Observed target value: N/A, Predicted target value: 17.7 mg/kg/day
LOEL (obs.), mg/kg/day
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
0.00
1.00
2.00
3.00
4.00
5.00
6.00
log Kow
スケールの変更
Descriptor X: log Kow
Accept prediction
Return to matrix
Select/filter data
Subcategorize
Mark chemicals by descriptor value
Filter points by test conditions
Mark focused chemical
Mark focused points
Remove marked chemicals/points
Clear existing marks
Selection navigation
Gap filling approach
Descriptors/data
Model/(Q)SAR
Calculation options
Visual options
Information
Miscellaneous
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A Data gap filling
1/170
Developed by LMC, Bulgaria
STOP

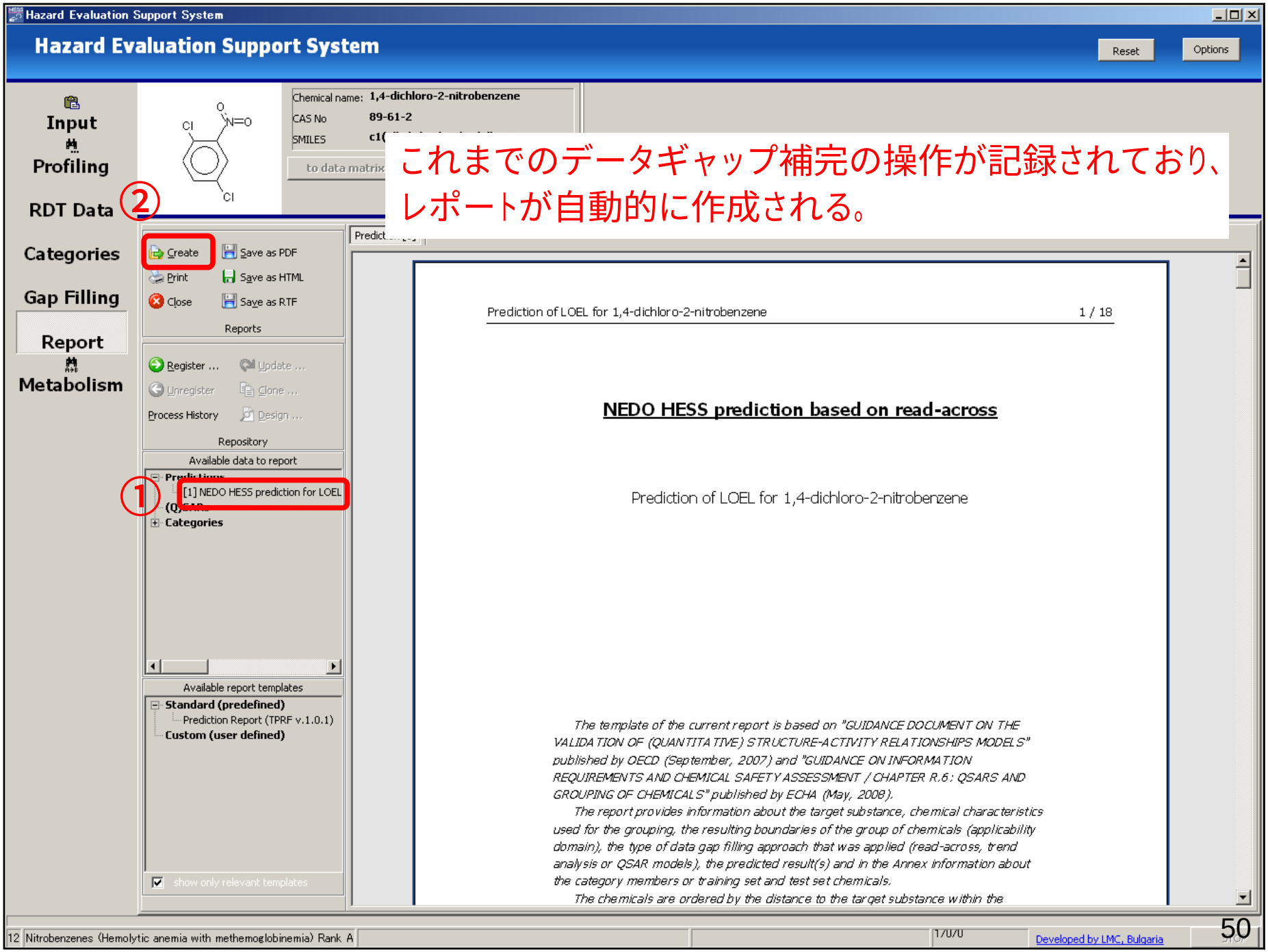
データギャップ補完に用いる類似物質の確認



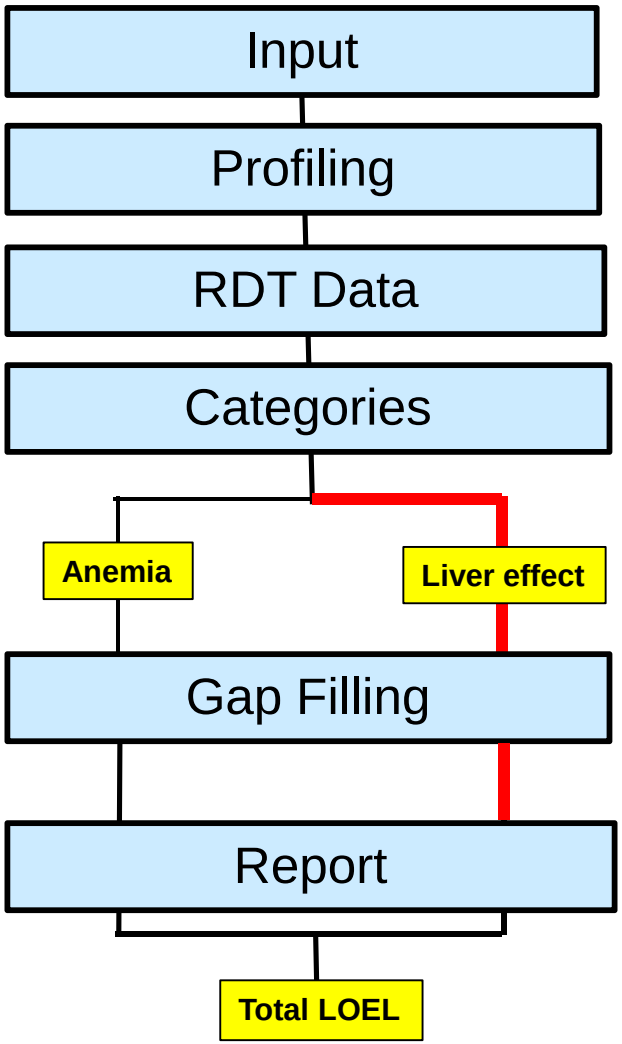


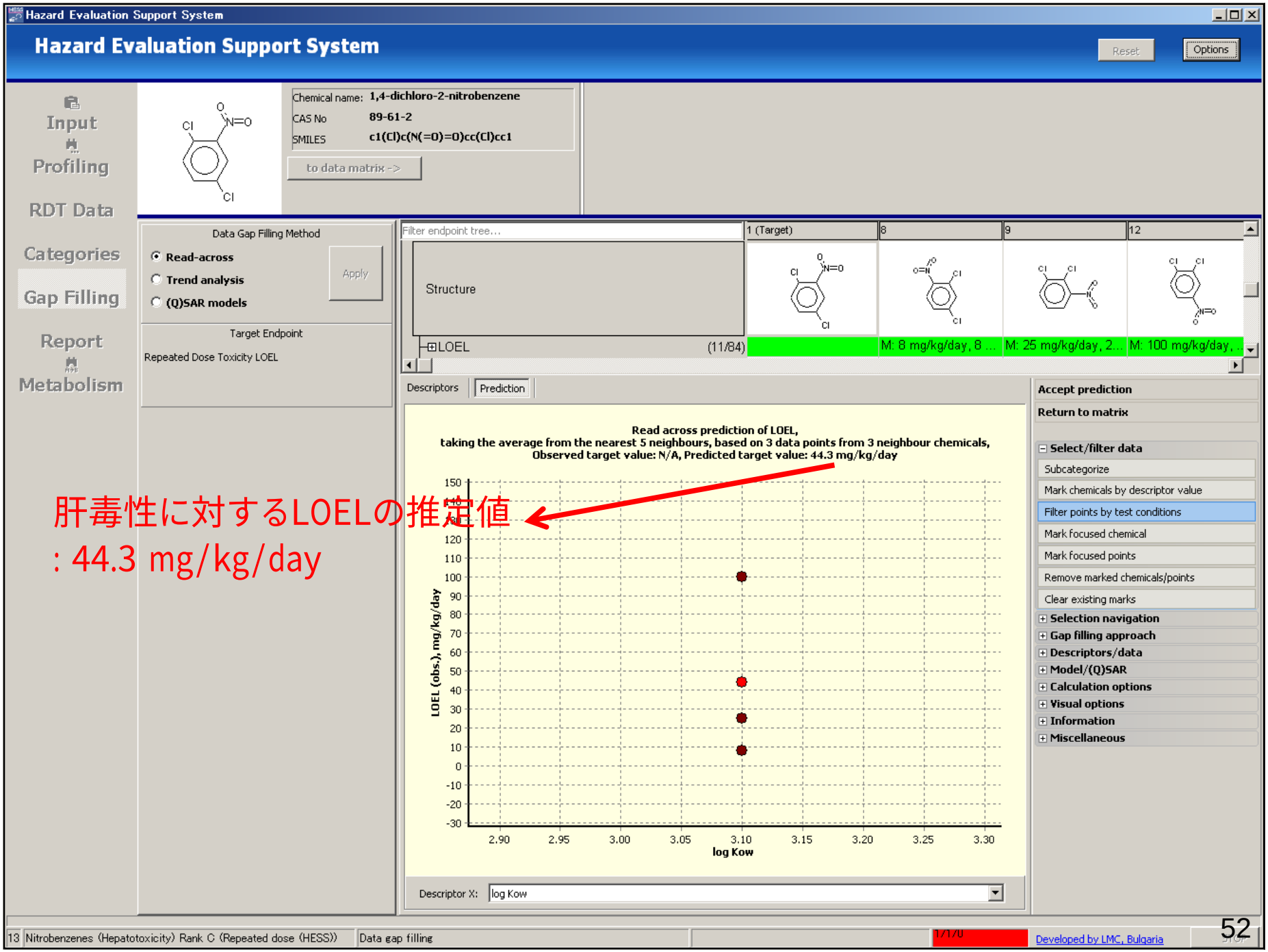
溶血性貧血に対するＬＯＥＬの推定値
: 17.7 mg/kg/day


Hazard Evaluation Support System
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
Substance Identity
Repeated Dose Toxicity
LOEL (11/140) Min
NOEL (11/249)
Profile
R: 17.7 mg/kg/day
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,...
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
Developed by LMC, Bulgaria


Hazard Evaluation Support System
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
