Risk Assessment and Chemical Regulation: Lessons in Global Information Sharing

Dr. Andrew Maier
Dr. Jay Zhao
Toxicology Excellence for Risk Assessment

Presentation Overview

Briefly describe:

- How most organizations estimate the risk posed by chemicals
- Trends in chemical risk assessment
- The globalization of risk assessment
- The growing need for information sharing
- The Alliance for Risk Assessment as a resource for information exchange

Presentation Overview

- Take home message:

  The *demand* for chemical risk assessment information is outpacing the *supply* of risk assessment information. Efficient sharing of information is a critical strategy for addressing this misalignment.

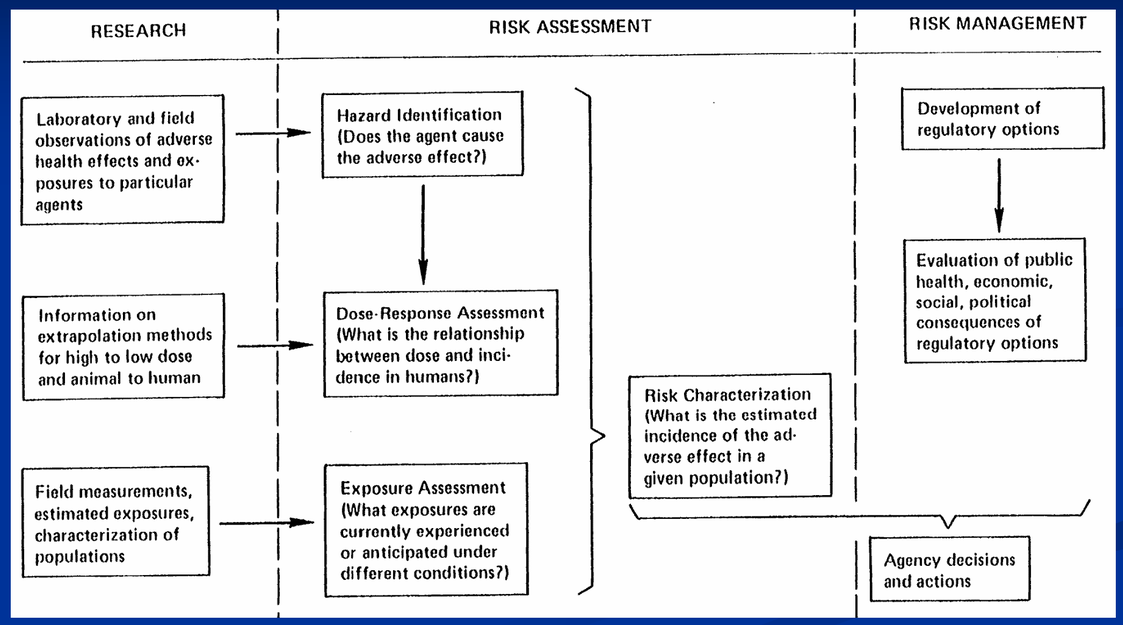
Risk Assessment

Risk Assessment

Human health risk assessors evaluate issues such as:

- the health impacts of community air and water due to point source and non-point source emissions, and
- the safety of food and every consumer product (or its ingredients, and
- the need to clean-up contaminated sites, and
- Response to chemical emergencies, etc…

Risk Assessment Paradigm



Trends in Risk Assessment

- Past:
  - Analysis efforts focused on selected high profile chemicals.
  - Heavy reliance on default assumptions
    - Humans are equally or more sensitive than test animals
    - Humans are highly variable in their sensitivity
    - Effects observed in high dose animal studies are relevant to effects that might occur in humans exposed to low doses
  - Use of strength of evidence approaches
  - Organizations complete assessments in isolation

