Use of Computational Toxicology for the Biological Evaluation of Medical Devices

SOT Medical Device Specialty Section Webinar
June 23, 2014

Ron Brown

FDA Center for Devices and Radiological Health

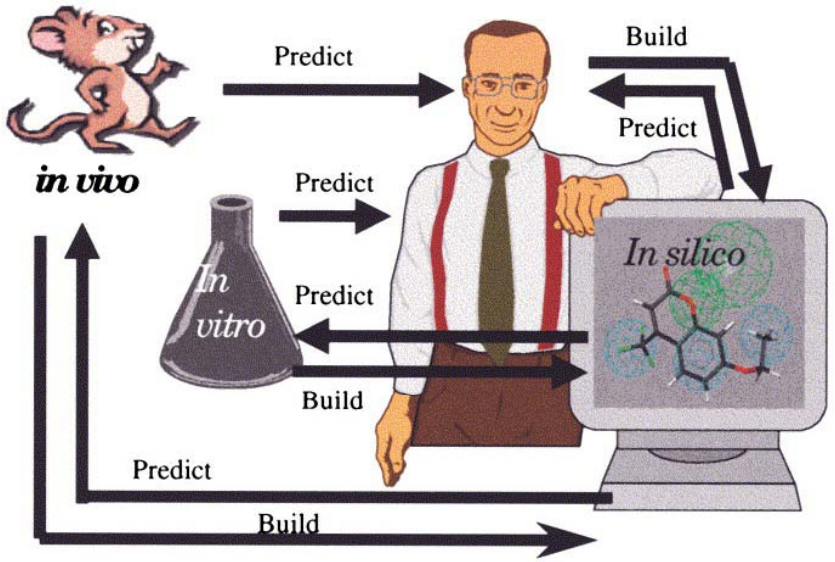
Office of Science and Engineering Laboratories

Overview

* What is computational toxicology?
* How can it be incorporated into the risk assessment process?
* Use of computational models
  * Where does computational toxicology fit into the new toxicity testing paradigms that are being proposed?
  * Regulatory acceptance of computational models for biocompatibility assessment
* Current efforts to develop and validate computational models for risk assessment of compounds released from device materials.

What is computational toxicology?

* **Computational toxicology is the application of mathematical and computer models to assess chemical hazards and risks to human health and the environment.**



Overview

* What is computational toxicology?
* How can it be incorporated into the risk assessment process?
* Applications of computational models
  * Where does computational toxicology fit into the new toxicity testing paradigms that are being proposed?
  * How do regulatory agencies and industry use computational models?
* Current efforts to develop and validate computational models for risk assessment of compounds released from device materials.

Steps in the Risk Assessment Process

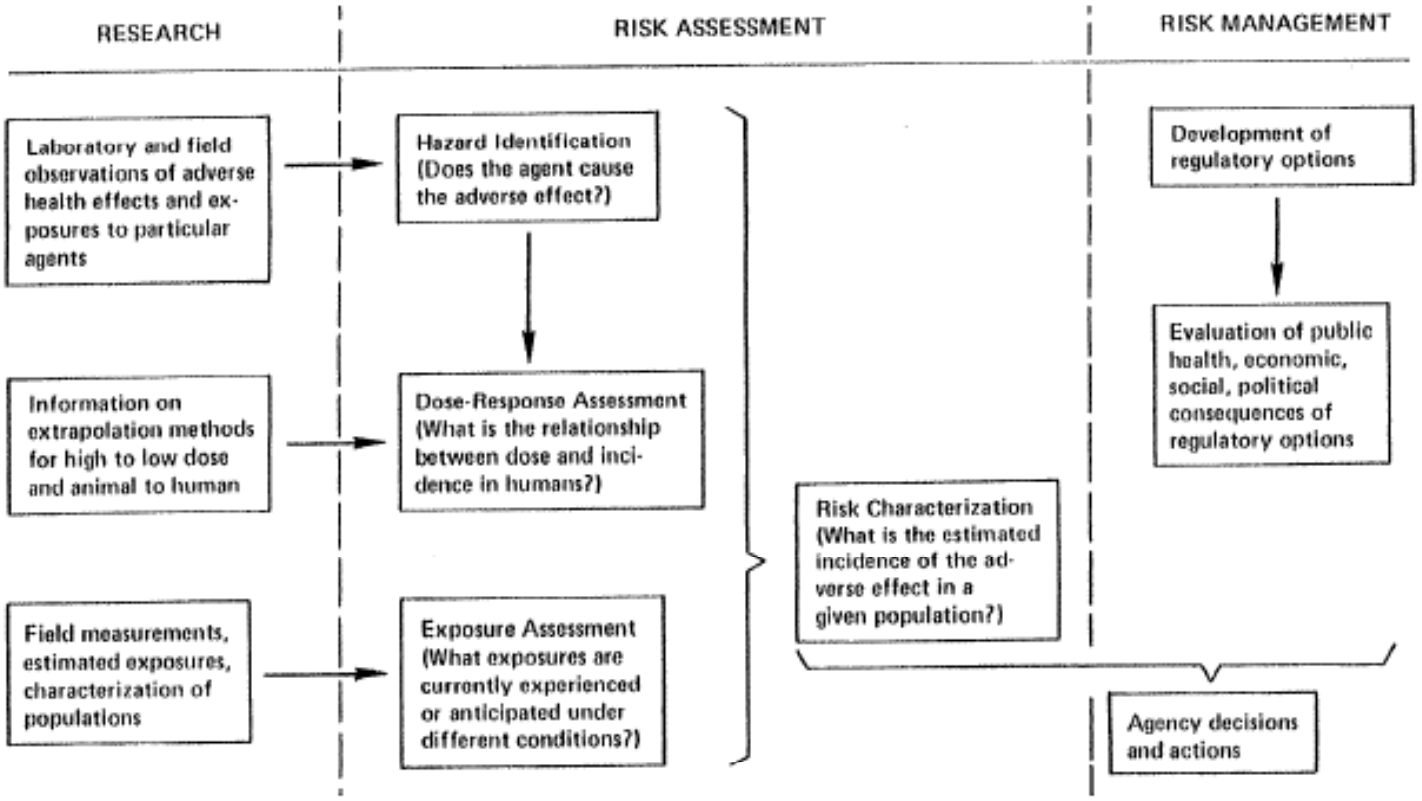


FIGURE I-1 Elements of risk assessment and risk management.

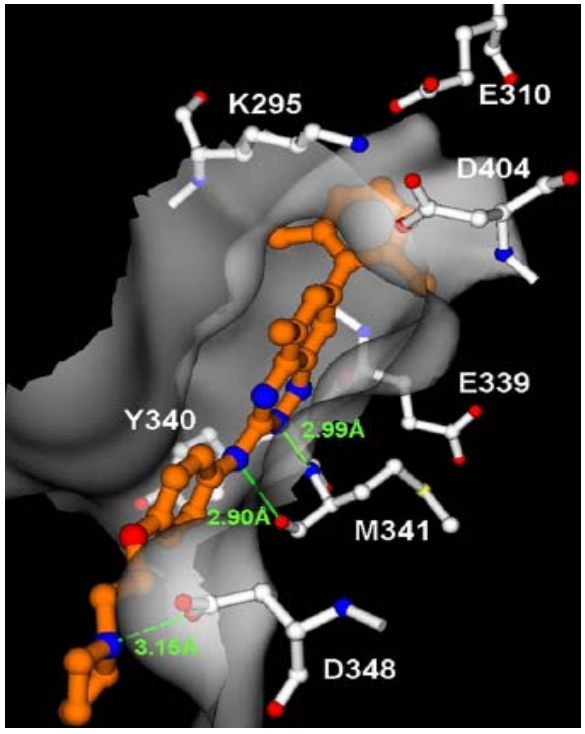
National Academy of Sciences "Red Book" (1983)

Use of computational methods in risk assessment
Hazard Identification

* Does the agent have the inherent capacity to induce an adverse health effect at any dose?

