The Development of an International Database of (Eco)Toxicity Testing Results

By

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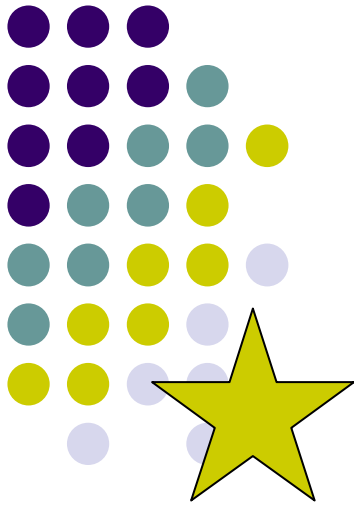
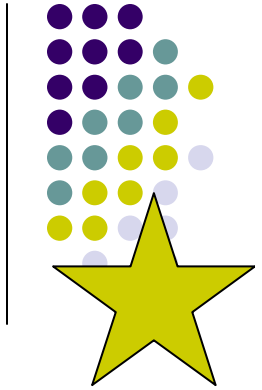
SoloSTAR Limited

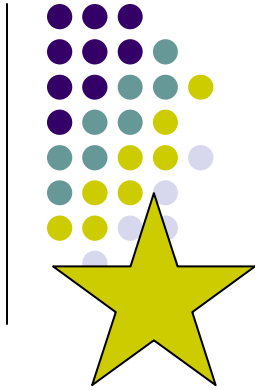


PRESENTATION OVERVIEW



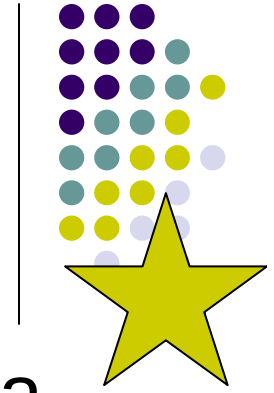
- Introduction
- International Toxicology Information Centre
- The ILSI/SAR database project
- The VITIC project
- Data issues faced
- Data solutions – some thoughts
- Conclusions

INTRODUCTION



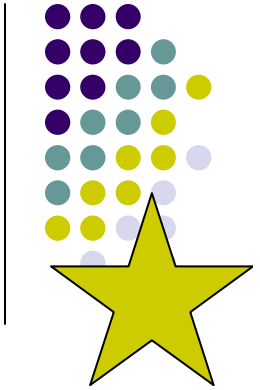
- My experiences in obtaining reference toxicity data for model development and validation
- SoloStar
- Unilever
- Lhasa

INTERNATIONAL TOXICOLOGY INFORMATION CENTRE (ITIC)



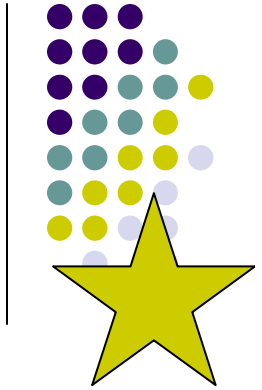
- Circa 1994 – A Lhasa Director had an idea
- 1997 – Feasibility study
- 1997/1998 Meetings in Europe and USA
- October 1998 – a conference call with about 10 interested companies organised by ILSI
- December 1998 meeting in Washington
- December 1999 meeting in Washington
- The idea of the ‘pilot project’ was born

ILSI/HESI SAR DATABASE PROJECT



- 2-Year pilot study started June 2000
- Lhasa were commissioned to build the program
- Based on the IUCLID database platform
- Project sponsors worked on the data – co-ordinated by ILSI
- Pilot study completed in late 2002

The Pilot Project

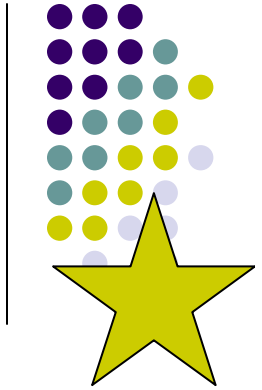


Phase 1:

- Identifying data and systems requirements
- Developing the software
- Adding some data
- Demonstration of system (August 2001)

