NJrisk PROJECT

For Implementing an Integrated Computational Tool to Support Prioritization of Chemicals of Emerging Concern

ANNUAL PROGRESS REPORT
July 1, 2015 to June 30, 2016

Submitted to Robert Mueller
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1 Summary Overview

The objective of the NJrisk project is to develop, text, and deploy an integrated tiered system coupling computational platforms to support prioritization of Chemicals of Current and of Emerging Concern.

1.1 Summary of Work Completed in Previous Project Years

A nine-month Pilot Study was conducted from July 2013 to March 2014, in order to complete the necessary groundwork for the subsequent implementation. The full study, which began in April 2014, uses two operational computational platforms for hazard and for exposure ranking, respectively METIS (Metanomics Information System), developed by DuPont, and PRoTEGE (Prioritization and Ranking of Toxic Exposures with GIS Extension), developed by the Computational Chemodynamics Laboratory of EOHSI. This effort also takes advantage of, and incorporates in the development of the new system, current and anticipated outcomes of ongoing efforts by Federal Agencies, such as the USEPA [see, e.g., 1,2,3 and Figure 1]. The goal is to implement an integrated software platform or "tool" (NJrisk) that will allow many types of users to assess both hazard and exposure potentials of chemicals that are found (or could be introduced) in the New Jersey environment and/or biota, and to prioritize these chemicals for regulatory action based on tiered risk analysis.

The pilot phase of the project, focused on a broadly representative set of 15 "pilot" chemicals of current and emerging concern. Case studies involving these 15 chemicals were used to establish initial software requirements and specifications for NJrisk, for completion through the subsequent implementation phases. The initial phase of the full study (from April 1, 2014 to June 30, 2015) expanded the list of the 15 "pilot" substances to 40 test-case chemicals of current and emerging concern (listed in the next sub-section), corresponding to various combinations of production volumes, physical and chemical properties, environmental distribution, industrial utilization, consumer usages, exposure pathways, etc.

1.2 List of Major Project Activities during the July 2015 to June 2016 period

During the current reporting period, from July 1, 2015 to June 30, 2016, development, testing and refinement of the NJrisk system continued, focusing on:

- The expansion of the information base for the NJrisk platform by incorporating linkages to additional data sources from both the
    - US Environmental Protection Agency (USEPA), and the
    - European Chemicals Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program.
- The incorporation of factors and results from USEtox (the UNEP-SETAC toxicity model, available from www.usetox.org).
- The addition of endocrine disruption as a toxicity pathway of concern.
- The establishment of a local (MySQL-based) ToxCast installation, to facilitate better integration of USEPA ToxCast-derived information into the online NJrisk platform.
- The preliminary assessment of available ecotoxicological information and selection of relevant ecotoxicity endpoints that will be utilized in developing an ecological risk matrix in subsequent phases of development of the NJrisk platform.
- The preliminary evaluation and testing of Multi-Criteria Decision Support schemes for cases when quantitative information is missing or uncertain and only qualitative (or "semi-quantitative") information on ongoing and potential uses of the chemical(s) of concern is available.
- The re-structuring, updating, and re-building of the software/code infrastructure supporting METIS and ProTEGE, as well as NJrisk, in order to
    - ensure compatibility with rapidly evolving database and web standards, and
    - facilitate long-term maintenance and sustainability of the codes involved as well as streamline the process of anticipated (and non-anticipated) modifications in the future.
- The establishment of a secure (non-public) GitHub repository for documenting and controlling alternative versions of new METIS, PRoTEGE annd NJrisk codes; this further enhances Quality Assurance testing procuderes for the codes under development.

In parallel to the above listed activities during the July 2015 to June 2016 period, another set of six diverse chemicals (or groups of chemicals) representing further challenges regarding available knowledge and information regarding properties, production, potential usages, etc. was added to the existing test-cases list, for further testing and enhancement of the NJrisk system. Preliminary results involving these additional chemicals are presented in the last Section of this Annual Report.

The Appendix of this Annual Report summarizes the structure of the (non-public) GitHub Repository for NJrisk codes.

2 Project Objectives and Methods

2.1 Rationale and Objectives

All regulatory agencies, nationally and internationally, face current challenges in their efforts to address concerns regarding the rapid introduction of many "new" chemicals or the use of "old" chemicals in new products, resulting to "new types of exposures" for human populations and ecosystems. A variety of approaches are being developed to support these efforts; our present effort directly addresses a critical State and National need.

A major attribute of the integrated NJrisk system currently under development is that, in addition to addressing chemicals of "current regulatory concern," it will also facilitate characterization of contaminants of "emerging concern." In general the term "emerging contaminants" refers to hazardous materials or mixtures that may have:

a. a perceived or real threat to human health, public safety or the environment;
b. no published or evolving health standards or guidelines;
c. insufficient or limited available toxicological information that is evolving or being re-evaluated; or
d. significant new sources, pathways, or detection limits.

Some major classes of Chemicals of Emerging Concern (CECs) include pharmaceutical and personal care products (PPCPs); engineered nanomaterials (ENMs) such as silver nanoparticles and carbon nanotubes; plasticizers, flame retardants, protective coatings; home cleaning products; and food additives.

In the pilot phase of this project, METIS and PRoTEGE were employed to conduct studies involving hazard and exposure characterization applications for a broadly representative set of 15 chemicals of current and emerging concern, These case studies were analyzed and evaluated in order to identify optimal ways for linking and merging appropriate METIS and PRoTEGE components and corresponding data retrieval and calculation procedures, and to establish initial software requirements and specifications for NJrisk that are being completed through the current and subsequent implementation phases. The initial phase of the full study (from April 1, 2014 to June 30, 2015) expanded the list of the 15 "pilot" substances to include the following 40 chemicals:

	Chemical	**CAS#**
1.	1,2,3–Trichlorobenzene	87-61-6
2.	2,4,5-Trichlorophenoxyacetic acid	93-76-5
3.	2,4-D	94-75-7
4.	Aldicarb	116-06-3
5.	Aroclor_1254	11097-69-1
6.	Arsenic	7440-38-2
7.	Atrazine	1912-24-9
8.	Bisphenol-A	80-05-7
9.	C10-13 Chloroalkanes	85535-84-8
10.	Cadmium	7440-43-9
11.	Carbaryl	63-25-2
12.	DDT	50-29-3
13.	decaBDE	1163-19-5
14.	DEHP, Di(2-ethylhexyl)phthalate	117-81-7
15.	Diethyl Phthalate	84-66-2

16.	Di-n-butylphtalate	84-74-2
17.	Ethane, 1,1,2,2-tetrachloro-	79-34-5
18.	Perchlorethylene	127-18-4
19.	Ethylene thiourea	96-45-7
20.	Ethylparaben	120-47-8
21.	Formaldehyde	50-00-0
22.	gamma-Hexachlorocyclohexane	58-89-9
23.	Lead	7439-92-1
24.	Malathion	121-75-5
25.	Manganese	7439-96-5
26.	Methoxychlor	72-43-5
27.	Methyl Mercury	22967-92-6
28.	n-Hexane	110-54-3
29.	octaBDE	32536-52-0
30.	Parathion	56-38-2
31.	Pentachlorophenol	87-86-5
32.	pentaBDE	32534-81-9
33.	Permethrin	52645-53-1
34.	PFOS	1763-23-1
35.	Phenol, (1,1-dimethylethyl)-4-methoxy-	25013-16-5
36.	Trifluralin	1582-09-8
37.	Tris (1,3-dichloro-2-propyl) phosphate	13674-87-8
38.	Tris (2-chloroethyl) phosphate	115-96-8
39.	Vinclozolin	50471-44-8
40.	Vinyl Chloride	75-01-4

The following six chemicals (or groups of chemicals) representing further challenges regarding available knowledge and information regarding properties, production, potential usages, etc. were added to the above test-cases list, for further testing and enhancement of the NJrisk system, during the current reporting period (7/1/2015-12/31/2015)

41.	C10-13 Chloroalkanes	85535-84-8
42.	Mid Chain Chlorinated Paraffins C14-17	85535-85-9
43.	Long Chain Chlorinated Paraffins C18-30+	63449-39-8
44.	1-Bromopropane	106-94-5
45.	1,4-Dioxane	123-91-1
46.	Brominated Phthalates Cluster	26040-51-7

2.2 Methods Employed in Developing and Deploying NJrisk

The ongoing research and development effort addresses Tiers 1, 2 and 3 of the Chemicals of Emerging Concern evaluation process depicted in Figure 1. Starting components are the initial screening of substances of concern (Tier 1) and the preliminary hazard and exposure assessment (Tier 2). These two steps provide a sound specific basis for extending the analysis into a Risk Assessment (Tier 3).

As stated earlier, the current effort utilizes components from two operational state-of-the-art platforms for hazard and for exposure characterization and ranking:

- METIS (Metanomics Information System), developed by DuPont, and
- PRoTEGE (Prioritization and Ranking of Toxic Exposures with GIS extension), developed by the Computational Chemodynamics Laboratory of EOHSI.

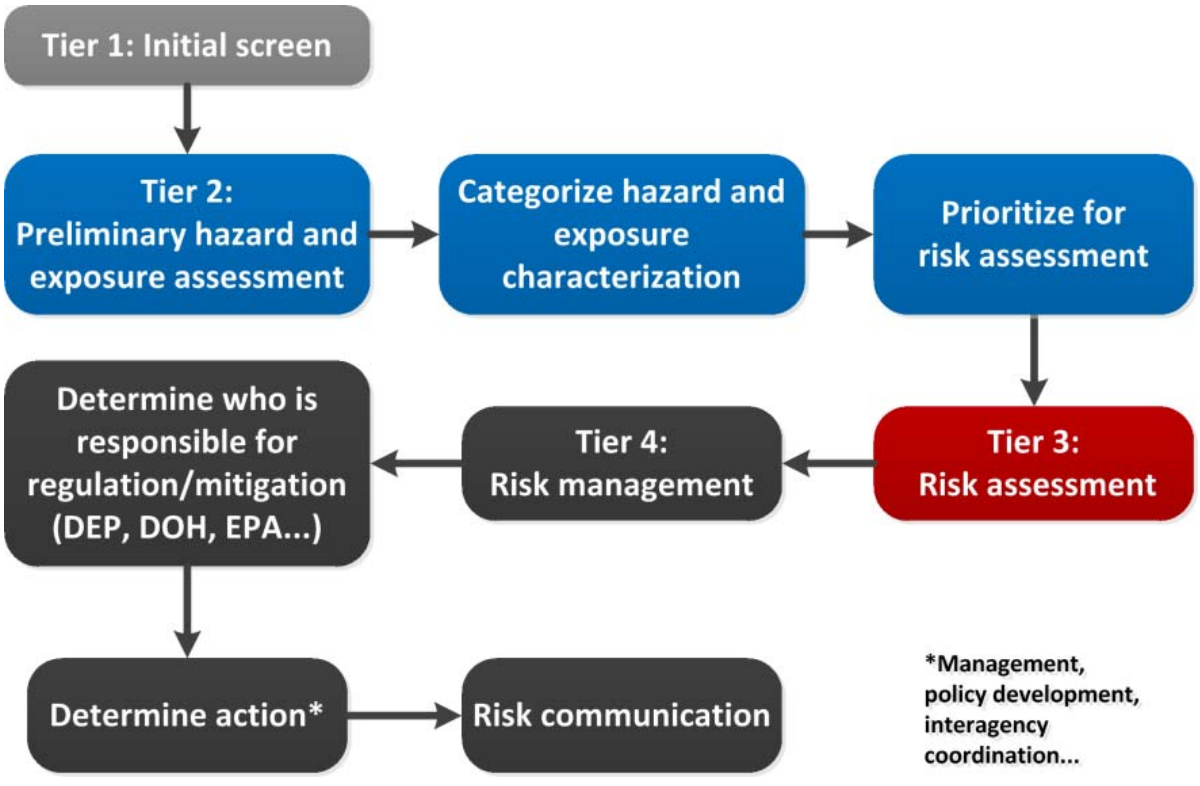


Figure 1. Overview of the Chemicals of Emerging Concern (CEC) evaluation process; adapted from NJ DEP SAB CEC Subcommittee [5]

METIS [4] is a chemical informatics platform that provides a screening level view of potential environmental fate and effects, human health concerns, and societal perception issues associated with a chemical of concern. As an example, Figure 2 depicts "METIS attributes" that have been retrieved in a systematic manner from a variety of databases for a representative chemical. Typically these attributes are:

- Environmental Persistence – indicates the predicted half-life in each environmental compartment,
- Soil Mobility – the potential for a chemical to migrate from soil into groundwater,
- Bioaccumulation – uses measured or estimated values to indicate the potential for a chemical to sorb to lipids,
- Aquatic Toxicity – the measured or estimated toxicity to aquatic organisms,
- CMR – indicates whether the compound is classified as known or suspected animal and/or human Carcinogen, Mutagen or Reproductive toxin,
- Public Perception – indicates that the chemical is present on a variety of regulatory, industrial and/or non-governmental lists that may influence how the public views a particular chemical,
- Environmental Impact – indicates the potential for the chemical to affect global warming and ozone depletion as compared to reference compounds,

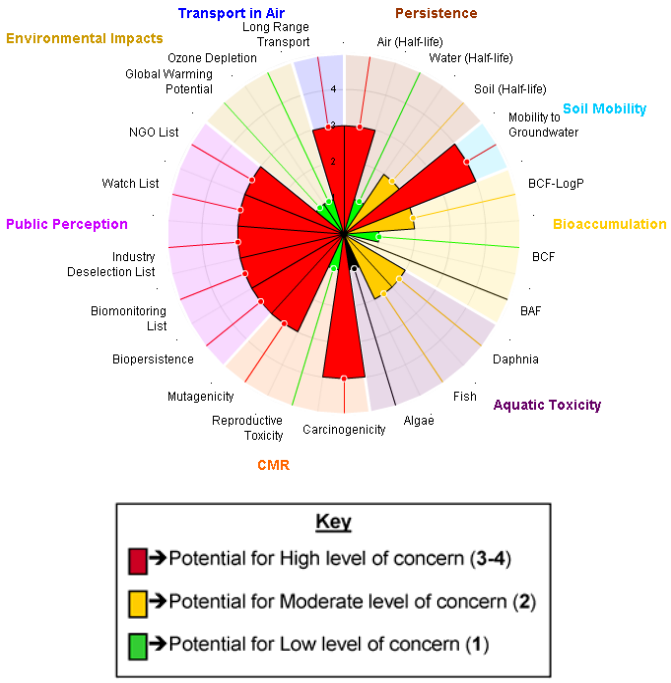


Figure 2. Hazard-related attributes of chemicals retrieved and plotted by the Metanomics Information System (METIS)

- Long Range Transport (Air) – the potential for the chemical to travel long distances from its point of entry into the environment,
- Environmental Partitioning (Fugacity) – steady-state partitioning of a chemical in the environment (Air, Water, Soil, Sediment) based on different emission scenarios.