* Use of computational models for hazard identification:

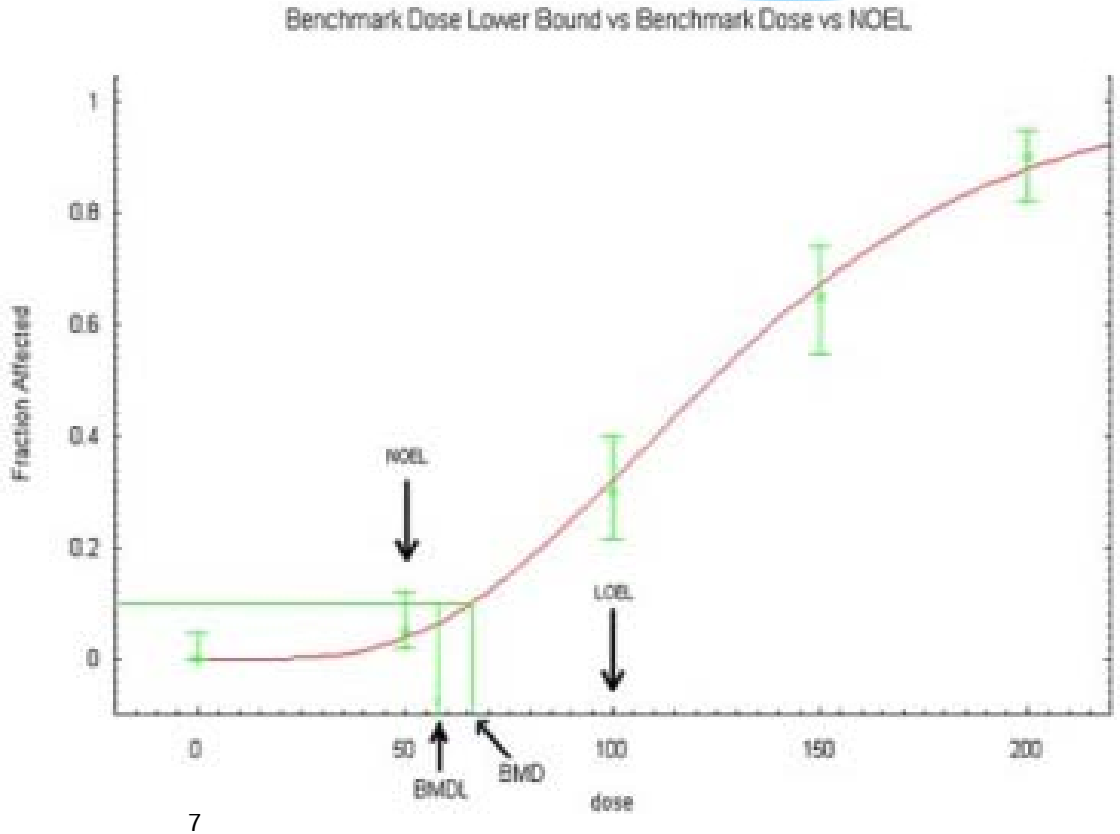
  * Structure-Activity Relationship (SAR) models



Use of computational methods in risk assessment

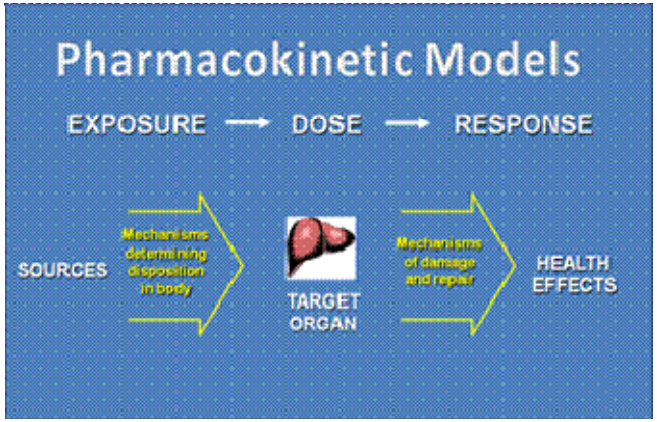
Dose-Response Assessment

* How does the frequency of the adverse event change with exposure?
* Use of computational models for dose-response assessment:
  * Cancer: High-to-low dose extrapolation models
  * Noncancer: Benchmark dose models



Use of computational methods in risk assessment
Exposure Assessment

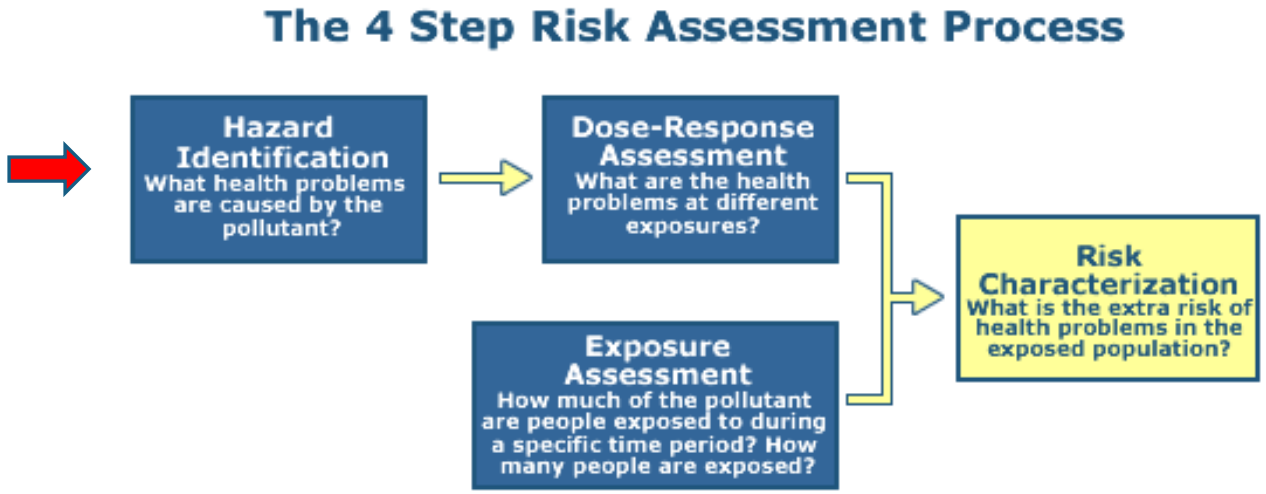
* How much of the compound are people exposed to?
* Use of computational models for exposure assessment:
  * Exposure models
  * Pharmacokinetic models



Use of computational methods in risk assessment

Risk Characterization

This presentation will focus on the use of computational models for hazard identification



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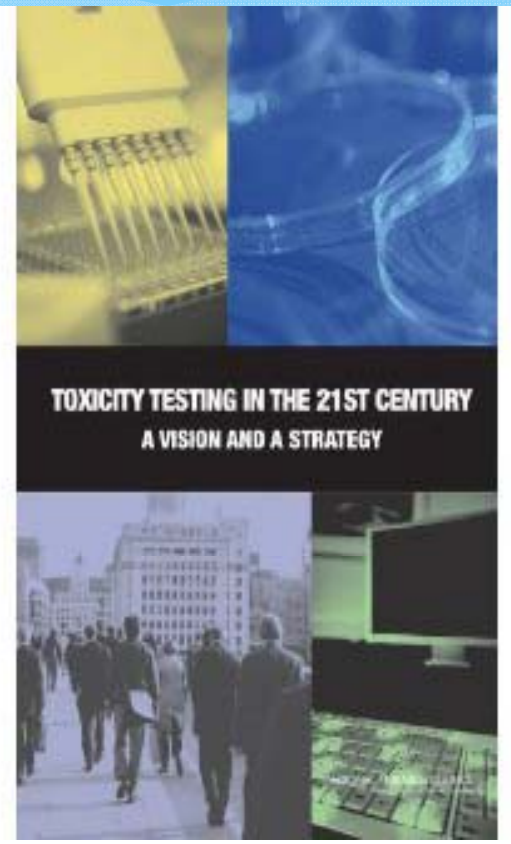
Toxicology Testing in the 21St Century
National Academy of Sciences (2007)

"Toxicity testing is approaching such a scientific pivot point. It is poised to take advantage of the revolutions in biology anc biotechnology. Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin."



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DOI: 10.1080/10937404.2010.483176

Taylor & Francis
Taylor & Francis Group

TOXICITY TESTING IN THE 21ST CENTURY: A VISION AND A STRATEGY

Daniel Krewski[1,2], Daniel Acosta, Jr.[3], Melvin Andersen[4], Henry Anderson[5], John C. Bailar III[6], Kim Boekelheide[7], Robert Brent[8], Gail Charnley[9], Vivian G. Cheung[10], Sidney Green, Jr.[11], Karl T. Kelsey[12], Nancy I. Kerkvliet[13], Abby A. Li[14], Lawrence McCray[15], Otto Meyer[16], Reid D. Patterson[17], William Pennie[18], Robert A. Scala[19], Gina M. Solomon[20], Martin Stephens[21], James Yager[22], Lauren Zeise[23], Staff of Committee on Toxicity Testing and Assessment of Environmental Agents

"Computational models could also play a role in the early identification of environmental agents potentially harmful to humans, although further testing would probably be needed. This new approach would be less expensive and less time-consuming than the current approach and result in much higher throughput."