Trends in Risk Assessment

- Present:
  - Increasing emphasis on hazard characterization and screening assessments for large numbers of chemicals
  - Selection of dose-response approaches based on integration with assessment of biological mode of action
  - Increasing use of data to replace or inform default assumptions
  - Use of weight of evidence approaches
  - Development of predictive toxicity models, in part due to animal welfare concerns

Trends in Risk Assessment

- Future:
  - WOE has opened door for innovative solutions in risk assessment and toxicology driven by:
    - Improved biology understanding (understanding of the mode of action)
    - Increased sophistication and validation of alternative study designs (e.g., gene knock-outs)
    - Routine use of quantitative tools, including biomathematical modeling, data mining and collection platforms (toxicogenomics) and predictive toxicology and QSAR
  - User friendly web platforms for data sharing

Growth in Risk Assessment

- Triggered by…
  - Control technology better able to reduce gross contamination, focus on smaller releases
  - New technologies for detecting lower amounts of pollutants is increasing knowledge of chemicals in the environment.
  - Significant advancement in scientific knowledge
    - Advances in basic biology (molecular and cellular biology), chemistry (computational chemistry), and mathematics (better statistical and dose-response tools) have expanded our ability to do assessments.
    - More subtle effects and sensitive populations are of increasing concern

Growth in Risk Assessment

- Triggered by….
  - Recognition of need to conduct risk assessment on broader range of chemical inventory
    - European Union REACH
    - Health Canada DSL
    - U.S. EPA HPV
  - Recognition of mixtures and multi-media exposure
  - Increasingly knowledgeable public who demand information

Globalization of Risk Assessment

Risk Assessment in Europe

What is REACH?

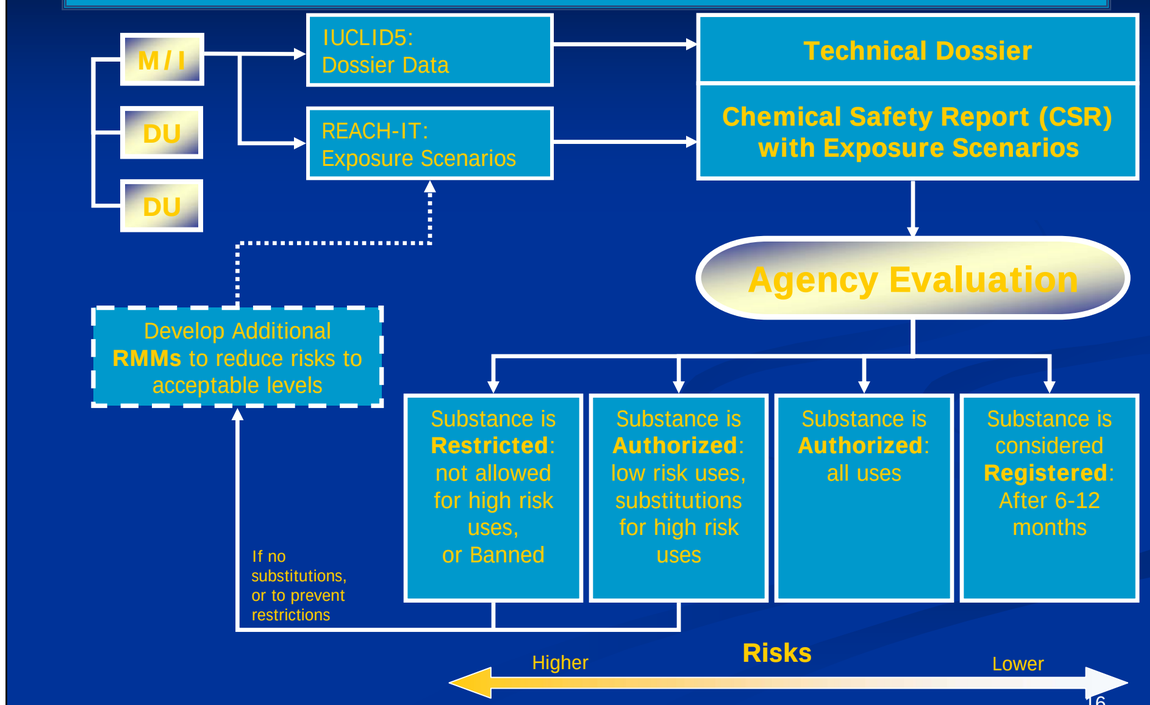
- **R**egistration, **E**valuation, **A**uthorisation and Restriction of **CH**emicals
  - Adopted by European Parliament: December 18, 2006
  - Effective June 1, 2007
- Regulates chemicals/products made in or imported into the European Union (EU)
  - Created one system for new and existing compounds
  - Transfers burden of proof to industry