METIS has been built on open-source software that provides access to an aggregated database and estimation tool set. METIS retrieves and assembles information from over 1,400 publicly available databases (see Table 1 for a representative set of these databases). These data resources may contain, but are not limited to, physical and chemical properties, hazard, toxicological, environmental and regulatory information. The input for METIS is simply the chemical name, CAS #, or chemical structure. METIS retrieves information and assembles it together into a comprehensible view in seconds to minutes versus weeks to months that could be required, in some cases, by conventional searches.

Table 1. Selected databases accessed by METIS (hosted locally)

Database	Expanded Name
BCF	Bio-concentration Factors Gold standard database (Cefic LRI, EURAS)
CDAT – CDR	Chemical Data Access Tool -Chemical Data Reporting
CCRIS	Chemical Carcinogenesis Research Information System
DIPPR	Design Institute for Physical Properties
ECOTOX	ECOTOXicology database
HSDB	Hazardous Substances Data Bank
MITI	Ministry of International Trade and Industry (Existing and New Chemical Substances List)
PBDB	
PHYSPROP	Physical Properties Database
PubChem	--
SRC BCF	SRC Bioconcentration Factor
ToxMiner	--

PRoTEGE [6,7] is an analysis and modeling platform that facilitates exposure calculations at multiple tiers, utilizing available data on:

- chemical production volumes,
- intrinsic properties that affect the environmental dynamics of the chemical (e.g. volatility, solubility, etc.),
- intrinsic properties (such as lipophilicity) that affect the biological dynamics (absorption, distribution, metabolism, elimination) of the chemical, and subsequent uptake/bioaccumulation by humans and wildlife,
- chemical transportation modes and amounts,
- chemical usage in industrial, agricultural, etc. applications,
- environmental release/disposal amounts and spatiotemporal pattern,
- chemical uses in consumer products and in foodstuffs,
- environmental concentrations of chemicals in multiple media (including food and beverages),
- age- and gender-specific population distributions of physiological and behavioral attributes.

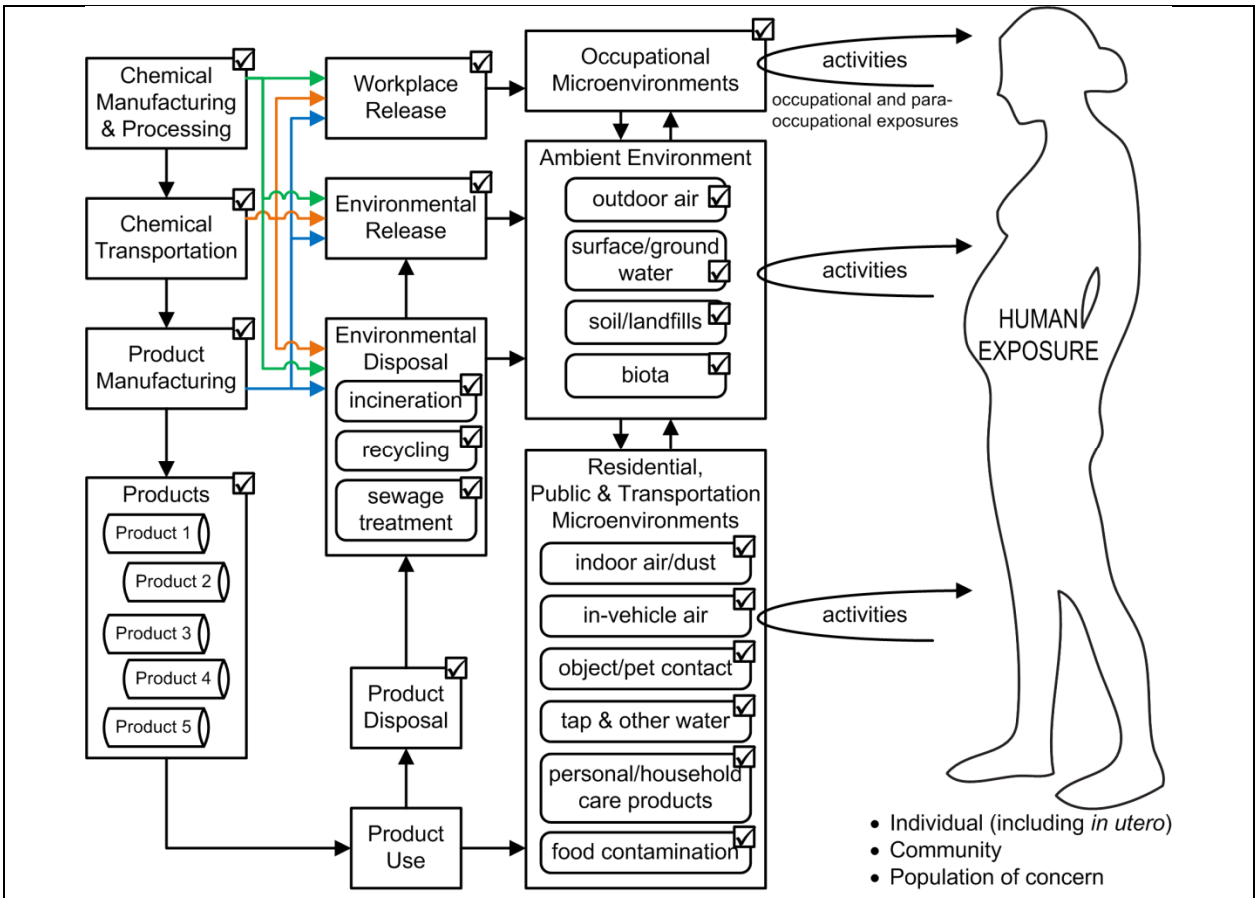


Figure 3. A schematic depiction of the conceptual framework of PRoTEGE (Prioritization and Ranking of Toxic Exposures with GIS Extension) [6,7]; this system uses a Life Cycle Assessment (LCA) approach to assess potential human exposures to chemicals that could take place during manufacturing, transportation, or using products containing these chemicals as well as following their environmental disposal.

PRoTEGE derives from and complements the Modeling ENvironment for TOtal Risk studies (MENTOR) [2,8-10], which supports detailed person-oriented ("bottom-up") source-to-dose exposure modeling for mixtures of multiple multimedia contaminants. MENTOR allows a study to focus on specific locations and subpopulations, but is both data and resource intensive. The simplified "top-down" population-oriented approach of PRoTEGE provides tiered estimates of exposures experienced by populations of concern, allowing calculations at the national, state or county level.

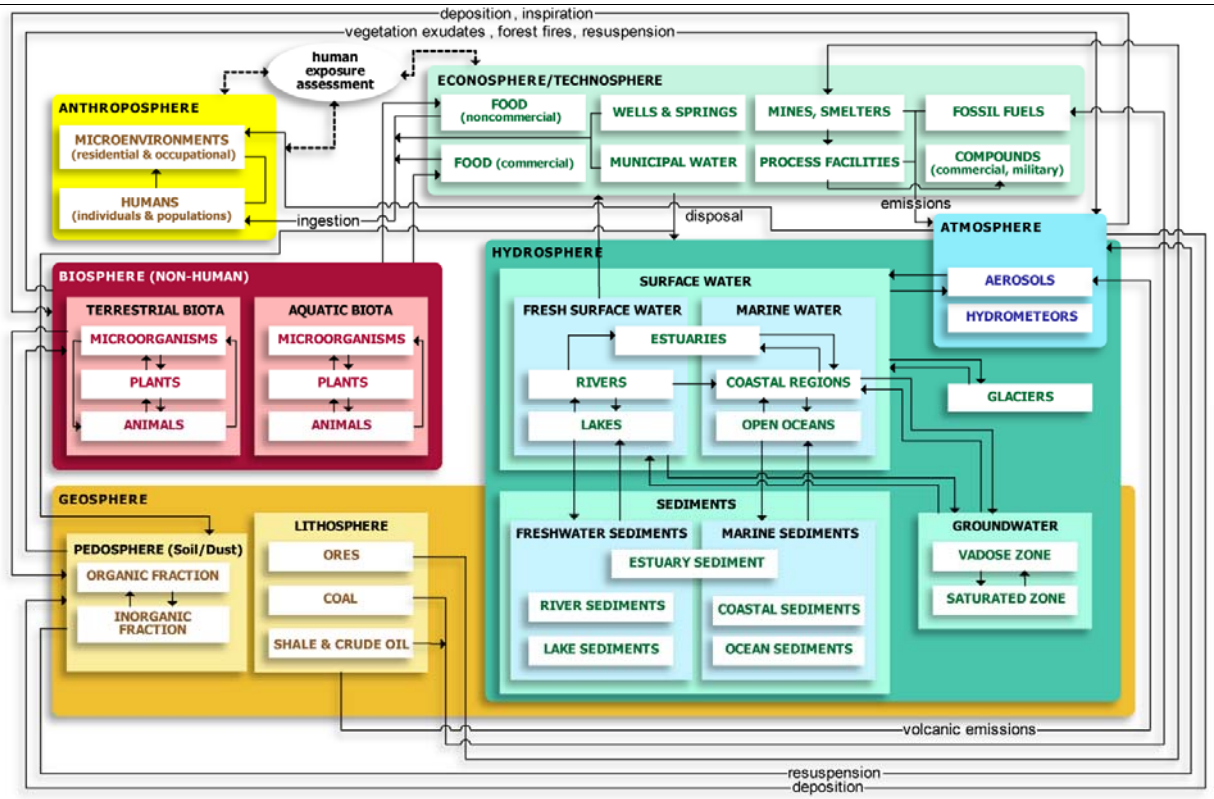


Figure 4. Multimedia/multipathway/multiroute exposure assessment in MENTOR (Modeling Environment for Total Risk studies) [2,8,9]; simplified modules of MENTOR focusing on human exposures have been developed for incorporation in PRoTEGE (Prioritization and Ranking of Toxic Exposures with GIS Extension) to support chemical ranking and screening when limited data are available. Additional PRoTEGE modules focusing on ecological exposures will be developed as part of the integrated NJrisk system.

The PRoTEGE approach takes advantage of, and integrates, both available measurements and model estimates to understand and quantify exposures of populations potentially at risk. Specifically, by utilizing over 50 available "information bases" (including various traditional databases and metadatabases, literature surveys, etc. as well as original studies reported in the literature – see Table 2) of environmental releases, chemical production and usage, multimedia environmental concentrations, and age- and gender-specific population distributions of major physiological and behavioral patterns, the estimates of PRoTEGE provide a reasonably realistic assessment of exposures that could be experienced by the general population or by subpopulations of concern.