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Margaret A. Hamburg is Commissioner of the U.S. Food and Drug Administration.

EDITORIAL

Advancing Regulatory Science

ENSURING THE SAFETY AND QUALITY OF FOOD AND MEDICAL PRODUCTS HAS NEVER BEEN MORE complicated. Societies around the world face increasingly complex challenges that require harnessing the best available science and technology on behalf of patients and consumers. This effort requires a strong field of regulatory science to develop new tools, standards, and approaches that efficiently and consistently assess the safety, efficacy, quality, and performance of products. Yet, despite being a critical component of the scientific enterprise, regulatory science has long been underappreciated and underfunded.

With an advanced field of regulatory science, new tools, including functional genomics, proteomics, metabolomics, high-throughput screening, and systems biology, can replace current toxicology assays with tests that incorporate the mechanistic underpinnings of disease and of underlying toxic side effects. This should allow the development, validation, and qualification of preclinical and clinical models that accelerate the evaluation of toxicities during drug development. The goals include developing biomarkers to predict toxicity and screen at-risk human subjects during clinical trials, as well as after new products are on the market. The FDA is also working to eventually replace animal testing with a combination of in silico and in vitro approaches. The inherent complexity of the vertebrate reproductive system repre-

Science, Vol 331 February, 2011


Advancing Regulatory Science at FDA
FDA

Advancing Regulatory Science at FDA

3. Use and develop computational methods and in silico *modeling:*

a) Improve the use of chemical Structure- Activity Relationship (SAR) models in the prediction of human risk and integrate this analysis into the review process;

b) Develop and implement approaches to link chemical structures and substructures to a wide range of information about product safety, disease targets, and toxicity mechanisms;

c) Develop clinical trial simulation models that can reveal interactions between drug or device effects, patient characteristics, and disease variables influencing outcomes;

d) Develop computer models of cells, organs, and systems to better predict product safety and efficacy;

e) Implement computer models that integrate pharmacokinetic, pharmacodynamic, materials science, or mechanistic safety data to predict clinical risk-benefit and confirm post-marketing safety in different patient populations; and

f) Develop and apply data mining, knowledge building, and data visualization tools to inform computer model development,

FDA Critical Path Opportunities Report (2006)

"Ambiguous results emanating from currently available test procedures are the greatest obstacles encountered by FDA scientists during product review. These frustrating questions occur daily within the FDA review process. "

"With new evaluative tools and techniques, we can improve medical product assessment. Specific examples of such tools—new biomarkers, improved animal models, better clinical trial designs and endpoints, *in silico testing* (computer simulation, rather than laboratory or animal testing)—are included in the Opportunities List. "

FDA can close these gaps and improve preclinical safety predictions by further investing in three particular areas of regulatory science:

- **evaluating and developing models and assays that better predict patient response**
- **identifying and evaluating more reliable biomarkers for monitoring toxicities, side effects, and abnormalities, and**
- **using computational tools to integrate and draw conclusions from a wide range of preclinical safety data types and sources.**

Use of computational toxicology in FDA
Drugs and food additives

Review

Toxicological and clinical computational analysis and the US FDA/CDER

R Daniel Benz
US Food and Drug Administration, Informatics and Computational Safety Analysis Staff, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Silver Spring, MD 20993, USA

***Expert Opin. Drug Metab. Tox.* 3(1):109-124**

Perspective

Regulatory use of computational toxicology tools and databases at the United States Food and Drug Administration's Office of Food Additive Safety

Kirk B Arvidson†, Ronald Chanderbhan, Kristi Muldoon-Jacobs, Julie Mayer & Adejoke Ogungbesan
†*US Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, HFS-275, 5100 Paint Branch Parkway, College Park, MD, USA*

***Expert Opin. Drug Metab. Tox.* 6(7):793-796**

DRAFT CONSENSUS GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7

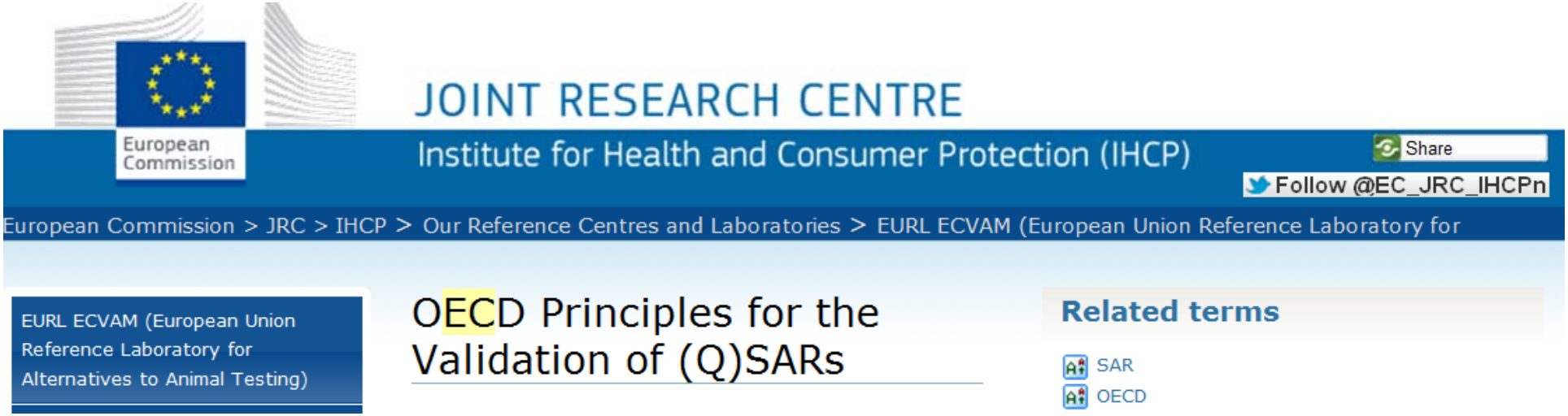
Method to determine if a compound is a potential genotoxic carcinogen in the absence of experimental data.

A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. (Q)SAR models utilizing these prediction methodologies should follow the validation principles set forth by the Organisation for Economic Co-operation and Development (OECD). (18)

The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no concern, and no further testing is required (Class 5 in Table 1).

Types of SAR models

Expert systems	Statistical models
Toxtree	LAZAR
OECD Toolbox	CAESAR
DEREK	MultiCase
Oncologic	Topkat