Note: Slides on REACH kindly provided by Dr. Bert Hakkinen of Gradient

Who and What Does REACH Affect?

- **Manufacturers and Importers** (M/I) of substances in amounts >1 tonne/year; no toxicity threshold
- **Downstream Users** (DU) must tell M/I how substance is used
- REACH regulates only **Substances** (*i.e.,* chemicals)
  - In Preparations, or sold as Pure Products
  - In Articles, if "intended to be released during normal or foreseeable conditions of use" (*e.g.,* ink in pen)

Chemical Safety Reports: Evaluation



Key Business Strategies for REACH

1. **Assess** organizational needs and information gaps early
2. **Communicate** up and down your Supply Chains – form coalitions
3. **Ask Suppliers to Pre-register** to buy time
4. **Devise** testing plans to fill data gaps
5. **Consider** production and design changes to minimize exposures

Risk Assessment in China

Risk Assessment in China

- Rapidly growing economy demands more enforceable and practical government regulations
- Limited funding limits governments in establishing comprehensive regulations to cope with growing economy in order to adequately protect public health
- Growing presence of international corporations – focus on requiring external parties to develop risk assessments.

Risk Assessment in China

- Current practice:
  - Using international risk values directly whenever they are available
  - When there is a need for such value, but it is not available from international databases, a new assessment might be conducted.

Risk Assessment in China

Issues with using international risk values directly whenever they are available

- While some risk values might be available from international databases, application of these values requires understanding the process of developing these values.
- Besides the risk values, exposure assessment could be a major challenge because exposure scenario varies significantly among different geological regions
- Defualt databases of “exposure factors” might not apply

Risk Assessment in China

Issues with conducting new risk assessments

- Funding for conducting new chemical risk assessments is the most challenging issue in developing countries.
- Developing new risk assessments also requires “know how” skill which might be insufficient in these countries.

Solutions

Harmonization

- *Harmonization is not standardization*
- Understanding the methods and practices used by various organizations
- Developing confidence in and acceptance of assessments using different approaches
- Willingness to work toward a convergence of methodologies as long-term goal
- Harmonization requires effective information sharing