Table 2. Partial list of information sources utilized in the PRoTEGE and NJrisk projects

Data Source Abbreviation	Expanded Name
PAC	Protective Action Criteria
NIOSH	National Institute for Occupational Safety and Health
ICSC	International Chemical Safety Cards
ToxProfs	Toxicological Profiles
IRIS	Integrated Risk Information System
HSDB	Hazardous Substance Databank
ITER	International Toxicity Estimates for Risk
McKay	Mackay's "Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals"
Howard	Howard's "Handbook of Environmental Fate and Exposure Data for Organic Chemicals"
RIVM rprts	RIVM National Institute for Public Health and the Environment reports
IARC	International Agency for Research on Cancer
PSAP	Priority Substances Assessment Program
NTP	National Toxicology Program database search
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
PFD	Pesticide Fate Database
MSDS	Material Safety Data Sheets
DSSTox	Distributed Structure-Searchable Toxicity
TMI	The Merck Index
SCP	Scorecard Chemical Profiles
HPVIS	High Production Volume Information System
ToxCast	Toxicity Forecaster
ToxRefDB	Toxicity Reference Database
GESTIS	GESTIS - Information system on hazardous substances of the German Social Accident Insurance
CEBS	Chemical Effects in Biological Systems
SIDS	Screening Information Data Set
EHPV	Expended High Production Volume
HPD	Household Products Database
IUR	Inventory Update Reporting
ECD	Existing Chemicals Database
SRD	Source Ranking Database
TRI	Toxics Release Inventory Program
NEI	National Emission Inventory
NGA	National Geochemical Atlas
NAWQA	National Water-Quality Assessment Program
AQS	Air Quality System
CPCat	Chemical/Product Categories Database
CERCLIS	Comprehensive Environmental Response, Compensation, and Liability Information System
NATA	National-Scale Air Toxics Assessments
TDS	Total Diet Study
SDWIS	Safe Drinking Water Information System
NHANES	National Health and Nutrition Examination Survey
NHEXAS	National Human Exposure Assessment Survey
ScLit	Scientific Literature
BME	Biomonitoring Equivalents
ERDEM	Exposure Related Dose Estimating Model

PRoTEGE incorporates various modeling methods that are available for developing screening estimates of exposure-relevant environmental concentrations of chemicals, including fugacity calculations [11,12], intake fractions [13,14], biomonitoring equivalents [15], etc.

When data are not available for a specific chemical, various assumptions need to be made; in these cases the estimates of PRoTEGE reflect plausible scenarios of chemical production, distribution, usage, disposal, etc.

Exposure metrics calculated by PRoTEGE provide semi-quantitative and quantitative (depending on the information that is available and the level/tier of analysis performed) measures of potential exposures to the chemical of concern. These metrics are based on a combination of available information on releases and concentrations, on types and degree of exposures reported in the literature, and expert judgment on various facets of the exposures. The four population-based metrics used for exposure ranking are: *pervasiveness*, *persistence*, *severity*, and *efficacy*.

- *Pervasiveness* reflects how widespread the exposures are (or could be) within the population of concern.
    - Quantitative factors that are considered in ranking pervasiveness include: fraction of administrative unit (e.g. counties or municipalities) where emissions or usage of the chemical are reported; production amounts for the chemical; extent of usage of the chemical in consumer products; percentage of ambient concentrations above a threshold, etc.
    - Semi-quantitative factors include information from the literature on whether exposures are wide-spread (e.g. based on the major release types), localized (e.g. based on transport scales), or limited to specific geographic areas (e.g. urban areas, farmland, coastal fishing regions, etc.).
- *Persistence* reflects the temporal frequency and/or duration of exposures experienced by the general population.
    - Factors that are considered in ranking persistence include: temporal patterns of emissions and releases, pattern of potential contact with the chemical through food consumption or usage of consumer products, environmental half-lives, chemical reactivity, etc.
    - Semi-quantitative factors include information on whether exposures are episodic, cyclical, or generally uniform over a long period of time.
- *Severity* reflects the potential for high levels of exposures.
    - Quantitative factors that are considered in ranking severity include: peak release rates, levels of peak concentrations, acute effects occurring at or near reported ambient or microenvironmental levels of the chemicals, etc.
    - Semi-quantitative factors include additional information on frequency of localized high releases, special behavior patterns that could lead to potentially high exposures, etc.
- *Efficacy* reflects the potential of the contact with the chemical to result in intake by humans (or other organisms of concern) and resulting in biologically relevant uptake.
    - Quantitative factors include biological partition coefficients, while semi-quantitative factors include information on the form of the chemical exposures (e.g. food matrix).

The above four exposure metrics of PRoTEGE are assigned integer values on a scale of 1 to 5 for each chemical considered, corresponding to “very low,” “low,” “moderate,” “high,” and “very high” exposure estimates, respectively. These rankings are calculated individually for the three major exposure routes: inhalation, ingestion, and dermal absorption; additionally, the rankings are averaged for the three routes to obtain an “aggregate ranking.”

2.2.1 Hazard, Exposure and Risk Characterization

The next paragraphs summarize the project implementation steps followed in the exploratory case studies for the test-case chemicals; in the current project phases these steps are iteratively being optimized, coded, and incorporated in the integrated computational system.

The conceptual approach being "automated" in the current project phase is schematically presented in Figure 5.

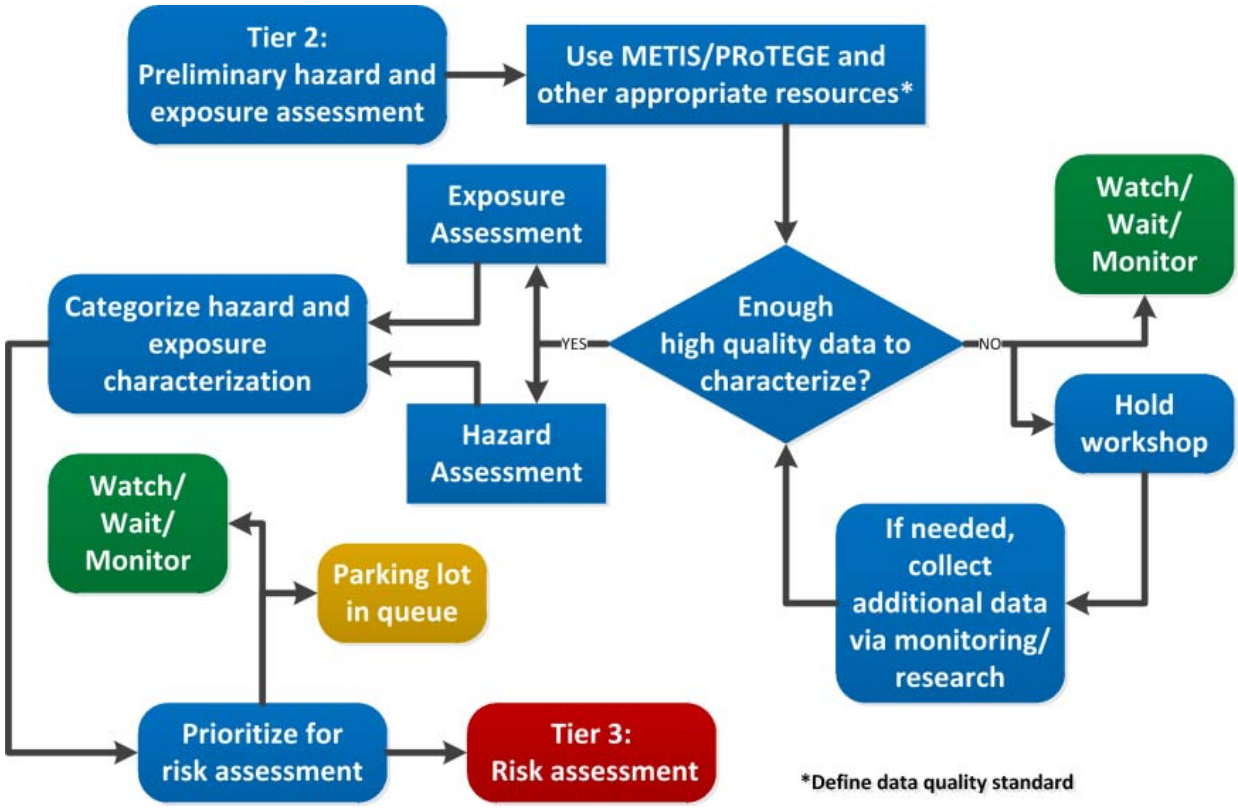


Figure 5. Tier 2 approach for preliminary hazard and exposure assessment employing PRoTEGE and METIS; adapted from NJ DEP SAB CEC Subcommittee [5]

2.2.1.1 Hazard characterization and categorization

Hazard characterization and categorization employs information retrieved using METIS, following the criteria described in:

- EPA - TSCA Work Plan Chemicals: Methods Document [16],
- EPA - Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation [17].

For hazards related to human health, evidence relevant to mammalian toxicity are considered, specifically:

- acute systemic toxicity,
- carcinogenicity, mutagenicity, reproductive/developmental toxicity (including endocrine disruption),
- neurobehavioral toxicity,

- repeated dose target organ toxicity,
- chemical respiratory sensitization.

These human health hazards are categorized as very high, high, moderate, low and very low, correspondingly, when there is:

- strong weight of evidence for mammalian toxicity (high hazard),
- uncertainty about or moderate weight of evidence or no data for mammalian toxicity (moderate hazard),
- weak weight of evidence for mammalian toxicity (low hazard).

Though the current focus is primarily on human health hazards, exposures and risks, exploratory work has also commenced for the consideration of ecological risks (that will be fully incorporated in the integrated NJrisk system in subsequent project phases).

For hazards related to ecological impact, evidence related to acute and/or chronic aquatic toxicity will be considered, specifically:

- fish toxicity,
- crustacean toxicity,
- algal toxicity.

Ecological hazards will be categorized as high, moderate and low when there is:

- strong weight of evidence for environmental (aquatic) toxicity (high hazard),
- uncertainty about or moderate weight of evidence or no data for environmental (aquatic) toxicity (moderate hazard),
- weak weight of evidence for environmental (aquatic) toxicity (low hazard).

One special issue with respect to hazard characterization involves chemicals that impact the endocrine system. The integrated framework will evaluate endocrine activity rather than simply characterizing hazards in terms of "endocrine disruption." Endocrine activity can be defined as a change in endocrine homeostasis caused by a chemical or other stressor from human activities (e.g., application of pesticides, the discharge of industrial chemicals to air, land, or water, or the use of synthetic chemicals in consumer products.). Data to be considered will include:

- *in vitro* data such as hormone receptor binding assays or ex vivo assays,
- *in vivo* data from studies of intact animals or wildlife (including aquatic organisms),
- ethically conducted human studies,
- *in vivo* short term exposures or altered (e.g., ovariectomized) animal models,
- structural similarity to known endocrine active substances using SAR tools such as AIM, QSAR, etc.

Each chemical of concern will be evaluated for evidence of presence of endocrine activity:

- If data show evidence of endocrine activity then the chemical is designated as *potentially endocrine active*, while noting caveats and limitations.
- If there are no data available to evaluate this endpoint, endocrine activity is unknown and would be marked to indicate the *absence of information*.

- If data conclude no evidence of activity (no binding, perturbation, or evidence of endocrine-related adverse effects) then the chemical will be designated as having *no evidence of endocrine activity*, noting caveats and limitations.

2.2.1.2 Exposure characterization and categorization

Exposure characterization and categorization employs PRoTEGE to quantify and rank (potential) exposures as very high, high, moderate, low, and very low:

- **Very High and High Exposures** are associated with presence of the chemical of (current or emerging) concern in:
  - New Jersey environmental media and biota at significant concentration levels or as significant levels of biomarker measurements (where, in both cases, significance is determined for each chemical in relation to threshold levels associated with hazardous effects of the chemical),
  - food, children's toys, cosmetics/personal care products, consumer products, etc.
- **Moderate Exposures** are associated with presence of the chemical of concern in New Jersey environmental media and biota at concentrations less than the levels considered significant above but that may be steadily increasing due to continuing use of the chemical in products or due to ongoing activity of emission sources.
- **Low and Very Exposures** are associated with presence of the chemical of concern in New Jersey environmental media and biota at low detectable concentrations or in new consumer products that have minor but potential increasing market penetration.

2.2.1.3 Risk characterization and categorization

Risk characterization and categorization ("tiered assessment") for each chemical of current or emerging concern employs the hazard and exposure rankings developed in the steps above. (These characterizations will ultimately include both human [mammalian] and ecological risk assessments and will determine whether or not a CEC candidate could be a significant risk that merits consideration on the New Jersey CEC prioritization list. The system will ultimately offer various options to the user, for both analysis and visualization.) One basic option for initial prioritization of chemicals for risk assessment is the calculation of a simple "prioritization score" that is defined as:

$$Prioritization\ Score = Hazard\ Category \times \left(1 + Exposure\ Category\right)$$

In the initial prioritization process, a value of 1, 2, 3, 4 and 5, respectively, is assigned to the very low, low, moderate, high, and very high categories of hazard and of exposure. In this process any value of the initial prioritization score higher than "12" results in a recommendation for further analysis. So a "very high" designation (assigning a value of "5") in any hazard or any exposure category by itself assures that the chemical is ranked for further prioritization in the framework.

Values of the initial prioritization score in the range of 8-12 are considered as identifying a "medium priority" chemical. Values of this score that are "20" or higher identify "very high priority" chemicals for further analysis. Figure 6 provides a visualization of this scoring via a "prioritization grid" for risk assessment. The initial prioritization scores, derived through the process described above, are depicted in the right hand side of the figure: the red cells

correspond to very high priority chemicals, the orange cells correspond to high priority chemicals, the yellow cells correspond to moderate priority chemicals, and the light green and dark green cells correspond to low and very low priority chemicals, respectively. The risk assessment grids in the left hand side of Figure 6 present the more detailed procedures analyzing and assessing relevant data and other information that is "condensed" into the scores used in the 5x5 grid of the right hand side of Figure 6.