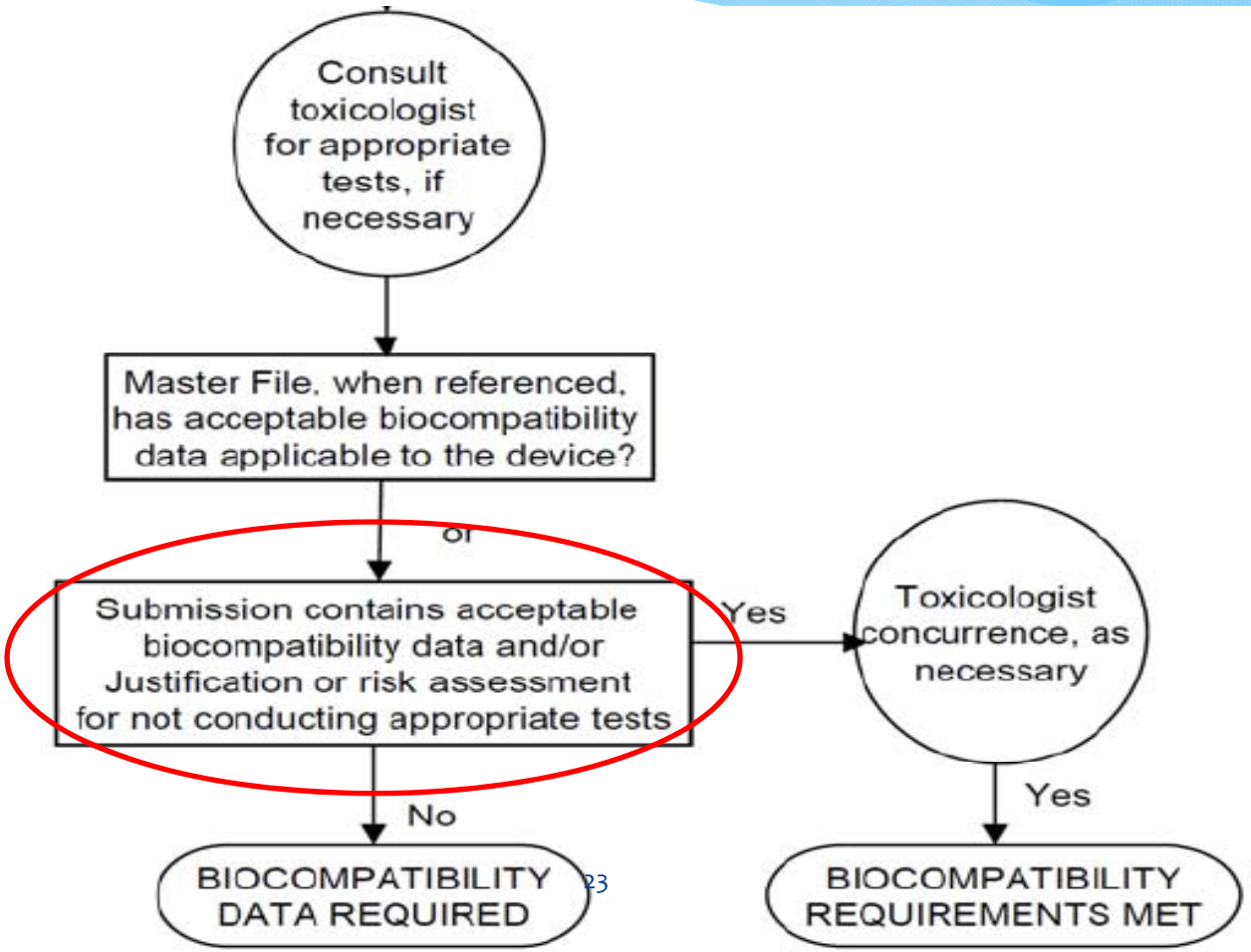


To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1) a defined endpoint
2) an unambiguous algorithm
3) a defined domain of applicability
4) appropriate measures of goodness-of-fit, robustness and predictivity
5) a mechanistic interpretation, if possible

http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/laboratories-research/predictive_toxicology/background/oecd-principles

Use of SAR models to assess the safety of compounds released from device materials



Draft FDA Biocompatibility Guidance
How can computational models be useful for the biological evaluation of devices

If the information above suggests that the chemical is bioavailable, the following toxicological information should be provided:

6. A safety assessment for each chemical entity using toxicity information from the literature and available, unpublished studies for all known toxic effects. Where the full toxicology profile for the chemical entity is not available, either from the supplier or from a previous medical device submission, the full battery of toxicity tests on the chemical entity (i.e., tests in addition to those outlined in Attachments A and B, including but not limited to genotoxicity; reproductive and developmental toxicity; and carcinogenicity) may also be needed or a scientific rationale provided for their omission.

Use of SAR Models to Determine Appropriate TTC Values

Structural alert for genotoxicity or carcinogenicity

Use 1.5 µg/day or equivalent value for TTC (may be adjusted for less-than-lifetime exposure)

No structural alert for genotoxicity or carcinogenicity

Use Cramer class values for TTC

(Toxtree can be used to assign Cramer Class values)

Recommendations for the use of SAR models for the biological assessment of medical devices

* CDRH does not have formal guidelines for the use of computational models for biocompatibility assessment

* The following recommendations may be useful if SAR modeling is used in a regulatory submission:

1. Follow ICH M7 guidelines
    * Use models for carcinogenicity/mutagenicity prediction
    * Use both an expert system and a statistical model
    * Follow OECD principles for validating the model

2. Use model predictions in conjunction with available biological data in a weight-of-evidence approach
    * Genotoxicity test results for device
    * Genotoxicity test results of individual extractables/leachables

Recommendations for the use of SAR models for the biological assessment of medical devices

* Computational models cannot provide predictions of all of the endpoints necessary for the biological evaluation of a medical device (e.g., cytotoxicity, implantation, hemocompatibility).

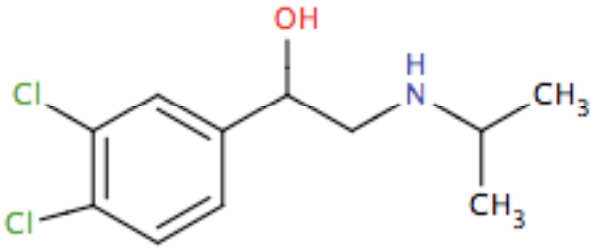
* Computational models do not typically provide information on the dose of a compound that is likely to produce adverse effect.

* Computational models are not able to predict the toxicity of all chemical compounds (e.g. metals) and all forms of compounds (e.g., nanoparticles).

Practical use of SAR models

* **How easy is it to use these models?**

* **Step-by-step example with one model (Toxtree)**

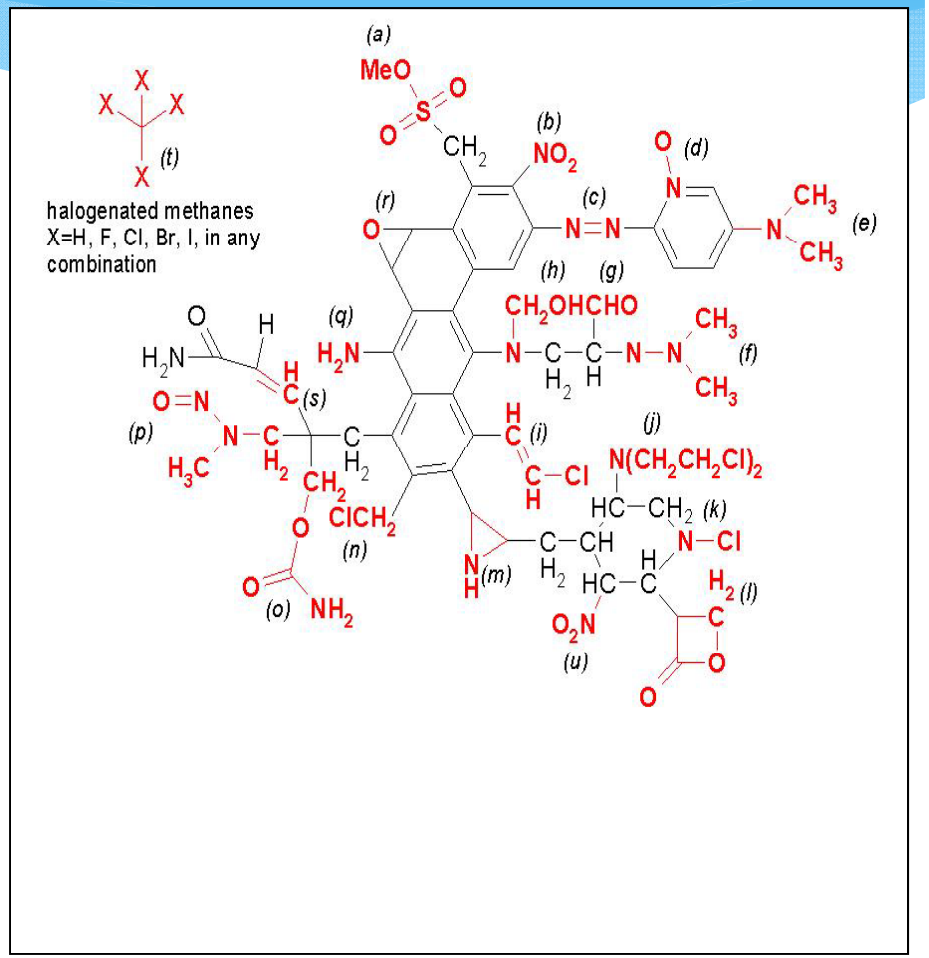


Structure Activity Relationships

How do these models work?