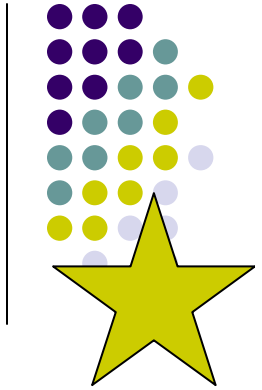
- **Phase 2:**
  - Continued software development
  - Add more data
  - Case studies
  - Questionnaire

Pilot Project - Data



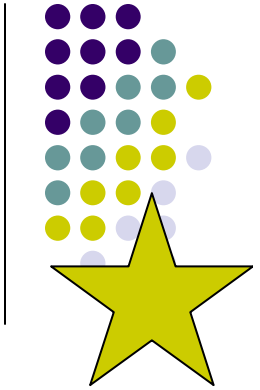
- **Phase 1** (until Dec. 2001)
  - We agreed on 4 toxicity endpoints
    - Skin sensitisation
    - Mutagenicity
    - Carcinogenicity
    - Hepatotoxicity
  - Set up subgroups for each endpoint
  - All work was done by conference calls

Pilot Project - Data



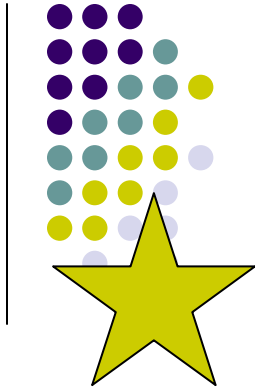
- **Phase 2** (until Dec. 2002)
  - Need to add more data
  - Carry out case studies
  - Questionnaire on usefulness of the system
  - Project milestone meeting June 2002
  - What next?

VITIC Database



- Very large toxicology database
- Database management tools
- Public & non-sensitive proprietary data
  - link US EPA DSS-Tox
- Sophisticated query functions
- Research new (Q)SARs in toxicology
- Identify new toxicological knowledge

DATA ISSUES

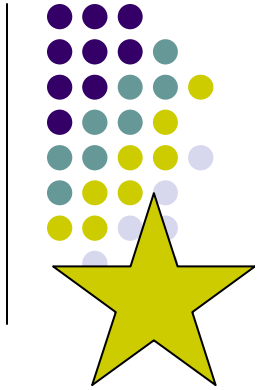


- What data main fields are required?
- Other data types needed
- Data sources
- Are chemical structures available?
- Data format
- Data quality
- Data interpretation

Skin sensitisation

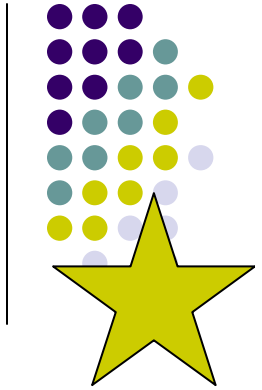
- **Main data fields**
  - GPMT
  - Buehler test
  - LLNA

Mutagenicity



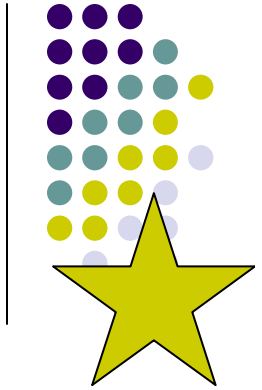
- **Main data fields**
  - Ames test (including strain)
  - Mouse Lymphoma (with & w/out metabolic activation)
  - Micronucleus test (in rat & mouse bone marrow)

Carcinogenicity



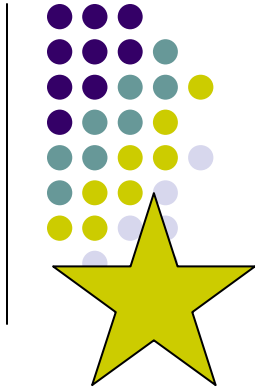
- **Main data fields**
  - Tumour type
  - Dose levels
  - Rat & mouse survival data (for male & female)
  - Organ systems where tumours develop