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。
②
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
[1] NEDO HESS prediction for LOEL
Categories
①
Available report templates
Standard (predefined)
Prediction Report (TPRF v.1.0.1)
Custom (user defined)
show only relevant templates
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
12 Nitrobenzenes (Hemolytic anemia with methemoglobinemia) Rank A
Developed by LMC, Bulgaria

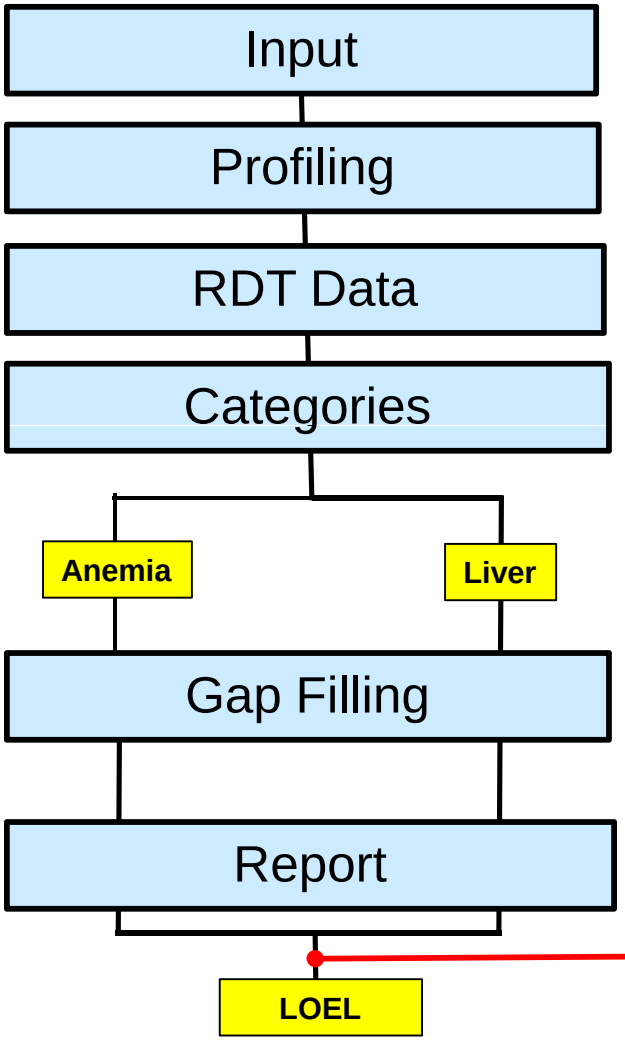
同様の操作を肝臓毒性に対して実施





肝毒性に対するLOELの推定値
: 44.3 mg/kg/day

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
：17.7 mg/kg/day
肝毒性に対するLOEL
：44.3 mg/kg/day

全身に対する LOEL
：17.7 mg/kg/day

最少値を選択