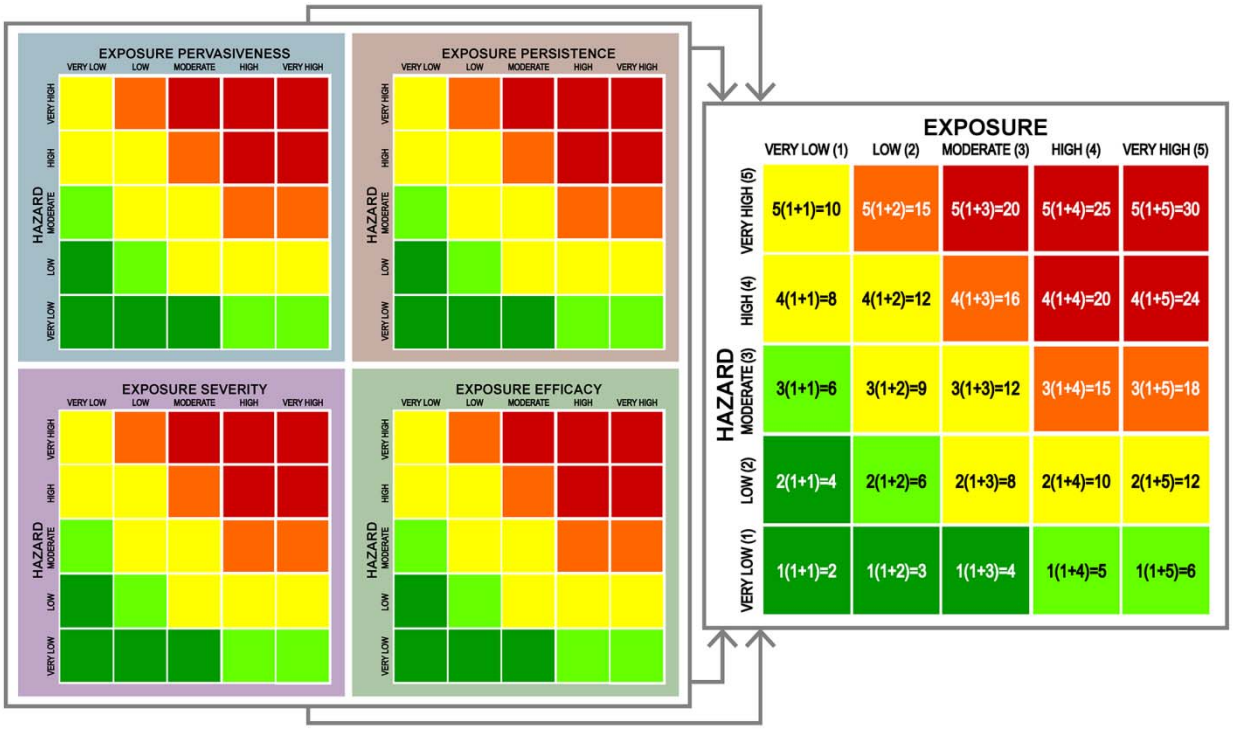


Figure 6. Prioritization grids for risk assessment. The left hand side represents metrics and scoring being developed using METIS and PRoTEGE in conjunction with available data and other information. The right hand side depicts a simple risk prioritization grid that uses "aggregated" information from the underlying processes to offer a user-friendly characterization and categorization of risk from chemicals of current and emerging concern.

2.3 Installation of METIS

In order to implement this project a secure, firewall-protected and password-accessible, "LAMP server" has been set up at the Computational Chemodynamics Laboratory (CCL) for hosting METIS[1] and for the incorporation of PRoTEGE modules and expanded databases in the integrated NJrisk system. "LAMP" is an acronym for the following components of the server structure:

- Linux operating system
- Apache web server application, using Hypertext Transfer Protocol (HTTP)
- MySQL (My Structured Query Language) relational data management system

[1] The installation of METIS on CCL's server took place under the expert guidance of Mario Chen, of Du Pont de Nemours & Co.

- PHP, Perl, and Python programming languages for dynamic web pages

The specific component versions of the present CCL LAMP server for METIS are:

- Linux Fedora v15 (Lovelock)
- Apache Tomcat v6.0.37
- MySQL v5.5.20
- Perl v5.12
- Python v2.7.3
- Javascript v1.8

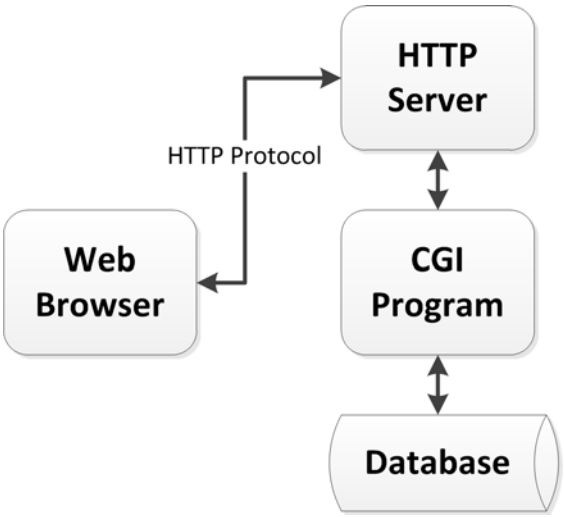


Figure 7. A general schematic for the interaction between a web browser and a LAMP server

The chain of events when accessing ("clicking on") a link in the METIS software is as follows:

- HTTP request is sent to the Apache Tomcat server with the user-specified data (e.g., chemical name, CAS number, etc.)
- The CGI program associated with the link is invoked
  - Every link in METIS is associated with a CGI program
  - All CGI programs are written in Perl
- The program opens a connection to MySQL and retrieves the user-specified data
- Then the program generates an HTML file, placing the retrieved data in the "place holders"
- The server provides this HTML file and the user is able to view the webpage from the web browser.

Apache Tomcat is being utilized as it is an open source web server that provides an environment for executing Java code. Common Gateway Interface (CGI) is enabled in Tomcat; it is required to produce dynamic web pages and it facilitates the exchange of information between the web server and a custom script (CGI script). The CGI scripts for METIS are written in Perl, although such scripts will also be written in Python, PHP, Java, C, etc. in the final implementation of NJrisk.

MySQL serves as the warehouse for the contents of METIS and is also utilized in the integrated NJrisk system. Currently, for METIS, the database contents are accessed through the Perl DBI (database-independent) interface.

3 Structure and Components of NJrisk

The implementation and the completion of the Pilot case studies, employing both METIS and PRoTEGE, were used to identify and assess potential issues of consistency, compatibility, etc. in data formats and core elements, and to develop plans for implementing the linking and integration of the two software tool sets in a manner to best address analysis of the risk-relevant problems at hand while optimizing user accessibility of options and outcomes. Special effort is being put in designing a system that is flexible and easy to use so as to substantially facilitate tasks involved in the risk analysis and management processes. The full implementation utilizes specific software requirements [18] and data/workflow models to optimize usability by employing principles of "user-centered design" [19]. Figure 9 illustrates the structure and components of the in-progress integrated NJrisk system, which incorporates all the databases currently utilized in METIS and PRoTEGE *and will eventually also include other publicly-available Federal databases*, as they become available.

When completed the full integrated NJrisk system:

- will facilitate characterizing and assessing separately both hazard and exposure potentials of chemicals found in the ambient environment and/or biota as well as in various residential, occupational, and public microenvironments;
- will specifically provide tools for *rapid screening of human and ecological health risk potential,* by using the above characterizations of hazard and exposure potentials;
- will support prioritization of chemicals for regulatory action based on potential and actual human health risks relevant to both the general population and to specific subpopulations of concern and ecological health risks relevant to wildlife in aquatic, terrestrial, and air environments; and
- will be expandable, allowing the users to incorporate information and address issues related not only to human but also to ecological health risks.

As mentioned above, development and application of NJrisk is also taking advantage of and incorporating the outcomes of various ongoing initiatives by Federal (as well as international) agencies to assemble information on the physicochemical and toxicological profiles of chemicals. Such outcomes, resulting in integrated databases, are listed in Figure 9 under "Federal Database Network" (see, e.g. [1,20,21]). As an example, a database that was already linked with METIS and PRoTEGE as part of the Pilot Phase of the project, and is expected to continue to be one of the data sources for NJrisk, is USEPA's ACToR (Aggregated Computational Toxicology Resource) [1] (see Table 3). This is an evolving database that allows access to various types of data on environmental chemicals, such as information on chemical structure, *in vitro* bioassays and *in vivo* toxicology assays. Chemicals in ACToR are compiled from sources that include the U.S. Environmental Protection Agency (USEPA), Centers for Disease Control (CDC), U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), state agencies, corresponding government agencies in Canada, Europe and Japan, universities, the World Health Organization (WHO) and non-governmental organizations (NGOs).

The integrated NJrisk system is being formulated and tested so as to ensure that it will be able to address a variety of specific issues, situations, and chemicals that would be of particular concern for the State of New Jersey. However, when completed it will be applicable at the national (US) scale and at any location (state/county/municipality) within the contiguous US. *Special attention is being given to the development of the user interface in order to optimize its*

functionality and simplicity, ensuring that users with a wide variety of backgrounds will be able to learn its usage quickly and access efficiently the integrated NJrisk system.

Table 3. Selected databases accessed by ACToR (a project currently in progress for the USEPA)

Database	Expanded Name
ATSDR reports	Agency for Toxic Substances and Disease Registry Reports
ChEMBL	--
Danish EPA – Reports	
DSSTox	Distributed Structure-Searchable Toxicity
ECHA chemicals	--
Endocrine Disruptor Screening Program Database	--
Environment Canada Domestic Substances List	--
EPA SRS	EPA Substance Registry Services
EPISuite data	Experimental data used for EpiSuite modeling program
ExpoCastDB	--
IRIS	Integrated Risk Information System
IUCLID	International Uniform Chemical Information Database
NIOSH-IDLH	NIOSH - Immediately Dangerous To Life or Health Concentrations
NIOSH-NPG	NIOSH Pocket Guide to Chemical Hazards
OECD List of HPV Chemicals	--
ToxCastDB	Toxicity Forecaster database
TOXNET Toxicological data	--
ToxRefDB	Toxicity Reference Database
TSCA	Toxic Substances Control Act (TSCA) Chemical Substances Inventory
USDA PDP	USDA Pesticide Data Program

4 Completed (7/2015 to 6/2016) and On-going Work

4.1 Implementation of software requirements

The findings of ongoing testing are currently being used to identify and assess potential issues of consistency, compatibility, etc. in data formats and core elements, and to establish protocols for implementing the linking and integration of the software components in a manner to best address analysis of the risk-relevant problems at hand, while optimizing user accessibility of options and outcomes. Special effort has been put in designing a system that is flexible and easy to use, so as to substantially facilitate tasks involved in the risk analysis and management processes. Ongoing effort involves establishing and refining specific software requirements [18] and developing complete data and workflow models for improved usability.

4.2 Adaptation and customization of "base" modules from METIS and PRoTEGE

This task is systematically selecting, customizing, linking, testing, and merging components from the two operational state-of-the-art platforms (METIS and PRoTEGE) for hazard and for exposure characterization and ranking. Customization of METIS modules involves recoding that is necessary for removing various accessibility restrictions currently embedded in that system in order to allow its future use by a wider community.

The NJrisk website (Figure 9), deployed as a "testing platform" for CCL and NJDEP researchers, is accessible via password protected login. It is built on a content management system (CMS) platform using PHP and CSS3 coding and draws information from a MySQL database. This website includes an introductory information page and access to the alpha version of NJrisk, where one can search for a chemical by name or CAS number and pull up a visualization for its

hazard profile (Figure 10). There is also a comment form for NJDEP researchers to provide feedback. The current version of the NJrisk testing platform is essentially a customized version of METIS and its output does not yet include the PRoTEGE "risk grid" or "exposure rose" that will be incorporated in the near future.

In parallel, CCL researchers have been developing and refining a local NJrisk module, that is currently undergoing online testing, which combines hazard and exposure ranking information visualized as a "hazard rose" and an "exposure rose" (for METIS hazard ranking values and PRoTEGE exposure ranking values, respectively) and a "risk grid" that shows a value based on calculation of exposure values from PRoTEGE with hazard values from METIS. This tool is also being developed on a CMS platform, making it fairly straightforward to merge all the modules of the NJrisk system.

4.2.1 How the local NJrisk module set works

This module takes the following inputs:

- Chemical (name or CAS number, with and without dashes)
- ChartType (Human Exposure Rose, Human Hazard Rose or Risk Grid).

The search page is run by "inputparse.php" which calls "main.py" function, which writes the results to text files. These text files are accessed by pages which call makeCharts.js to make the exposure charts, hazard charts, and risk grids.