Evidence for Collaboration

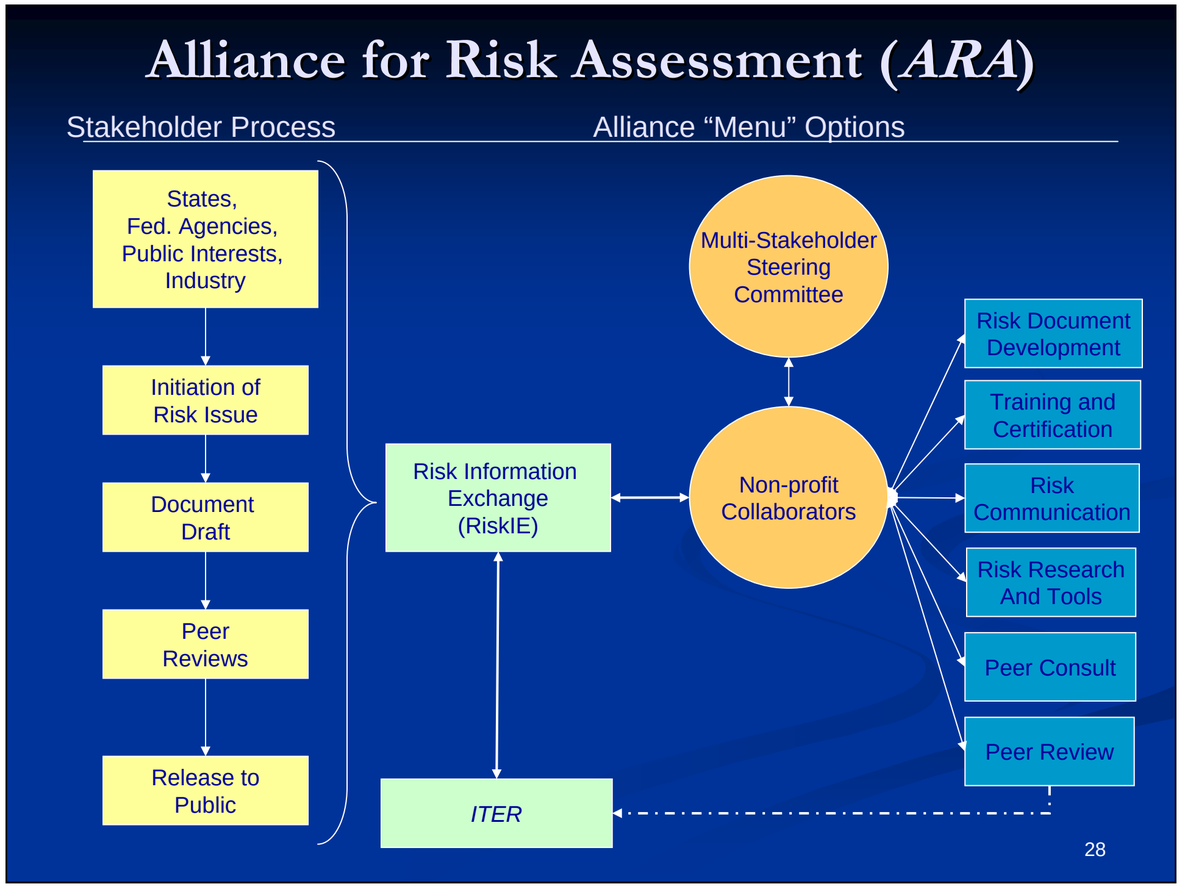
- Many international initiatives reflect desire of risk science community for increasing partnerships
  - The activity of the MSWG!
  - SRA Europe – June 2007 : "Building Bridges Issues for Future Risk Research"
  - International Programme for Chemical Safety (IPCS) Harmonization Project
  - OECD – Toxicity Test Protocols, Hazard Labeling
  - US:European and US:Asian Partnerships

Benefits of Collaboration

- Promotes science-based decision making by ensuring all key data and ideas are fully considered
- Enhances harmonization and consistency in risk assessments thru an open, transparent, multi-stakeholder approaches
- Makes use of groups of experts that are normally not available within a single organization
- Shares costs and human resources among multiple stakeholders to increase output for the broader risk community
- Can be achieved while allowing groups to control their own process

Alliance for Risk Assessment (*ARA*)