Hepatotoxicity



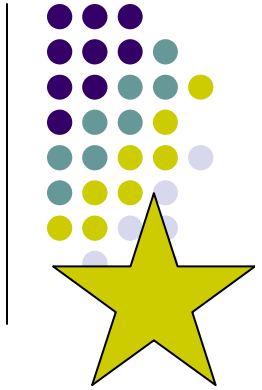
- **Broad endpoint**
  - Preclinical data
  - Clinical data
- **Focused on known hepatic toxicants**
  - Peroxisome proliferators
  - Non-peroxisome proliferators as controls
  - Planned to gather toxicological data for 20-25 compounds
- **Characterisation of hepatotoxicity**
  - Initially 34 indicators

OTHER DATA TYPES



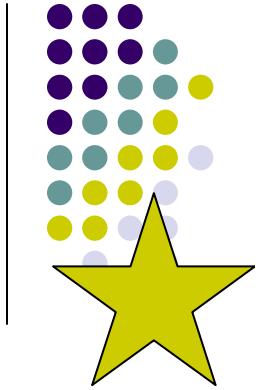
- Chemical name, structure and CAS no.
- Physicochemical data
- Specific data essential for characterising the toxic endpoint
- EG – Skin sensitisation data included, study type, induction and challenge concentrations and volumes, vehicles used, route of administration, species, strain and sex of animals, no. of animals, results, sensitisation ratio, GLP, year of study, controls, remarks.

Other Endpoints



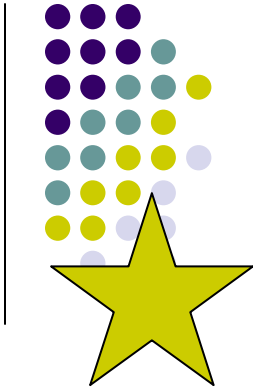
- **Endrocrine disruption**
- **Safety Pharmacology**
  - Cardiovascular
  - CNS
  - Respiratory
- **Environmental**

Other Endpoints



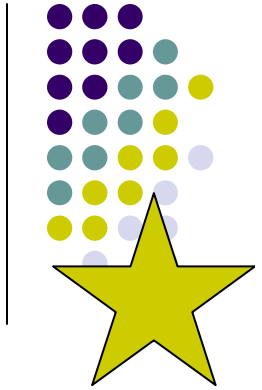
- **Subgroups formed for:**
  - Cardiovascular toxicity
  - Environmental toxicity

PUBLIC DATA SOURCES



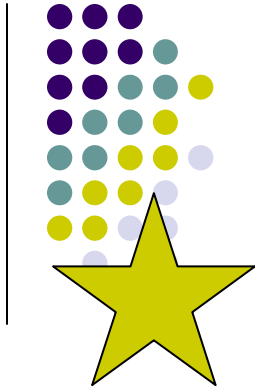
- Skin sensitisation – CIR reviews, IUCLID, scientific literature
- Carcinogenicity – Gold database, NCI/NTP, IUCLID and literature
- Mutagenicity - NTP, IUCLID
- Fish toxicity – EPA, Richard Walmsley's Green Screen data
- Hepatotoxicity – Literature
- Cardiovascular toxicity HERG – Literature

PRIVATE DATA SOURCES



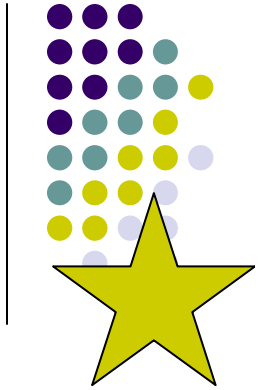
- ILSI/SAR Database Pilot Study
- VITIC - Donation of genetic in vitro data

CHEMICAL STRUCTURES



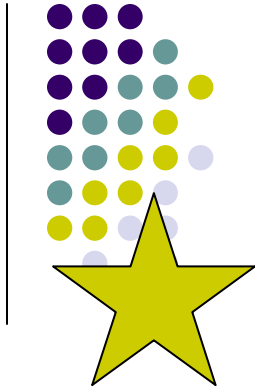
- Import
- Download
- Draw your own
- Format