* Certain functional groups are associated with toxic or carcinogenic effects

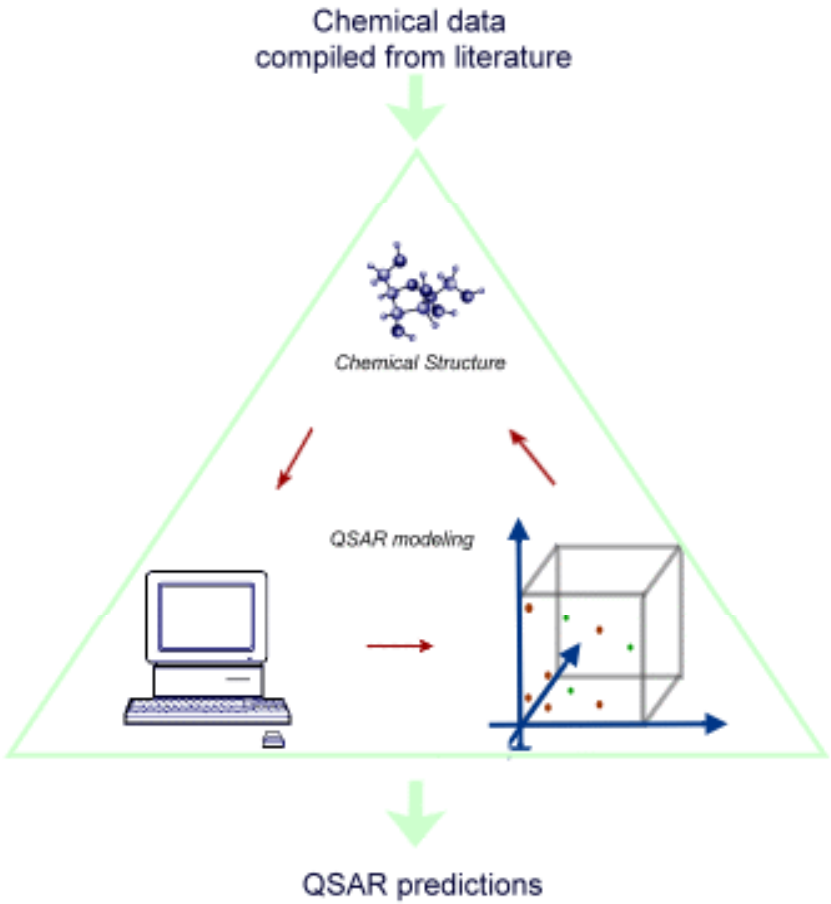
* Example: Ashby alerts, linked to carcinogenicity



Structure Activity Relationships

How do these models work?

SAR models capitalize on the relationship between structure and biological activity to predict the toxicity of compounds that have not undergone toxicity testing.



Example of how to use computational tox models

* **Toxtree - European Commission Joint Research Center/ Ideaconsult, Ltd.**

* **http://toxtree.sourceforge.net/**
* **http://apps.ideaconsult.net:8080/ToxPredict**

* **Modules for:**
  * **Carcinogenicity/mutagenicity**
  * **Skin and eye irritation**
  * **Skin sensitization**

Toxtree

How does it work?

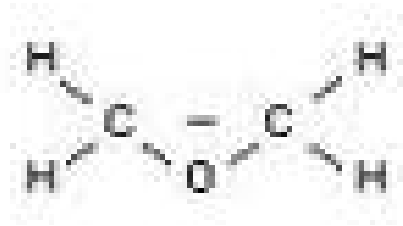
Decision-tree algorithm that goes through each of the component structures of the molecule looking for known toxic structures and basing the response on whether those structures are present in structure being tested.

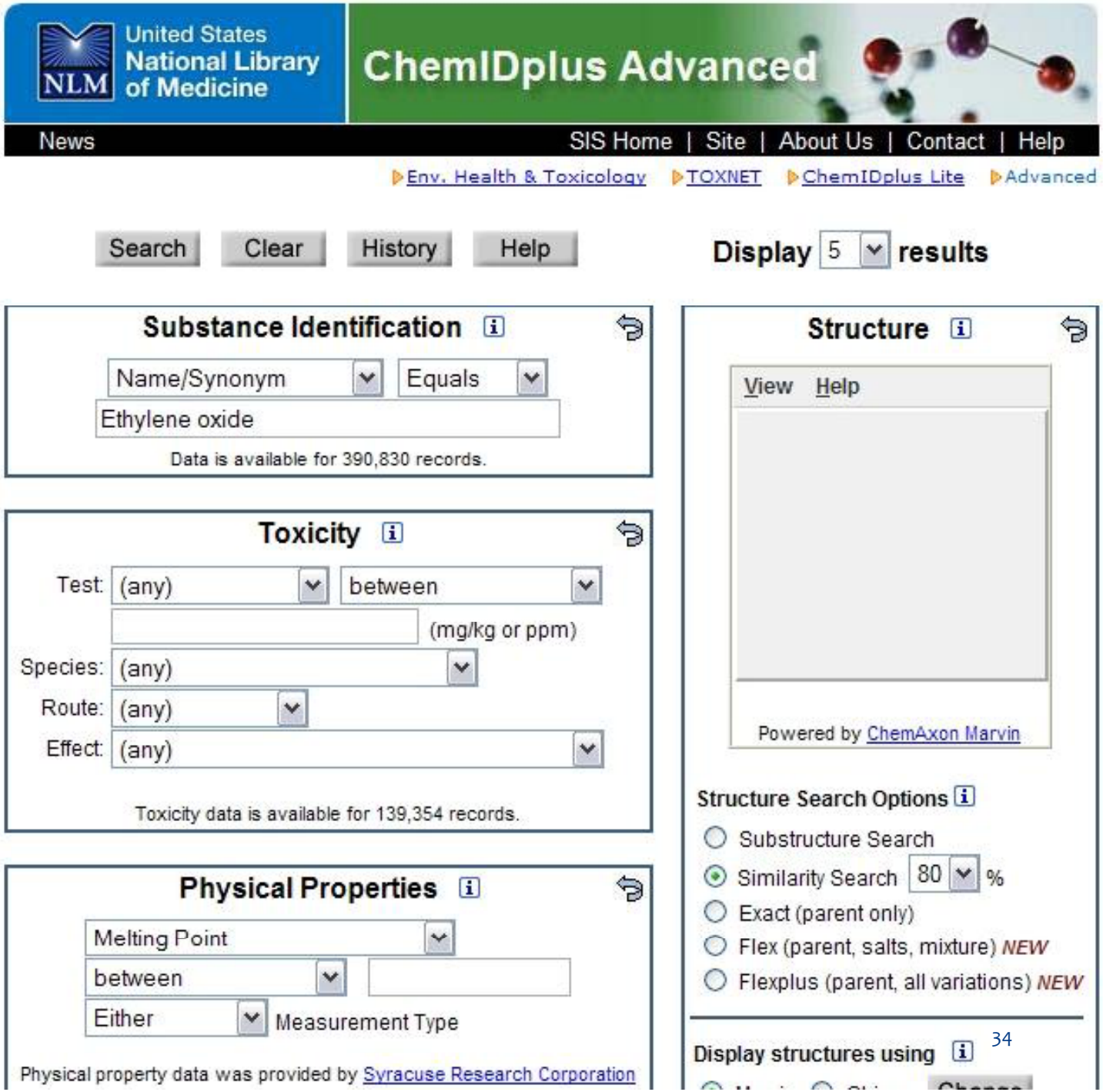
- QSA1. Acyl halides?
- QSA2. Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid?
- QSA3. N-methylol derivative?
- QSA4. Monohaloalkene?
- QSA5. S or N mustard?
- QSA6. Propiolactones and propiosultones?
- QSA7. Epoxides and aziridines?
- QSA8. Aliphatic halogens?

How do we represent compound structure in the models?

* **SMILES codes**
* **Test-based representations of chemical structure**
* **Obtain on various databases:**
  * **ChemID**
  * **EPA ACToR**
  * **ChemSpider**

Ethylene oxide

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Advanced
Search
Clear
History
Help
Display 5 results
Substance Identification
Name/Synonym
Equals
Ethylene oxide
Data is available for 390,830 records.
Toxicity
Test: (any)
between
(mg/kg or ppm)
Species: (any)
Route: (any)
Effect: (any)
Toxicity data is available for 139,354 records.
Physical Properties
Melting Point
between
Either
Measurement Type
Physical property data was provided by Syracuse Research Corporation
Structure
View
Help
Powered by ChemAxon Marvin
Structure Search Options
Substructure Search
Similarity Search 80 %
Exact (parent only)
Flex (parent, salts, mixture) NEW
Flexplus (parent, all variations) NEW
Display structures using

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Full Record

Ethylene oxide
RN: 75-21-8

Structure Descriptors

InChI
InChI=1/C2H4O/c1-2-3-1/h1-2H2
Download | View Full InChI

Smiles
C1CO1
Download

Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach) v1.60

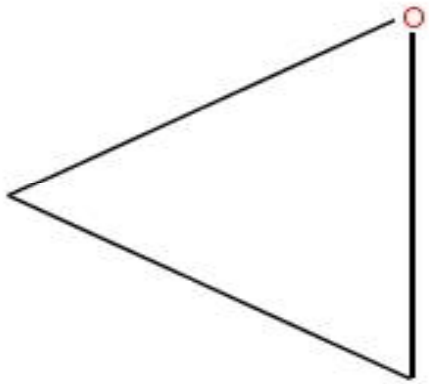
File Edit Chemical Compound Toxic Hazard Method Help

<< >> Enter SMILES: C1CO1 Go!