- Scripts include:
  - **irissearch.py** – Calculates values for exposure chart.
  - **makeCharts.js** - makes the human hazard and human exposure rose charts and human health risk grids; the coordinates for human health risk grids are calculated here.
  - **cmrsearch.py** (translated from Perl to Python) – gets data for human hazard rose chart.
  - **substancelist.txt** – CAS numbers of chemicals from IRIS. When searching for a chemical, that chemical is compared with this list. Returns result if the chemical is in this list (main.py finds the CAS number for the chemical and that CAS number is searched within this list).
  - **main.py** – Gets the chemical name from **inputparse.php**; Calls **irissearch.py** and **cmrsearch.py** functions and writes results to text files, **irisdata.txt** (info for the table that is added below the exposure chart), **cmrdata.txt** (info for Hazard chart and table below the chart) and **exposuredata.txt** (info for Exposure chart).

4.3 Testing and evaluation of Multi-criteria Decision Support Ranking Schemes

An important aspect of the (currently continuing) work that was initiated during the July 2015 to June 2016 period involved evaluation and testing of Multi-Criteria Decision Support (MCDS) schemes for cases when quantitative information is missing or uncertain and only qualitative, or "semi-quantitative,") information regarding ongoing and potential uses of the chemical(s) of

concern is available. Approaches similar to those described in the *Institute of Medicine Workshop Report on "Identifying and Reducing Environmental Health Risks of Chemicals in Our Society"* (National Academy Press, 2014) have been considered and code development for implementation of the MCDS algorithms is ongoing.
As an example, in one approach under consideration (similar to the one descibed in the IOM Workshop above, pp. 94-95), the exposure ranking for a chemical is determined by adding scores from three components:

- use pattern,
- production volume, and
- persistence and bioaccumulation.

The use pattern score is derived from the Chemical Data Reporting Rule (i.e the rule by which, under TSCA, companies report periodically on substances that are currently in commerce.
Substances used by potentially sensitive consumers (e.g. children or pregnant women) are assigned a score of 5 (very high), substances used by the general consumer population receive a score of 4 (high), those in commercial use get a 3 (moderate), those in industrial use get a 2 (low), and those in intermediate use get a 1 (very low). Production volume scores are 5 (more than 100 million pounds), 4 (10 million to 100 million pounds), 3 (1 million to 10 million pounds), 2 (25,000 to 1 million pounds), and 1 (less than 25,000 pounds). The persistence and bioaccumulation scores are 5 for substances that are both persistent and bioaccumulative, 3 for those that are either persistent or bioaccumulative, and 1 for those that are neither persistent nor bioaccumulative. The three scores are added together to develop a "qualitative" overall exposure score, which is then used to assign substances to an exposure range: very low (3 or 4), low (5 to 7), moderate (8 or 9), high (10 or 11), and vey high (12 and higher).

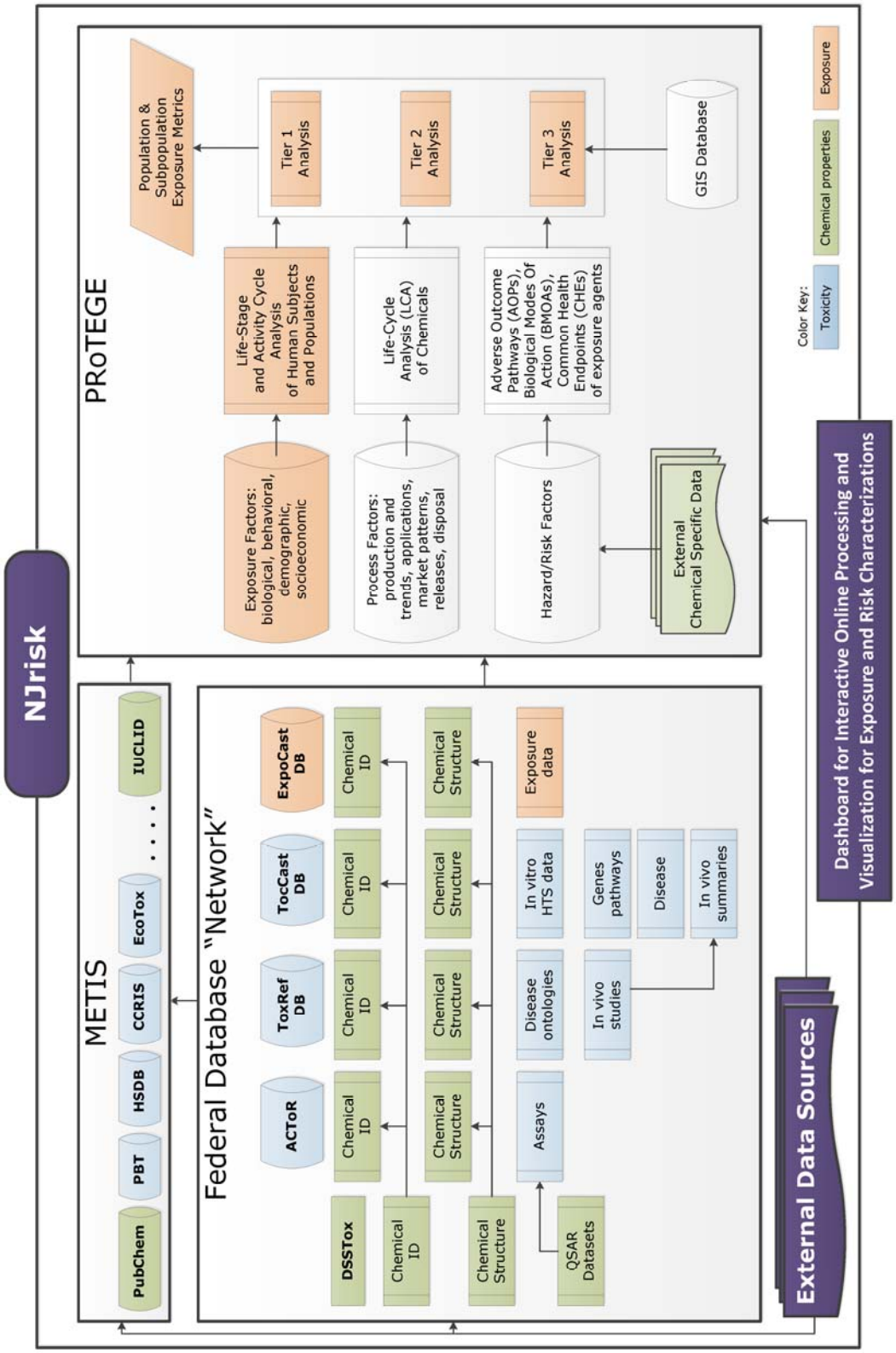


Figure 8. NJrisk – structure and components of an integrated system to allow easy user access to outcomes from PRoTEGE and METIS in conjunction with various extant databases that are available or under development at USEPA and other Federal agencies

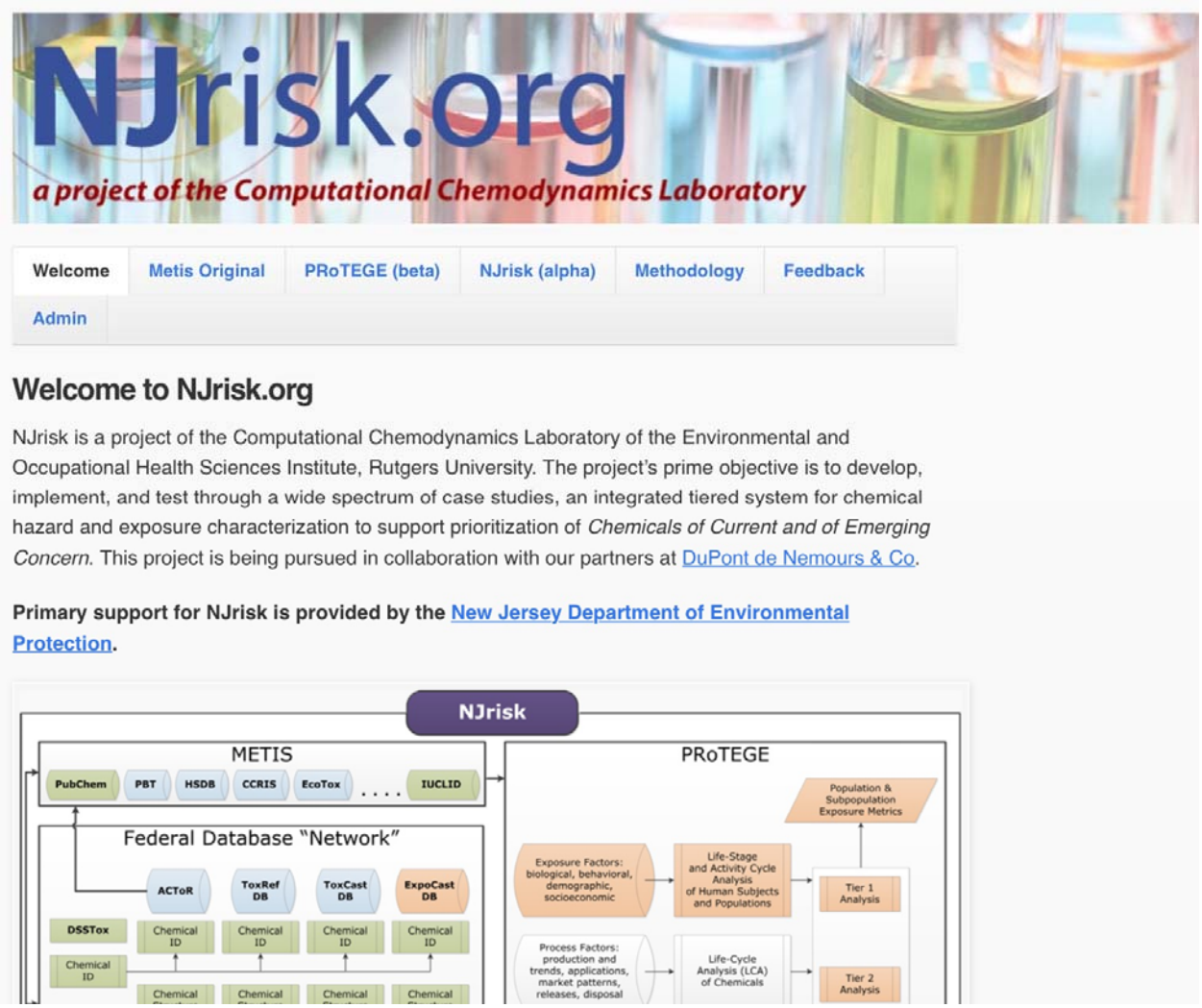


Figure 9. The njrisk.org website provides a testing platform for CCL and NJ DEP researchers

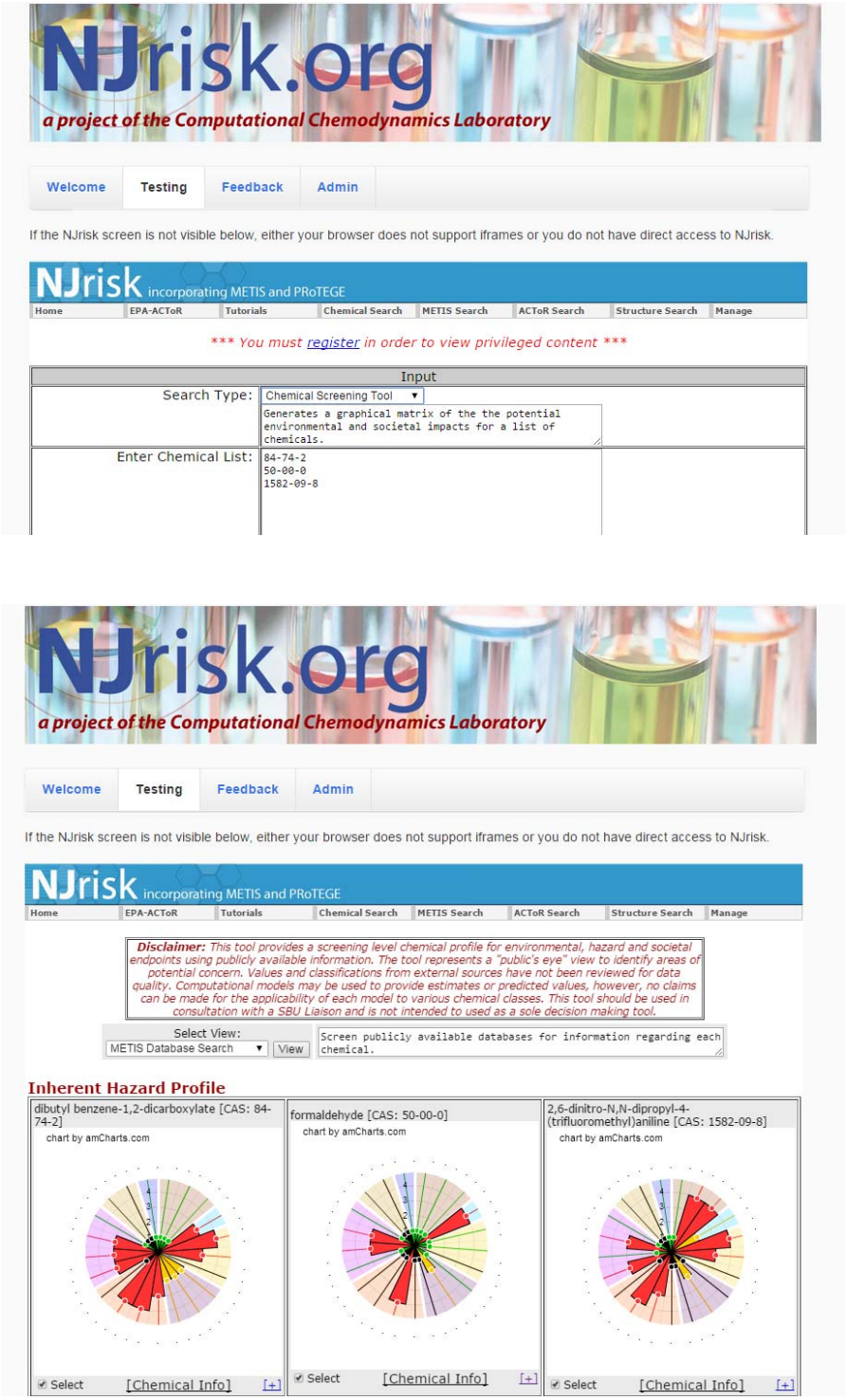


Figure 10. The "alpha" version of NJrisk allows the user to search for a chemical by name or CAS number and display a visualization for its hazard profile.