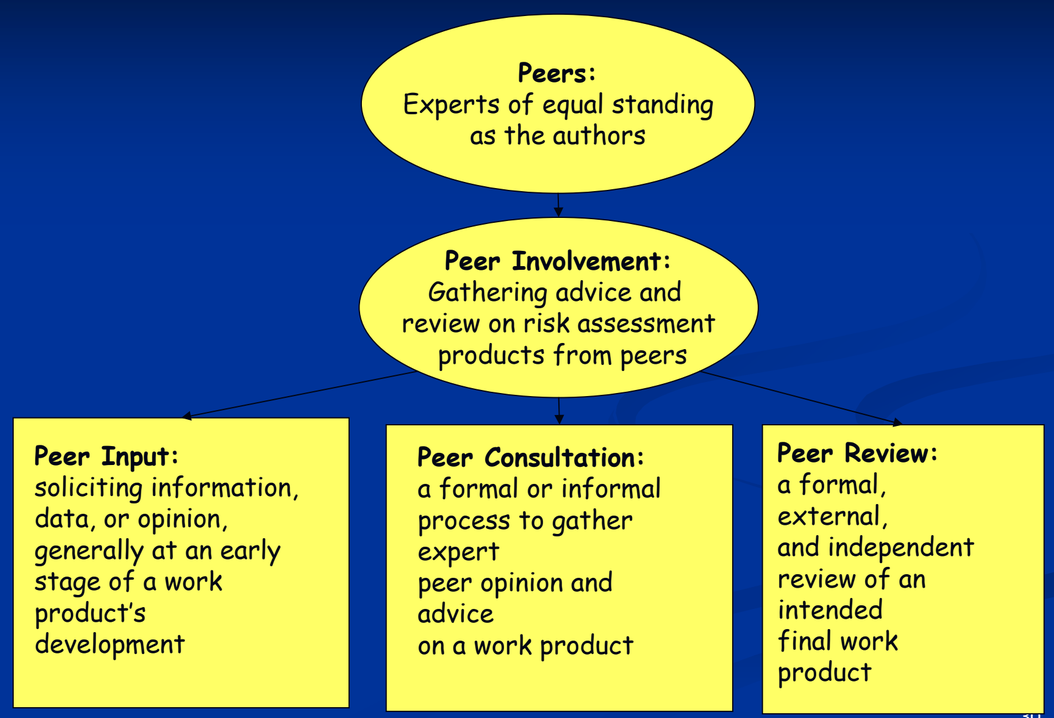
A process to facilitate communication and collaboration toward development of useful and timely risk science products.



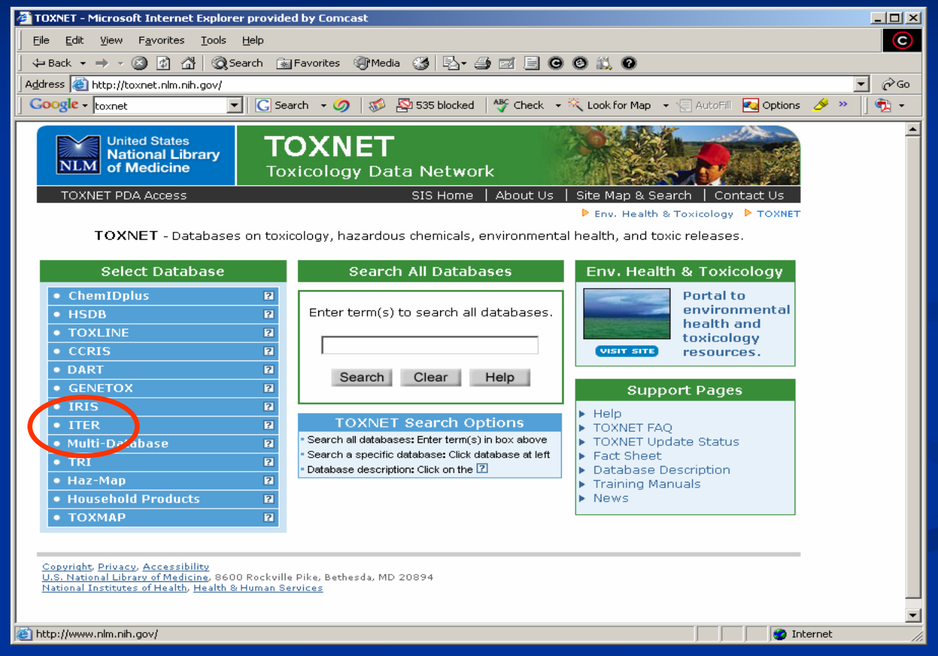
The *ARA* Sand Box

- The *ARA* seeks collaboration building and there is a role for all players…
- Players: federal government, local government, tribes, industry, for-profit consultants, NGOs.
- Roles:
  - users - use of work products, use of information exchange, work product vetting,
  - experts assisting others (e.g., peer review panel members; linking needs with experts)
  - developing work products
  - Steering Committee membership