Available structure attributes

Benigni / Bossa rulebase ...	,SA1N,SA2N,SA3N,SA4N...
Comment	Created from SMILES
Error when applying the ...	NO
FORMULA	C2H4O
For a better assessment ...	NO
No alerts for carcinogeni...	NO
Potential S. typhimurium ...	NO
Potential carcinogen bas...	NO
QSAR6,8 applicable?	NO
SA1	NO
SA10	NO

Structure diagram



First Prev 1 / 1 Next Last

Toxic Hazard by Benigni / Bossa rulebase (for mutagenicity and carcinogenicity)

Estimate

Structural Alert for genotoxic carcinogenicity

Structural Alert for nongenotoxic carcinogenicity

No alerts for carcinogenic activity

Potential S. typhimurium TA100 mutagen based

Verbose explanation

/ Bossa rulebase (for mutagenicity and carcinogenicity)

```
.Acyl halides          No
.Alkyl (C<5) or benzyl ester of sulp
.N-methylol derivatives      No
.Monohaloalkene        No
.S or N mustard        No
.Propiolactones and propiosultones
 Epoxides and aziridines     Yes
.Aliphatic halogens    No
.Alkyl nitrite         No
1.Simple aldehyde      No
2.Quinones  No
```

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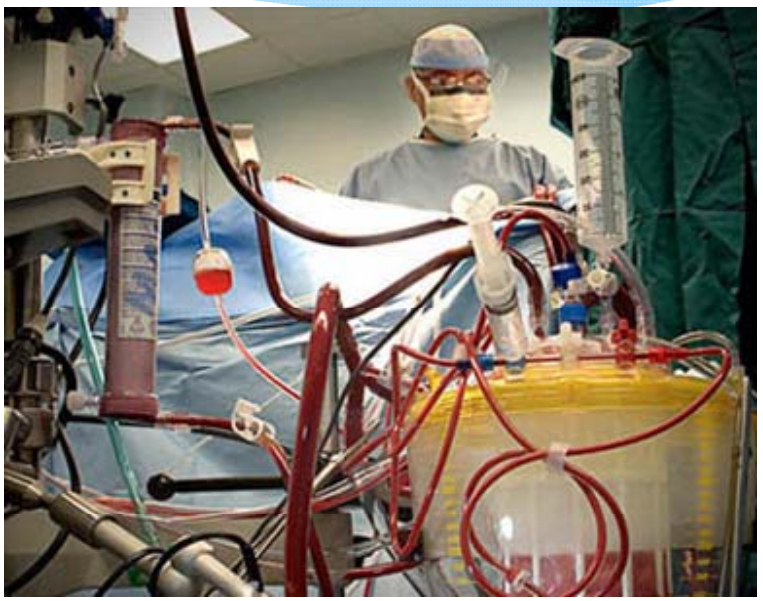
Validation of models for risk assessment

* FDA/CDRH is interested in evaluating the applicability domain of current SAR models since many have been developed and validated for drugs and environmental compounds (e.g., pesticides).

* How well do these models predict the toxicity of compounds released from medical devices?



Example

Predicting how fast cars can go

Observation: Red cars go fast, blue cars go slow

Teach model how to predict based on this training set

Use the model to predict the speed of cars

Unknowns

Applicability domain

What cars is the model applicable for?

In silico mutagenicity prediction for leachable compounds from dental devices

* Collaborative project between investigators at FDA and 3M Corp. One of the first applications of QSAR modeling to predict the toxicity of compounds released from dental/medical devices.

* Presented at the 2012 SOT meeting.

* Use of consensus approach (agreement among multiple models) improves the sensitivity/specificity of the predictions compared to the use of individual models.

Toxicological Sciences 127(1), 1–9 (2012)
doi:10.1093/toxsci/kfs095
Advance Access publication March 2, 2012

Predictive Modeling of Chemical Hazard by Integrating Numerical Descriptors of Chemical Structures and Short-term Toxicity Assay Data

Ivan Rusyn,*,1 Alexander Sedykh,† Yen Low,*,† Kathryn Z. Guyton,‡ and Alexander Tropsha†

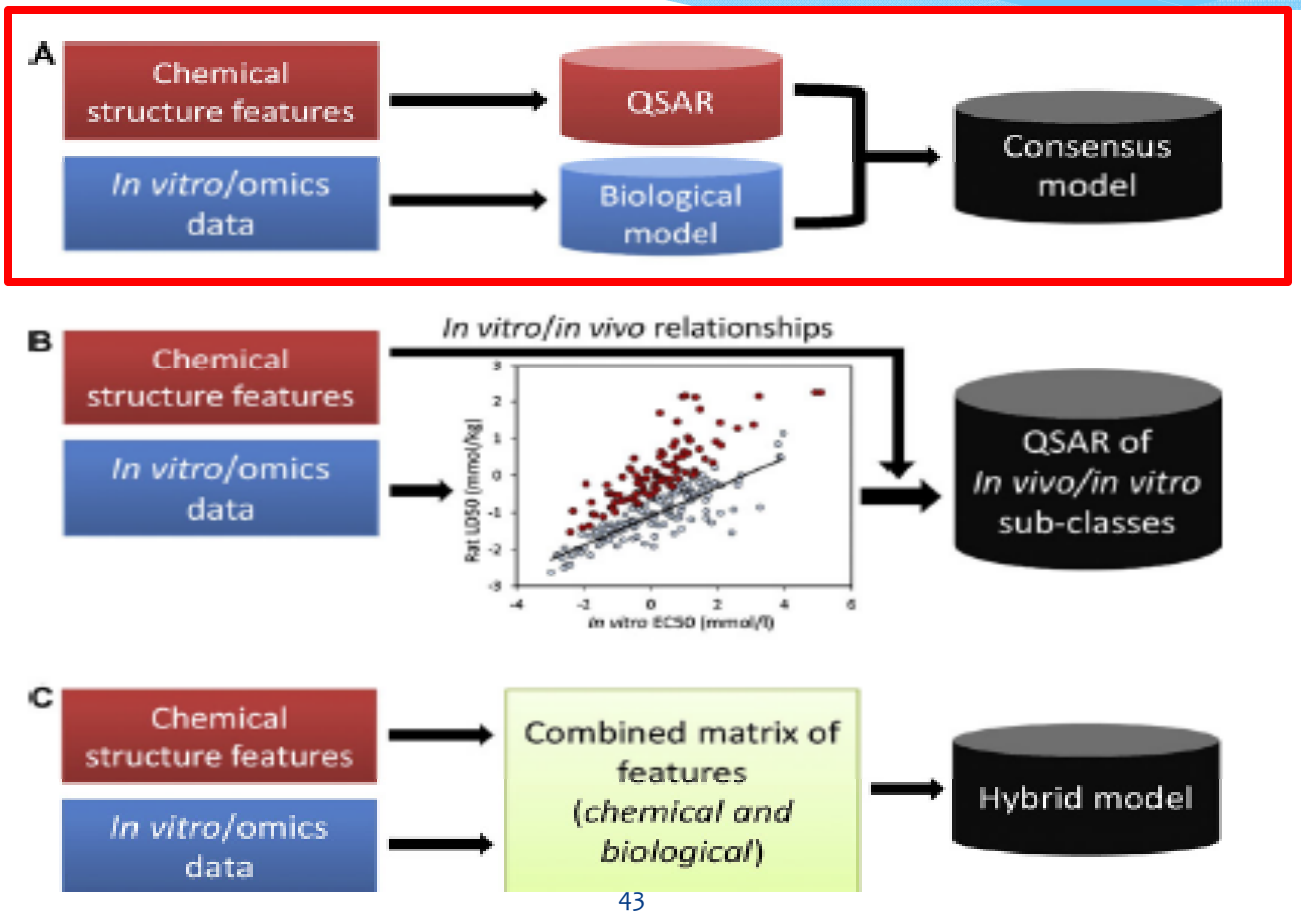


FIG. 1. Strategies for utilizing biological and chemical data in predictive modeling of *in vivo* toxicity.