5 Results of Exploratory Case Studies for Six Additional Chemicals/Chemical Groups

In the following pages:

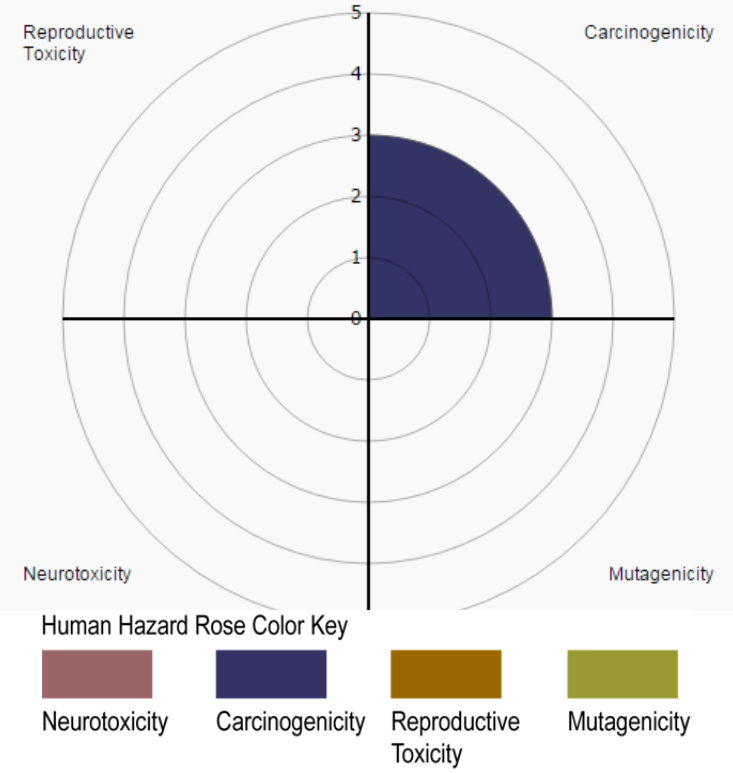
- a "human hazard rose"
- a "human exposure rose" and
- a "human health risk grid" (showing a value based on calculation of exposure values from PRoTEGE combined with with hazard values from METIS and other sources linked to the NJrisk platform)

are presented for each of the six test-case chemicals (or groups of chemicals) that were added to the list of the 40 test-case chemicals during the latest reporting period.

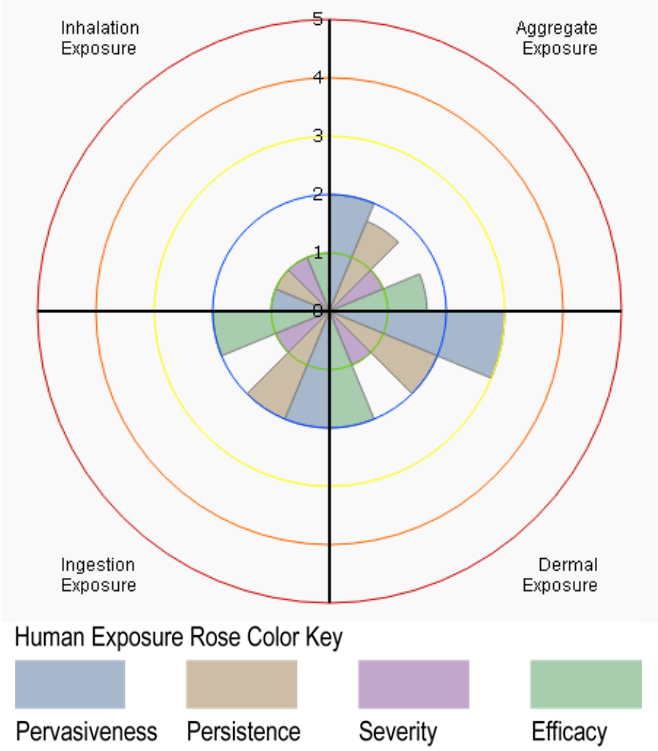
IMPORTANT NOTE: The preliminary numerical and graphical estimates and rankings of hazard, exposure, and human health risks appearing on the following pages are being derived solely for the purpose of developing and testing the PRoTEGE and NJrisk systems and reflect work that is currently in progress and therefore incomplete. These preliminary estimates may, at this point, be using only a subset of the information sources available for completing calculations and should be expected to change, possibly substantially, in subsequent phases of the development of the PRoTEGE and NJrisk systems.

NJrisk Preliminary Results for C10-13 Chloroalkanes

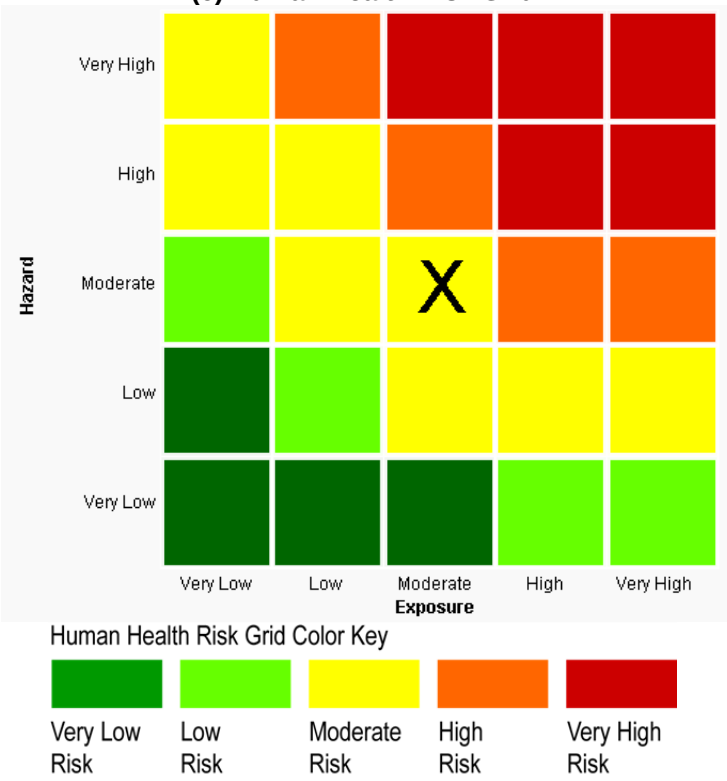
(a) Human Hazard Rose



(b) Human Exposure Rose



(c) Human Health Risk Grid



(a) Human Hazard
Estimated ranking of human hazard risk from C10-13 Chloroalkanes, in terms of neurotoxicity, carcinogenicity, reproductive toxicity, and mutagenicity.

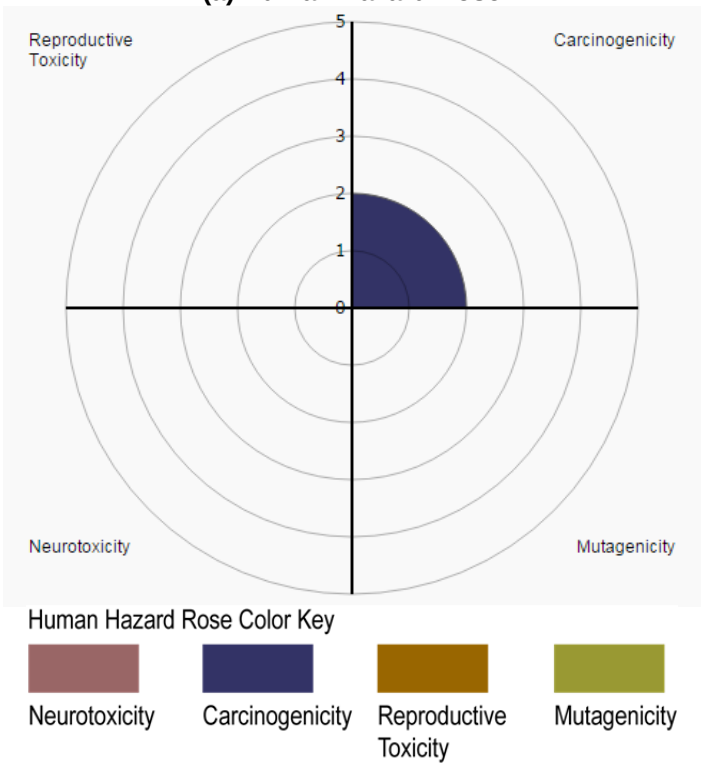
(b) Human Exposure
Estimated human exposure ranking based on semi-quantitative metrics of pervasiveness, persistence, severity, and efficacy of C10-13 Chloroalkanes (refer to page 12 for a more detailed explanation of these metrics).

(c) Human Health Risk
Estimated human health risk from C10-13 Chloroalkanes, based on calculation of exposure values from PRoTEGE combined with hazard values from METIS (refer to page 15 for a more detailed explanation of how this ranking is calcualted).

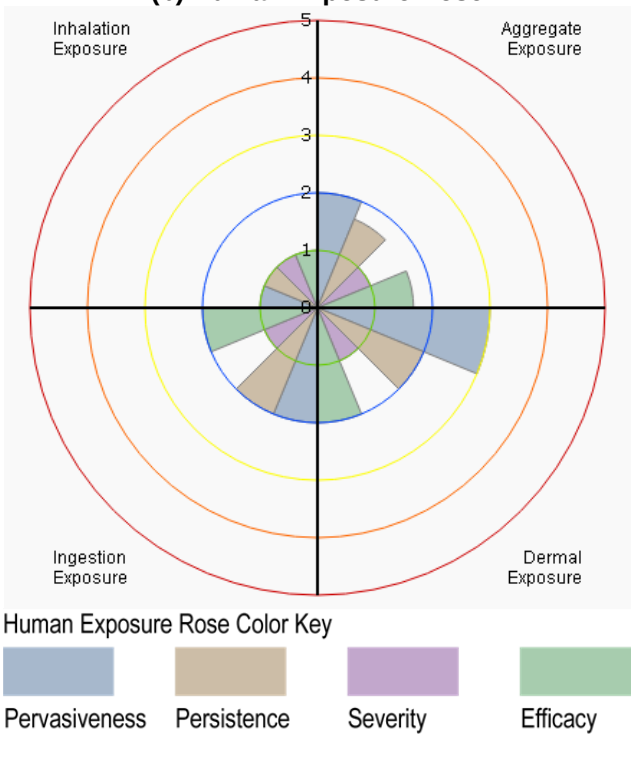
IMPORTANT NOTE: All results are preliminary and are shown for demonstration and testing purposes only

NJrisk Preliminary Results for Mid Chain Chlorinated Paraffins C14-17

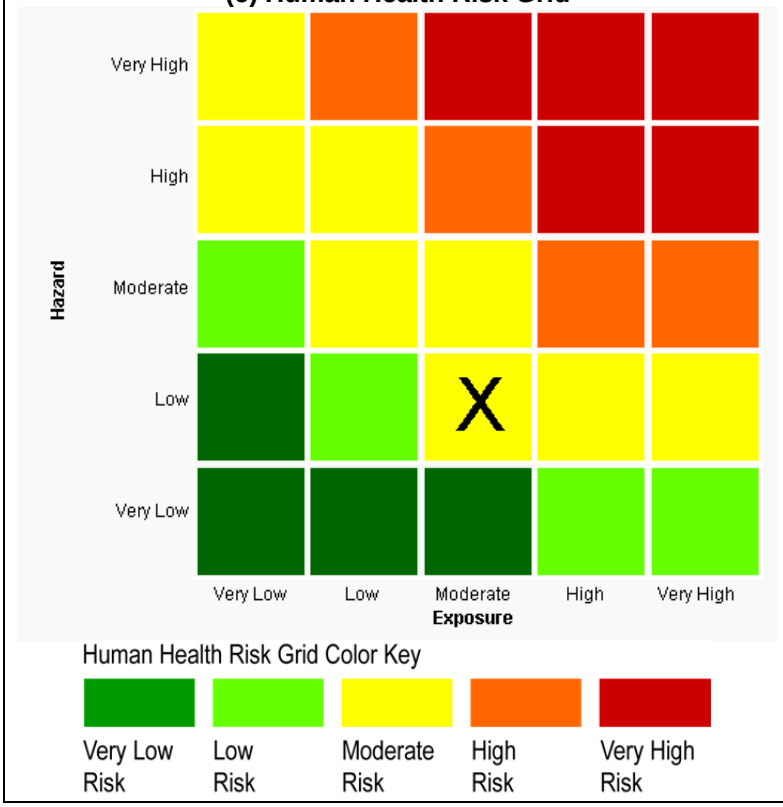
(a) Human Hazard Rose



(b) Human Exposure Rose



(c) Human Health Risk Grid



(a) Human Hazard
Estimated ranking of human hazard risk from Mid Chain Chlorinated Paraffins C14-17, in terms of neurotoxicity, carcinogenicity, reproductive toxicity, and mutagenicity.