Peer Involvement – a tool for collaboration



NLM's Toxnet



ARSENIC, INORGANIC

CASRN: 7440-38-2

For other data, click on the Table of Contents

Risk Data - Noncancer Oral:

ITER Noncancer Oral Risk Table for: ARSENIC, INORGANIC

Risk Value Parameter\ Organization	ATSDR	Health Canada	IARC	ITER	NSF Intl	RIVM	U.S.EPA
Risk Value Name	chronic MRL	NA	--	NA	--	TDI	RfD
Risk Value*	3E-4	NA	--	see below	--	1E-3	3E-4
Year	2000	1992	--	1999	--	2000	1993
Basis (Experimental)*	NA	NA	--	NA	--	NOAEL 0.0021	NOAEL 0.0008
Basis (Adjusted)*	NOAEL 0.0008	NA	--	NA	--	NA	NA
Uncertainty Factor	3	NA	--	NA	--	2	3
Critical Organ or Effect	skin	NA	--	NA	--	skin	skin
Species	human	NA	--	NA	--	human	human
Study	Tseng et al., 1968; Tseng, 1977	NA	--	NA	--	Health Council of The Netherlands, 1993	Tseng, 1977; Tseng et al., 1968
View Specifics:	Click here	Click here	--	Click here	--	Click here	Click here

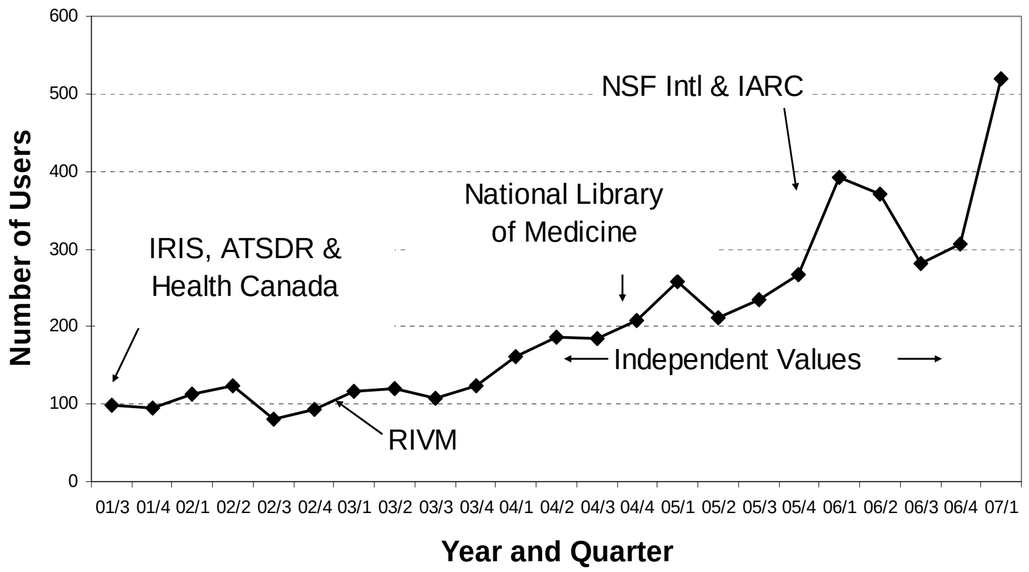
**In mg/kg body weight per day, unless otherwise specified.*

Synopsis:

ATSDR, Health Canada, RIVM, and U.S. EPA have evaluated the noncancer oral toxicity data for inorganic arsenic. Health Canada did not derive a risk estimate for noncancer toxicity since carcinogenicity is considered the critical endpoint. Both EPA and ATSDR risk values are based on the same study and use the same choice of critical effect, NOAEL and uncertainty factor.