Predictive Ability of *In Vitro Genotoxicity* Data for Carcinogenicity

	Ames (56)	MN (60)	H2AXISV (59)	Vitotox (60)	Radarscreen (60)	RAD51 (60)	Cytstatin A (60)	P53 (60)	Nrf2 (60)	COMET (11)
Accuracy	67.8	65	71.1	63.3	61.6	63.3	65	68.3	61.6	54.5
Sensitivity	43.3	41.9	51.6	41.9	45.1	35.4	41.9	48.3	54.8	44.4
Specificity	96.1	89.6	92.8	86.2	79.3	93.1	89.6	89.6	68.9	100

Predictive Ability of Computational Models for Carcinogenicity

	Toxtree	Lazar
Accuracy	45.4545	72.7273
Sensitivity	44.4444	66.6667
Specificity	50	100

Predictive Ability of Consensus Approach In Vitro Data and Toxtree

	Ames (56)	MN (60)	H2AXISV (59)	Vitotox (60)	Radarscreen (60)	RAD51 (60)	Cytstatin A (60)	P53 (60)	Nrf2 (60)	COMET (11)
Accuracy	66.7	65.2	68.4	63.7	60.3	63.8	63.7	69.0	60.3	54.5
Sensitivity	60.7	65.2	72.44	62.1	65.5	62.1	65.5	69.0	75.9	55.6
Specificity	73.1	65.2	64.3	65.5	55.1	65.5	62.1	69.0	44.8	50

Sensitivity (Ames)

in vitro data alone: 43.3%
model alone: 44.4%
hybrid: 60.7%

Sensitivity (p53)

in vitro data alone: 48.3%
model alone: 44.4%
Hybrid: 69.0%

Ability of QSAR models and expert systems to predict carcinogenicity as a function of carcinogenic potency and chemical structural class

Artem Korolev[1,2], Prachi Pradeep[2,3], Stephen Merrill[2,3], Shannon White[2], Ron Brown[2]
[1]UMBC, Catonsville, MD; [2]CDRH, US Food and Drug Administration, Silver Spring, MD; [3]Marquette University, Milwaukee, WI

Background

QSAR models and expert systems have the potential to predict the carcinogenicity of compounds based on their chemical structure.

Although these models have been shown to accurately predict the carcinogenicity of compounds with diverse chemical structures, it's not clear whether these computational approaches perform better for certain chemical classes and potency levels.

In this project, we have identified the structural classes associated with the highest and lowest accuracy for two models, Toxtree and Lazar.

The results of this project will allow CDRH staff to determine when model-derived predictions of carcinogenicity can be confidently used to support regulatory decision making.

Methods

Identify and compile an experimental dataset of compounds with a range of TD_{50} values (dose that produces tumors in 50% of treated animals) from the Carcinogenic Potency Database.

Run the compounds through Toxtree software using the Benigni-Bossa rulebase decision tree and through Lazar software by selecting endpoints for carcinogenicity and mutagenicity.

Compare the results given by the models with the experimental data and determine the predictive ability of the models as a function of Toxtree structural class and potency.

DSSTox Carcinogenic Potency DBS MultiCellCall predictions were used to determine the accuracy of the Lazar model and the presence of structural alerts used to determine the accuracy of the Toxtree model.

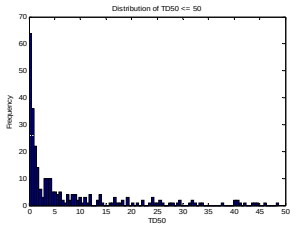
Results

Predictive ability as a function of structural class

Structural Class	Percentage of Correct Predictions Toxtree	Percentage of Correct Predictions Lazar
Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid	75	75
N-methylol derivatives	50	50
Monohaloalkene	83.3333	83.3333
S or N mustard	85.7143	57.1429
Propiolactones and propiosultones	100	75
Epoxides and aziridines	56.5217	47.8261
Aliphatic halogens	48.9796	46.9388
Alkyl nitrite	100	100
α,β unsaturated carbonyls	52.6316	28.9474
simple aldehyde	50	50
Quinones	90.9091	81.8182
Hydrazine	61.2903	54.8387
Aliphatic azo and azoxy	100	100
Isocyanate and isothiocyanate groups	50	25
Alkyl carbamate and thiocarbamate	100	100
Thiocarbonyl (Nongenotoxic carcinogens)	55	45
Polycyclic Aromatic Hydrocarbons	75	66.6667
Heterocyclic Polycyclic Aromatic Hydrocarbons	85.7143	85.7143
Halogenated Cycloalkanes (Nongenotoxic carcinogens)	50	50
Alkyl and aryl N-nitroso groups	82.5688	81.6514
Azide and triazene groups	66.6667	33.3333
Aliphatic N-nitro	66.6667	66.6667
α,β unsaturated alkoxy	100	50
aromatic nitroso group	100	75
Aromatic ring N-oxide	100	100
Nitro aromatic	64.4737	61.8421
Primary aromatic amine, hydroxyl amine and its derived esters (with restrictions)	67.2131	62.2951
Aromatic diazo	83.3333	50
Coumarins and Furocoumarins	42.8571	28.5714
Pyrrolizidine Alkaloids	100	0
Alkenylbenzenes	50	33.3333
Steroidal estrogens	0	0
substituted phenoxyacid	100	100
substituted n-alkylcarboxylic acids	26.6667	6.6667
phthalate diesters and monoesters	50	25
Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene	60	60
pentachlorophenol	100	100
o-phenylphenol	50	50
imidazole and benzimidazole	50	50
dicarboximide	50	50
Benzensulfonic ethers	25	0
1,3-Benzodioxoles	66.6667	44.4444
alkyl halides	33.3333	33.3333
aN=Na. Aromatic diazo	83.3333	50
ar-N=CH2 Derived aromatic amines	100	100
Aromatic mono- and dialkylamine	100	71.4286
Aromatic N-acyl amine	57.8947	47.3684
Halogenated benzene (Nongenotoxic carcinogens)	43.75	25

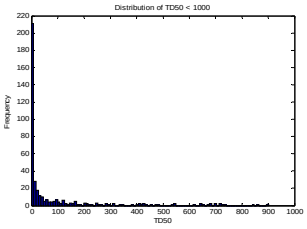
Predictive ability as a function of carcinogenic potency

Case 1: TD_{50} < 50 mg/kg/day



Potency Bin Number	Potency	Count	Accuracy Toxtree	Accuracy Lazar
1	TD_{50} < 5	181	91.1602	83.4254
2	5 ≤ TD_{50} < 10	34	91.1765	88.2353
3	10 ≤ TD_{50} < 15	17	70.5882	70.5882
4	15 ≤ TD_{50} < 20	12	91.6667	100
5	20 ≤ TD_{50} < 25	9	88.8889	77.7778
6	25 ≤ TD_{50} < 30	9	100	77.7778
7	30 ≤ TD_{50} < 35	6	83.3333	100
8	35 ≤ TD_{50} < 40	1	100	100
9	40 ≤ TD_{50} < 45	9	66.6667	66.6667
10	45 ≤ TD_{50} < 50	2	50	100

Case 2: TD_{50} < 1000 mg/kg/day



Potency Bin Number	Potency	Count	Accuracy Toxtree	Accuracy Lazar
1	TD_{50} < 100	310	88.3871	83.871
2	100 ≤ TD_{50} < 200	27	70.3704	74.0741
3	200 ≤ TD_{50} < 300	15	60	66.6667
4	300 ≤ TD_{50} < 400	5	100	80
5	400 ≤ TD_{50} < 500	10	30	60
6	500 ≤ TD_{50} < 600	3	66.6667	100
7	600 ≤ TD_{50} < 700	7	85.7143	85.7143
8	700 ≤ TD_{50} < 800	6	66.6667	66.6667
9	800 ≤ TD_{50} < 900	2	100	50
10	900 ≤ TD_{50} < 1000	1	0	0

Conclusions

The ability of both Toxtree and Lazar software programs to predict the carcinogenic potential of compounds differs for compounds in various structural classes. Future efforts will be directed to determining why the difference in predictive ability exists as a function of structural class.

There is a good concordance between model-derived estimates of carcinogenicity using the Toxtree and Lazar models.

Both models are able to predict carcinogenicity with a high degree of accuracy for very potent carcinogens (TD50 < 50), but there is insufficient data to evaluate model predictive performance for weak carcinogens.

Acknowledgments

The efforts of Ed Gordon on poster preparation are gratefully acknowledged.