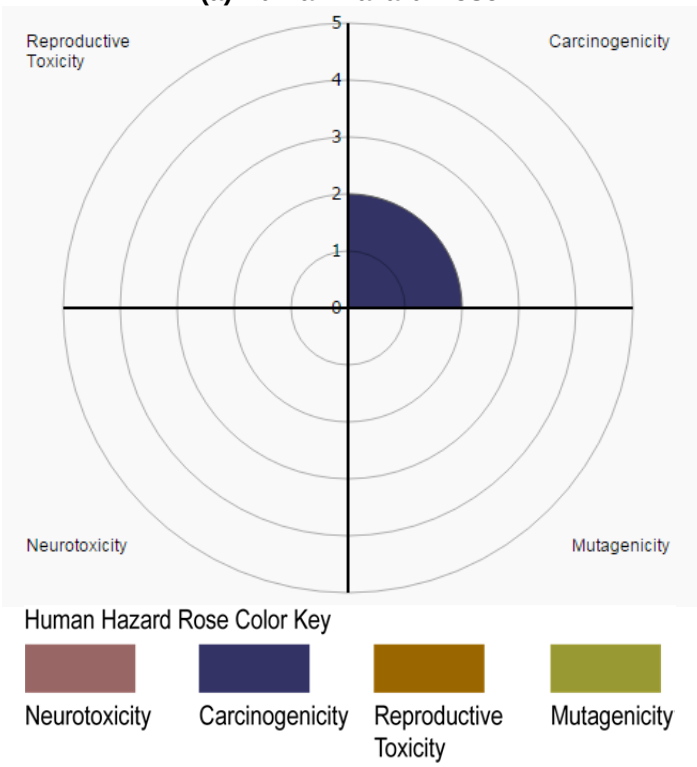
(b) Human Exposure
Estimated human exposure ranking based on semi-quantitative metrics of pervasiveness, persistence, severity, and efficacy of Mid Chain Chlorinated Paraffins C14-17.

(c) Human Health Risk
Estimated human health risk from Mid Chain Chlorinated Paraffins C14-17, based on calculation of exposure values from PRoTEGE combined with hazard values from METIS.

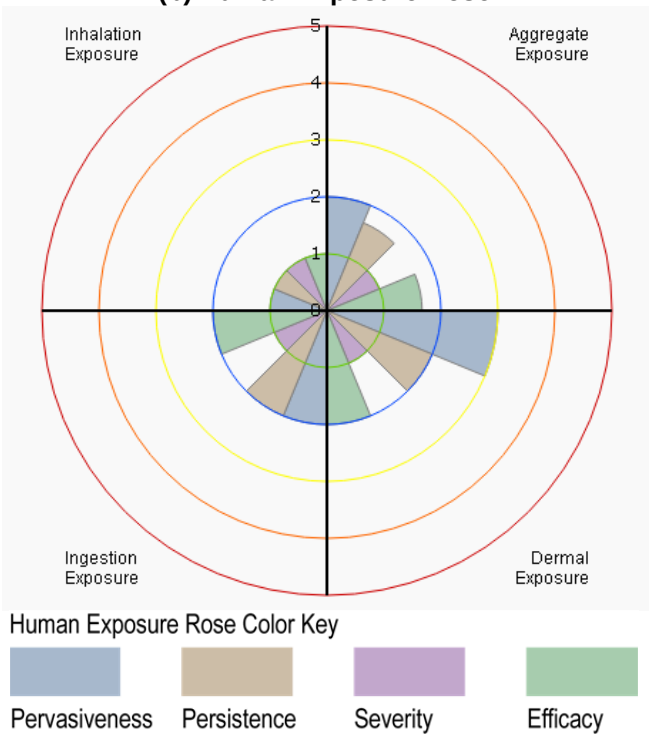
IMPORTANT NOTE: All results are preliminary and are shown for demonstration and testing purposes only

NJrisk Preliminary Results for Long Chain Chlorinated Paraffins C18-30+

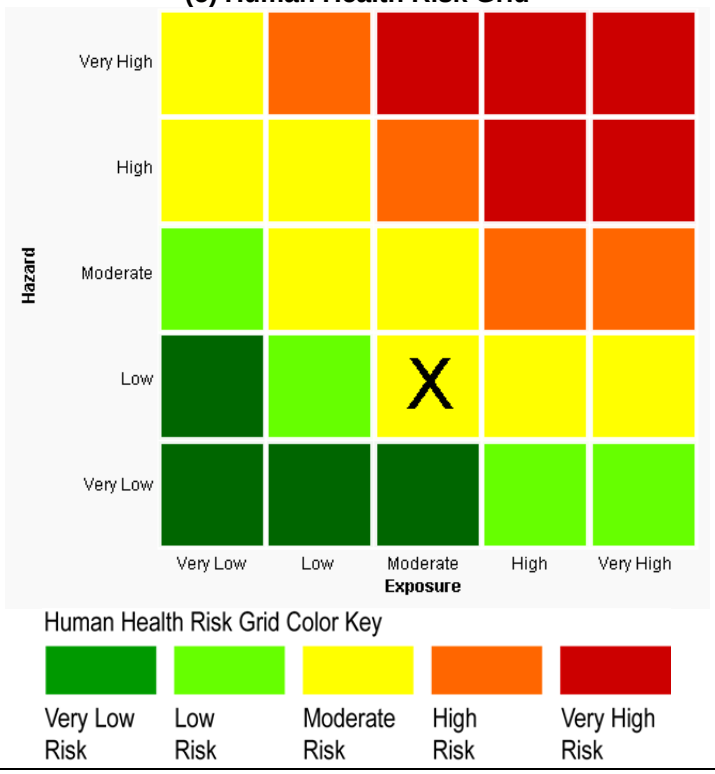
(a) Human Hazard Rose



(b) Human Exposure Rose



(c) Human Health Risk Grid



(a) Human Hazard
Estimated ranking of human hazard risk from Long Chain Chlorinated Paraffins C18-30+, in terms of neurotoxicity, carcinogenicity, reproductive toxicity, and mutagenicity.

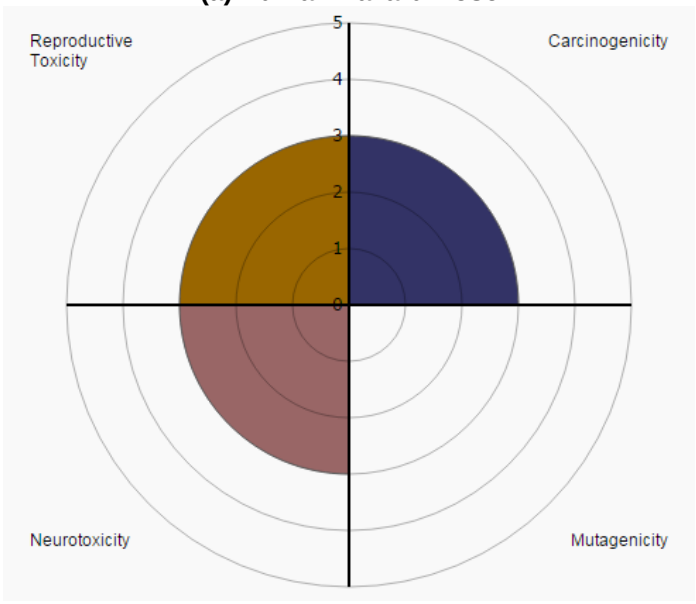
(b) Human Exposure
Estimated human exposure ranking based on semi-quantitative metrics of pervasiveness, persistence, severity, and efficacy of Long Chain Chlorinated Paraffins C18-30+.

(c) Human Health Risk
Estimated human health risk from Long Chain Chlorinated Paraffins C18-30+, based on calculation of exposure values from PRoTEGE combined with hazard values from METIS.

IMPORTANT NOTE: All results are preliminary and are shown for demonstration and testing purposes only

NJrisk Preliminary Results for 1-Bromopropane

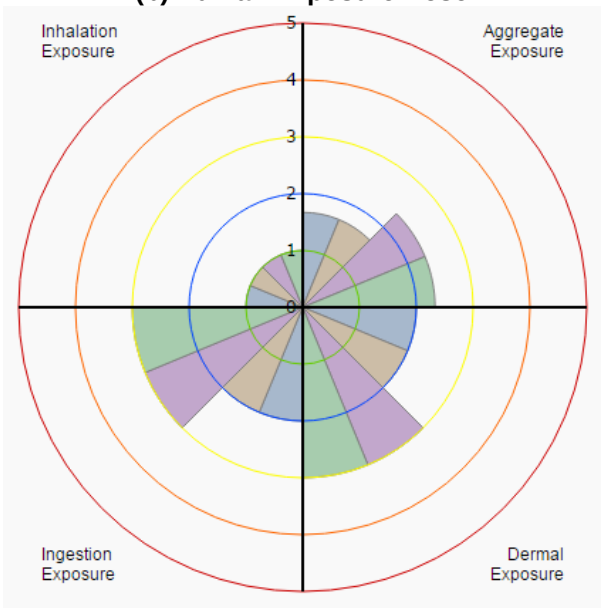
(a) Human Hazard Rose



Human Hazard Rose Color Key

Neurotoxicity | Carcinogenicity | Reproductive Toxicity | Mutagenicity

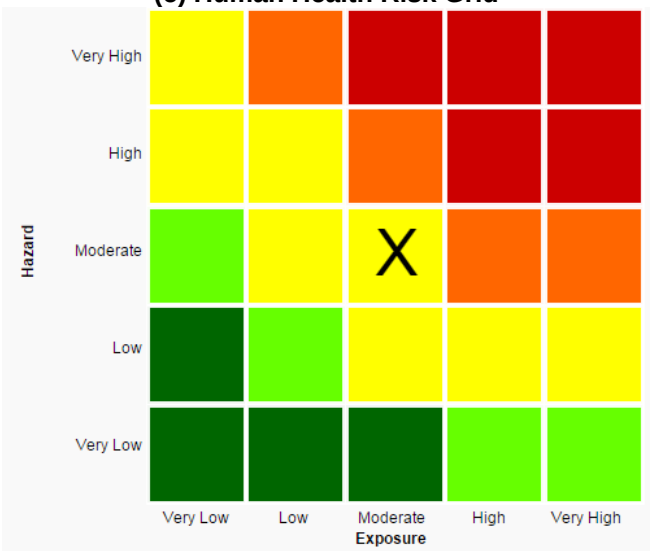
(b) Human Exposure Rose



Human Exposure Rose Color Key

Pervasiveness | Persistence | Severity | Efficacy

(c) Human Health Risk Grid



Human Health Risk Grid Color Key

Very Low Risk | Low Risk | Moderate Risk | High Risk | Very High Risk

(a) Human Hazard
Estimated ranking of human hazard risk from 1-Bromopropane, in terms of neurotoxicity, carcinogenicity, reproductive toxicity, and mutagenicity.

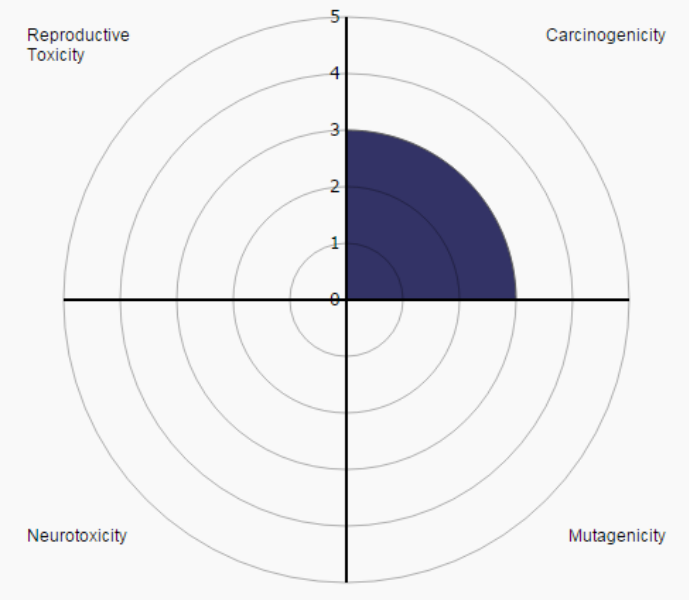
(b) Human Exposure
Estimated human exposure ranking based on semi-quantitative metrics of pervasiveness, persistence, severity, and efficacy of 1-Bromopropane.