RIVM derived a tolerable daily intake (TDI) of 0.001 mg/kg-day for critical effects on the skin in humans. This value is based on a NOAEL of 0.0021 mg/kg-day that was derived by Vermeire et al. (1991) from the World Health Organization provisional maximum tolerable weekly intake (PTWI) of organic arsenic of 15 mg/kg bw/week for adults of 70 kg of body weight. This PTWI was derived from a LOAEL of chronic intake of 100 ug arsenic/L in drinking water by humans, assuming a daily intake of drinking water of 1.5 L/day. RIVM used uncertainty factor of 2 to compensate for observation errors in an epidemiological study. Thus, the TDI is derived as follows: (100 ug arsenic/L x 1.5 L/day) / (70 kg) / (2) = 1 ug/kg-day (0.001 mg/kg-day).

ITER Daily Users



ARA Information Sharing Efforts

- Additional resources being built in collaboration with US National Library of Medicine and using in-kind support from international organizations
- Develop Risk Information Exchange (RiskIE) – for communication of in-progress risk assessments
- Inclusion of State/Regional Risk value data
- Development of Link Library to access other sources of data not included in database
- Source for other technical products – peer consultation reports, training modules, etc.

Toxicity Information Sources

Some On-line Databases of Chemical Human Hazard Data Sources*

- Toxicology Data Network (TOXNET) (http://toxnet.nlm.nih.gov/)
- TSCATS (http://www.syrres.com/esc/tscats.htm)
- IPCS INCHEM (http://www.inchem.org/)
- NTP (http://ntp-server.niehs.nih.gov/)
- ATSDR (http://www.atsdr.cdc.gov/toxpro2.html)
- EPA HPV Challenge Program (http://www.epa.gov/chemrtk/volchall.htm)
- EU ESIS (http://ecb.jrc.it/esis/)
- RAIS (http://rais.ornl.gov/)
- US NTP (http://ntp.niehs.nih.gov/)

Toxicity Information Sources

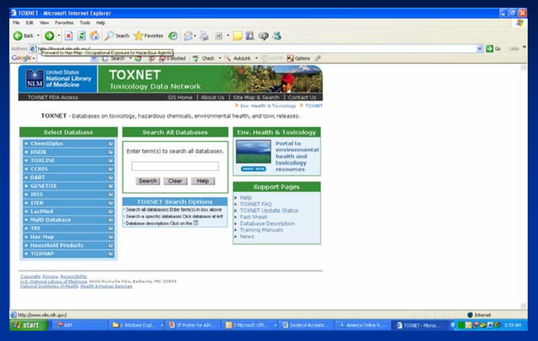
Some On-line Structure Activity Resources

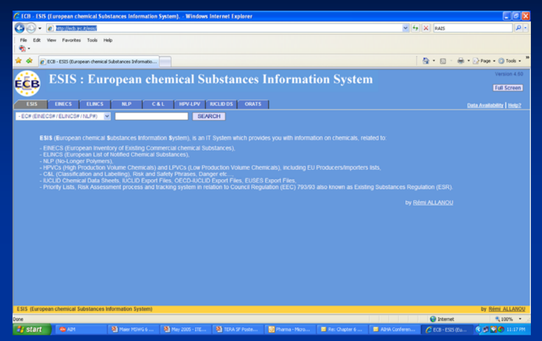
- Public Domain Tools for conducting similarity of substructure searches:
  - CHEMIDPlus.chem.sis.nlm.nih.gov/chemidplus/
  - TSCATS: http://esc.syrres.com/efdb/tscats.htm
  - AIM (Analog Identification Methodology) (in development)
- QSAR software Programs
  - Free ware: Toxtree (EU JRC), Oncologic (EPA OPPT)
  - Commercial: DEREK, MultiCASE, TOPKAT, Leadscope