Application of SAR models to address regulatory issues

Proceedings of the ASME/FDA 2013 1st Annual Frontiers in Medical Devices: Applications of Computer Modeling and Simulation
FMD2013
September 11-13, 2013, Washington, DC, USA

Use of QSAR Modeling to Predict the Carcinogenicity of Color Additives

Ronald Brown[1], Shannon White[1], Jennifer Goode[1], Prachi Pradeep[2], Stephen Merrill[1,2]
US FDA Center for Devices and Radiological Health (CDRH)[1], Silver Spring, MD and Marquette University[2], Milwaukee, WI

Model	Sensitivity	Specificity	Negative PV	Positive PV
Lazar	0.82	1.00	0.81	1.00
Toxtree	0.81	0.47	0.69	0.63
OECD	0.67	0.25	0.36	0.54

Useful resources


Toxicology and Applied Pharmacology 254 (2011) 181–197

Contents lists available at ScienceDirect

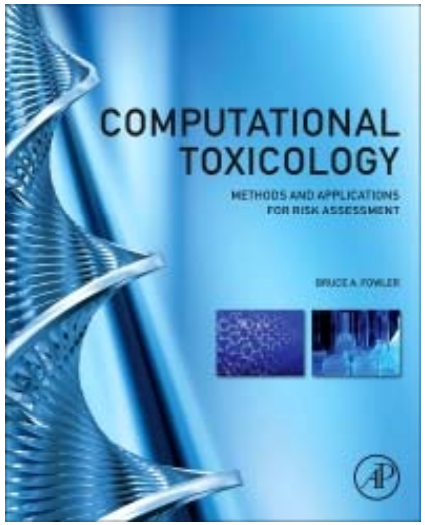
Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

SAR/QSAR methods in public health practice

Eugene Demchuk *, Patricia Ruiz, Selene Chou, Bruce A. Fowler

Agency for Toxic Substances and Disease Registry (ATSDR), Division of Toxicology and Environmental Medicine, Atlanta, GA 30333, USA



Review of QSAR Models and Software Tools for Predicting Genotoxicity and Carcinogenicity

Rositsa Serafimova, Mojca Fuart Gatnik and Andrew Worth


Regulatory Toxicology and Pharmacology 66 (2013) 301–314

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

A comparative survey of chemistry-driven *in silico* methods to identify hazardous substances under REACH

Monika Nendza [a,*], Silke Gabbert [b], Ralph Kühne [c], Anna Lombardo [d], Alessandra Roncaglioni [d], Emilio Benfenati [d], Romualdo Benigni [e], Cecilia Bossa [e], Sebastian Strempel [f], Martin Scheringer [f], Alberto Fernández [g], Robert Rallo [h], Francesc Giralt [g], Sabcho Dimitrov [i], Ovanes Mekenyan [i], Frank Bringezu [j], Gerrit Schüürmann [c,k]

ORCHESTRA

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Commission of the European Communities
through the FP7-COOPERATION contract 226521 - ORCHESTRA

PUBLICSPACE
RESEARCH DISSEMINATION

QSARs in REACH? uses, issues and priorities

QSAR models aim to offer fast, rigorous and reliable evaluations of chemical toxicity. So will they be accepted within the EU REACH regulations? This documentary is based on 20 interviews with key regulators, industry representatives and expert QSAR developers. It addresses current limitations, issues and priorities. It's a 30-min professional briefing. More at **ORCHESTRA-QSAR.eu**

The documentary is intended primarily for toxicologists, regulators and developers of QSAR models. We have tried to ensure that it is also accessible to a wider audience. It was researched and produced by **PublicSpace.ac.uk** as part of the European EC FP7 funded **ORCHESTRA-QSAR.eu** project (contract 226521).

The 2007 EU legislation for the Registration, Evaluation, Authorisation & restriction of CHemicals (REACH) now requires industry to evaluate the toxicity not just of new chemicals, but of around 30,000 existing chemical substances that are in use but which have never been subject to regulatory-approved testing. Where reliable experimental data on the toxicity of chemicals already exists, toxicologists can use QSAR models to predict the toxicity of other chemicals with related molecular structures. Thousands of chemicals can be evaluated quickly and cheaply, which makes large scale evaluation and screening feasible while reducing the need for animal testing. There are limitations and different approaches, but US regulatory authorities have developed and used QSARs for many years. In this documentary we explore the issues and priorities.

QSARs in REACH? 1. Introduction & Regulatory perspectives


QSARs in REACH?
1. Introduction &


QSARs in REACH?
2. What makes a good

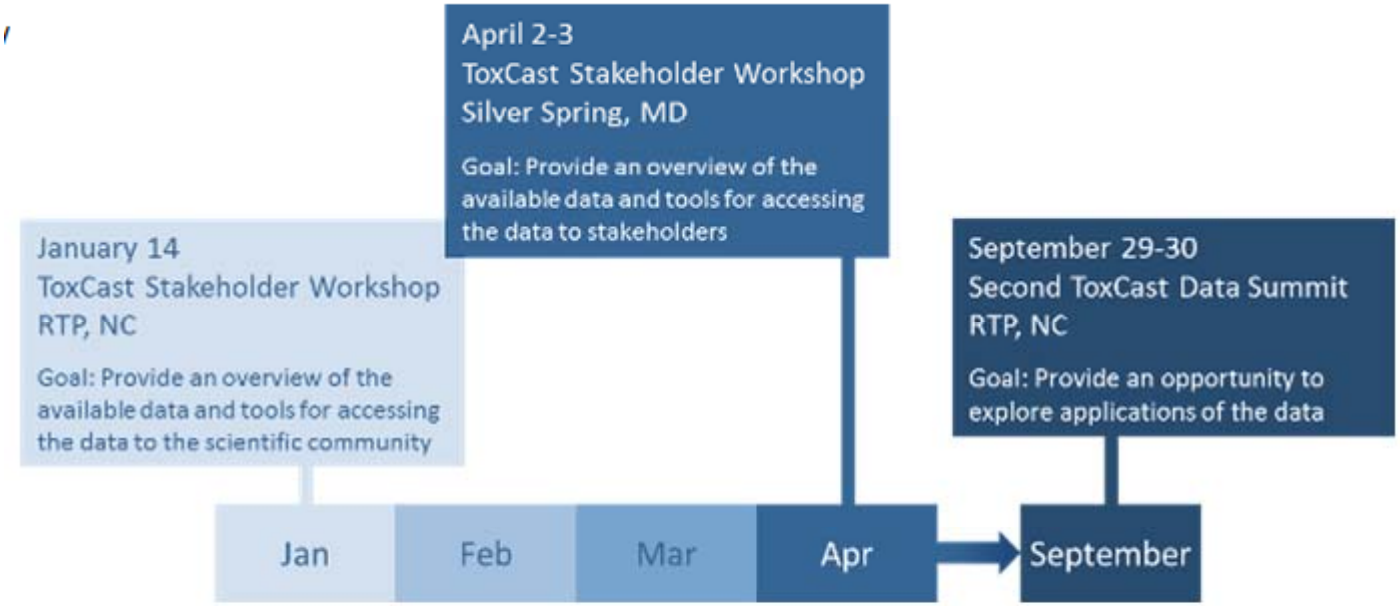

QSARs in REACH?
3. Industry perspectives.


QSARs in REACH?
4. Future directions.

ToxCast Data Summit | September 29-30, 2014 | Research Triangle Park, North Carolina

HOME | REGISTRATION | ABSTRACTS

Announcement: The Data Summit has been scheduled for September 29-30, 2014.



Take home messages

* **The biological safety of medical devices is typically assessed by conducting biocompatibility testing of an extract of the device or the device itself; however, there is growing interest in an alternate approach that involves characterizing the chemical composition of the device extract and conducting a risk assessment on the compounds identified in the extract.**

* **One limitation to the practical implementation of this chemical characterization/risk assessment approach is the lack of toxicity data for many compounds released from device materials. To address this need, computational toxicology models, such as Structure-Activity Relationship (SAR) models, are being increasingly used to predict the toxicity or carcinogenicity of compounds based on their chemical structure.**

Take home messages

* When the chemical characterization/risk assessment approach is used to assess the biological safety of the device, and we don't have the toxicity data necessary to establish a Tolerable Intake (TI) value for each compound, expert systems like Toxtree can be used to determine which TTC value to use for the risk assessment.

* SAR models can also be used to provide justification for not performing some (but not all) biocompatibility tests, but they should ideally be used as one component in a weight-of-evidence approach.

* There are no CDRH criteria for the use of computational models in regulatory submissions, but guidance in ICH M7 is useful.

Take home messages

* **Many SAR models are available (expert systems, statistical models). Many are menu-driven, user friendly, and publically available.**

* **Depending on the endpoint, most models are not ready for regulatory use. Models need to be validated using data from compounds that are known to be released from device materials.**