(c) Human Health Risk
Estimated human health risk from 1-Bromopropane, based on calculation of exposure values from PRoTEGE combined with hazard values from METIS.

IMPORTANT NOTE: All results are preliminary and are shown for demonstration and testing purposes only

NJrisk Preliminary Results for 1,4-Dioxane

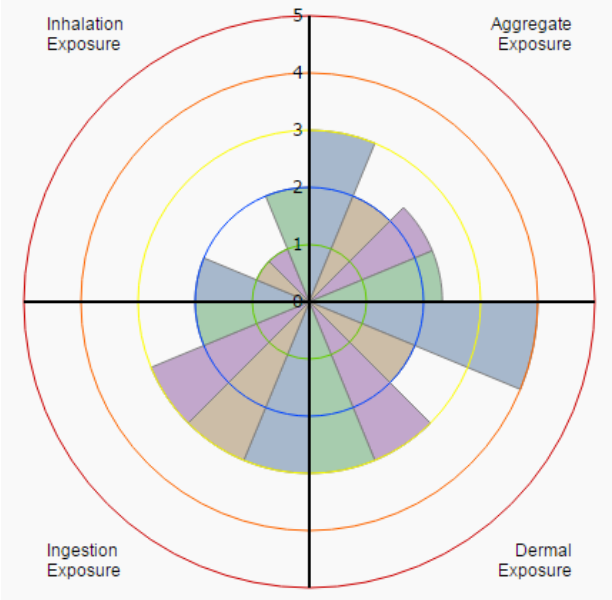
(a) Human Hazard Rose



Human Hazard Rose Color Key

Neurotoxicity | Carcinogenicity | Reproductive Toxicity | Mutagenicity

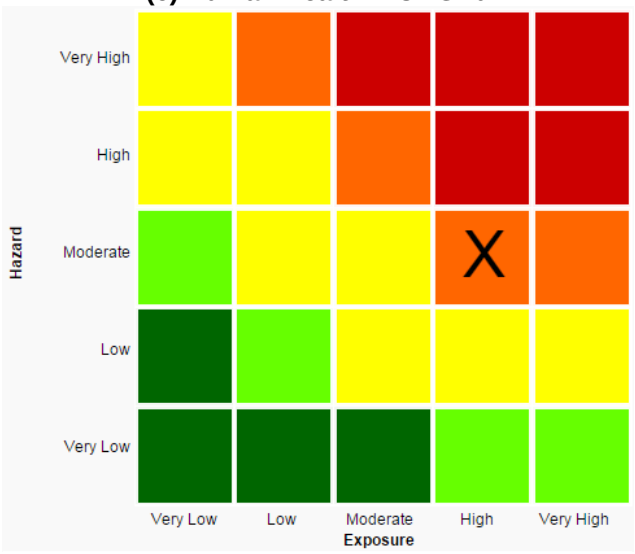
(b) Human Exposure Rose



Human Exposure Rose Color Key

Pervasiveness | Persistence | Severity | Efficacy

(c) Human Health Risk Grid



Human Health Risk Grid Color Key

Very Low Risk | Low Risk | Moderate Risk | High Risk | Very High Risk

(a) Human Hazard
Estimated ranking of human hazard risk from 1,4-Dioxane, in terms of neurotoxicity, carcinogenicity, reproductive toxicity, and mutagenicity.

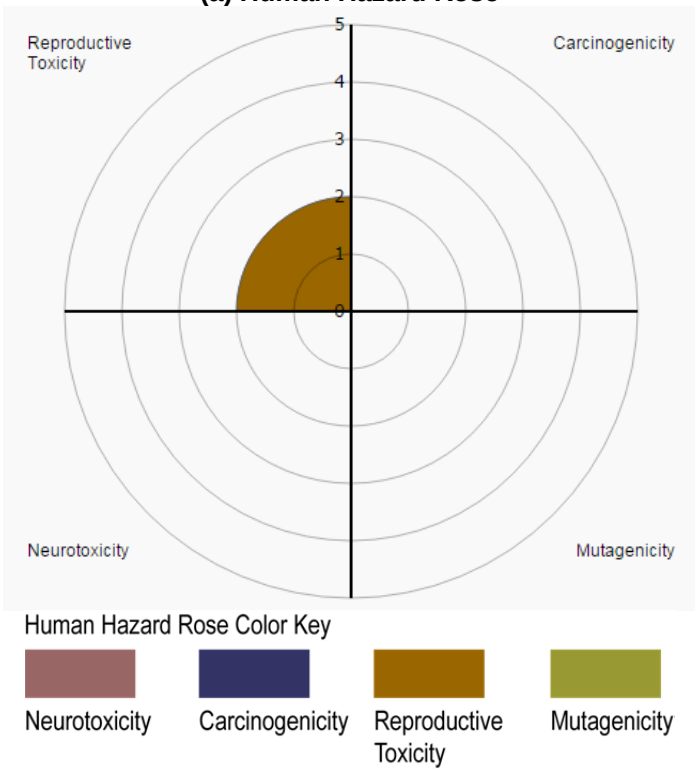
(b) Human Exposure
Estimated human exposure ranking based on semi-quantitative metrics of pervasiveness, persistence, severity, and efficacy of 1,4-Dioxane.

(c) Human Health Risk
Estimated human health risk from 1,4-Dioxane, based on calculation of exposure values from PRoTEGE combined with hazard values from METIS.

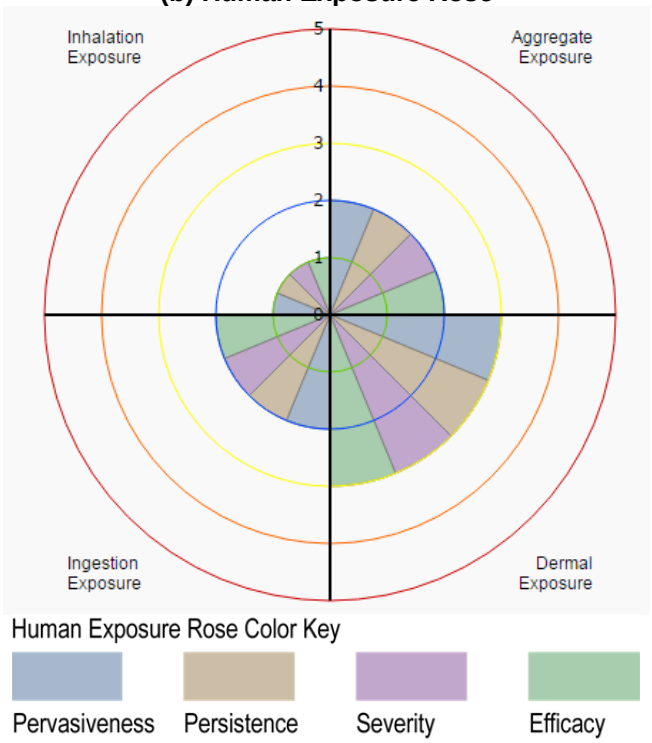
IMPORTANT NOTE: All results are preliminary and are shown for demonstration and testing purposes only

NJrisk Preliminary Results for Brominated Phthalates Cluster

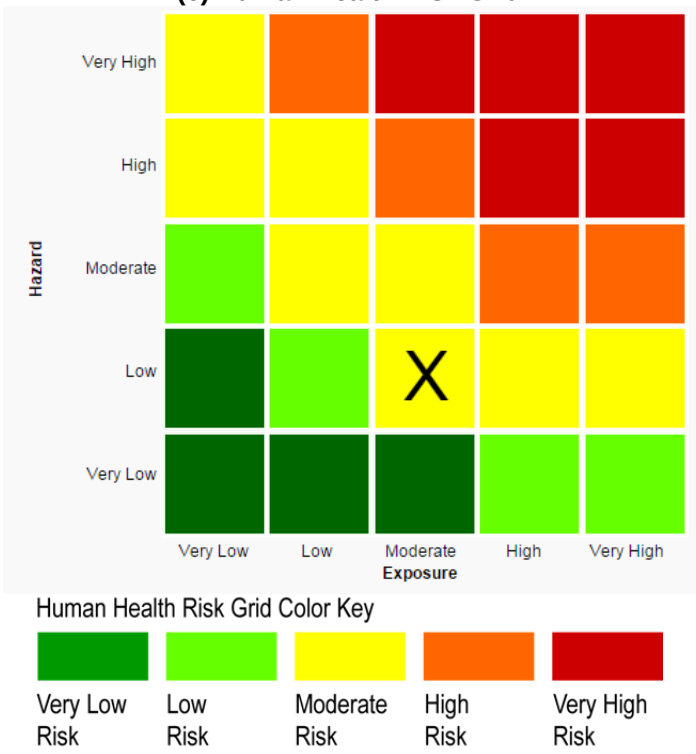
(a) Human Hazard Rose



(b) Human Exposure Rose



(c) Human Health Risk Grid



(a) Human Hazard
Estimated ranking of human hazard risk from Brominated Phthalates Cluster, in terms of neurotoxicity, carcinogenicity, reproductive toxicity, and mutagenicity.

(b) Human Exposure
Estimated human exposure ranking based on semi-quantitative metrics of pervasiveness, persistence, severity, and efficacy of Brominated Phthalates Cluster.

(c) Human Health Risk
Estimated human health risk from Brominated Phthalates Cluster, based on calculation of exposure values from PRoTEGE combined with hazard values from METIS.

IMPORTANT NOTE: All results are preliminary and are shown for demonstration and testing purposes only

Appendix: GitHub Repository Structure for NJrisk Codes

Overview

The NJRisk source is divided into three main directories: src, test, and wordpress_theme.

- src - The Python source code for the NJRisk service.
- test - Unit, functional, and behavioral tests for NJRisk services.
- wordpress_theme - Wordpress theme for njrisk.org.

Development of NJRisk uses the Git flow model. Primary development happens on a `develop` branch and `master` hosts versions production versions that have been deployed and tested in a staging environment. Developers should also be familiar with best practices (e.g., How to Write a Git Commit Message).

Prerequisites (Vagrant virtual machine)

The recommended way to bootstrap an instance of NJRisk on a development machine is to use Vagrant. The NJRisk source code comes with a Vagrantfile for initializing a virtual machine with all of the necessary dependencies. After installing Vagrant, the developer needs to run the following commands:

```
$ git clone git@github.com:ccl-group/njrisk.git
$ cd njrisk
$ git submodule init && git submodule update
$ vagrant up
$ git submodule deinit  # optional, removes large NJRisk SQL files
```

Prerequisites (local development)

Python must be installed on the local system. It is included by default on Linux and Mac, but must be installed separately for Windows users. Please see the Python installation instructions for more details.

The developer should also install pyenv to manage her/his development environment inside of a Python virtual environment. This will prevent NJRisk specific dependencies from polluting the global Python installation.

Create a virtualenv for NJRisk (one time):

```
$ pyenv install 2.7.2            # installs python 2.7.2 in pyenv
$ pyenv virtualenv 2.7.2 njrisk  # creates a virtualenv called njrisk using python 2.7.2
```

When developing for NJRisk, the developer must activate the virtualenv for his/her session:

```
$ pyenv activate njrisk
(njrisk)$ python --version
Python 2.7.2
```

Install prerequisite Python packages into the virtualenv using pip (one time):

```
(njrisk)$ pip install -r requirements.txt
```

Get the source code:

```
(njrisk)$ git clone git@github.com:ccl/njrisk.git
(njrisk)$ cd njrisk
```

Configuration

NJRisk connects to multiple databases to retrieve content. These databases are configured by a file called `settings.py`. The `src` directory contains a documented example settings file called `settings.sample.py`. NJRisk developers and system administrators must copy this file to `settings.py` and configure it to use the appropriate credentials for their environment.

Running

The NJRisk scripts can be directly run in two different modes or hosted in a Web Server Gateway Interface (WSGI) compliant server.

Command-line Query

Querying can be performed by running the main.py script with the `query` subcommand and a CAS number:

```
(njrisk)$ python main.py query 50-00-0
```

Flask embedded server

For debugging, the script can also host itself as a standalone Flask application:

```
(njrisk)$ python main.py server --host 127.0.0.1 --port 5000
```

The server will be available at the host and port specified, and the search interface will be available at /search, e.g. http://localhost:5000/search?q=50-00-0.

Apache Web Server Gateway Interface

On Linux:

```
# a2enmod wsgi
```

Add the following WSGI configuration to the Apache host:

```
WSGIDaemonProcess njrisk user=njrisk group=njrisk threads=5
WSGIScriptAlias /njrisk /path/to/njrisk/src/njrisk.wsgi
<Directory /path/to/njrisk/src>
    WSGIProcessGroup njrisk
    WSGIApplicationGroup %{GLOBAL}
    Order allow,deny
    Allow from all
</Directory>
<Location /njrisk>
    Order allow,deny
    Allow from all
</Location>
```

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