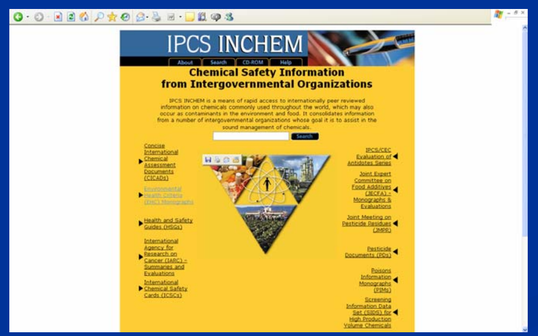
Other types of data bases… MSDS, occupational exposure limits, pharmaceuticals, exposure factors, toxicology study data, genomics and bioinformatics, etc…

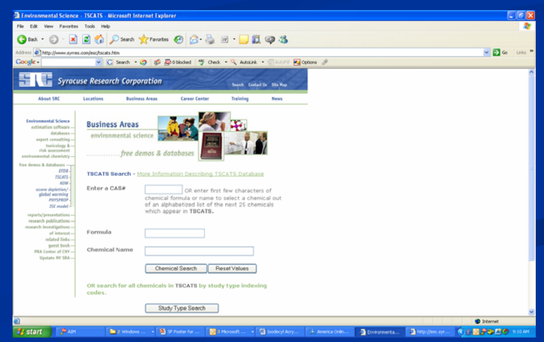
Current efforts to standardize data inputs and build linkages – (Recent Power of Aggregated Toxicity Data Workshop).

On-line Toxicity Data Sources



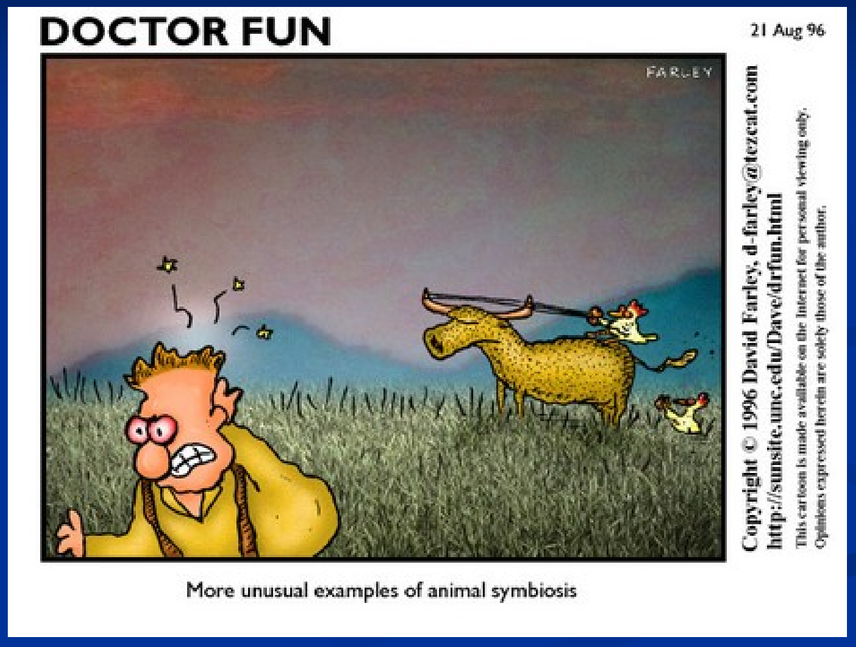






www.allianceforrisk.org

Collaboration is Powerful



More unusual examples of animal symbiosis

Discussion Questions

- Are there additional key drivers for growth in risk assessment?
- What are the barriers to collaboration?
- Where do you get your chemical safety information?
- Is there a role for expert input and review of toxicity and risk assessment information?