DATA FORMAT



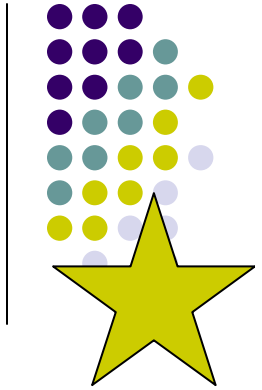
- Data comes in a variety of formats
- Electronic data is helpful
- The structure of electronic data is important
- For (Q)SARs how the data are expressed is vital
  - Classification = sensitising (strong)
  - No. of animals = 15
  - Sensitisation rate = 12
  - Result = 80%

DATA QUALITY



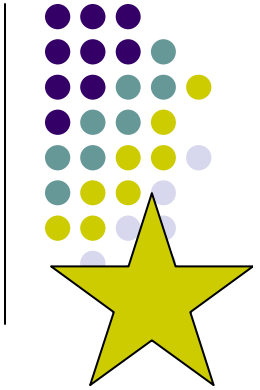
- Important to flag data
- Not just ‘good’ or ‘bad’ data
- Provide information on data quality
- EG – is it to OECD protocols? How many labs. have same result?
- Give the user the choice and let them decide

DATA INTERPRETATION



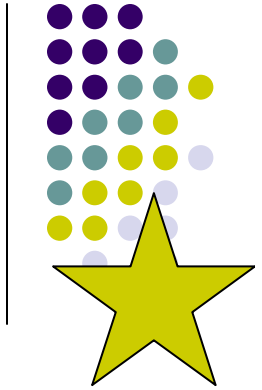
- Toxicology is a multidiscipline science
- Need to understand the data for each endpoint
- Need to know the significance of various parameters
- Need to know where to put data in the database
- EG - HERG

SOME SOLUTIONS TO DATA ISSUES



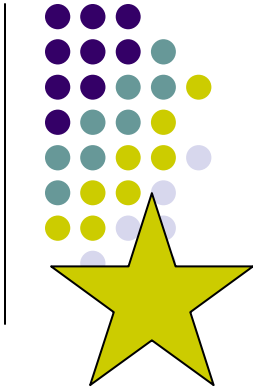
- Collaboration
- Data sharing
- Purpose-built database

COLLABORATION



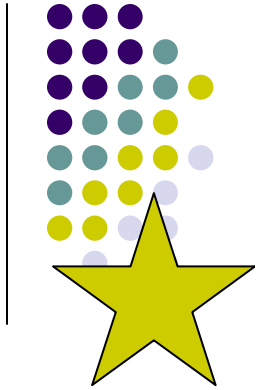
- Industry Consortia
- ILSI/HESI SAR Database Committee
- Lhasa
- EU COST Action 282 – Data in Life Science

DATA SHARING



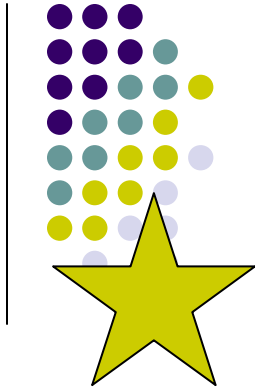
- Providing improved & larger datasets for QSAR models
- Improving SAR as a predictive tool for toxicology
- To reduce animal testing
- To save time and reduce costs

PURPOSE-BUILT DATABASE



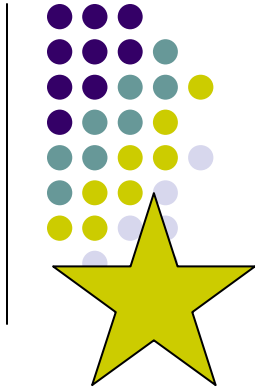
- International Toxicology Information Centre (ITIC)
- Feasibility study
- ILSI/HESI SAR Database Pilot Project
- The VITIC project

Increases in the number of data records



	Pilot records July ‘02	May ‘04 **(2004.1)**	December ‘04 **(2004.2)**
HERG	0	126	401
Hepatotoxicity	43	156	319
Sensitization	1844	2685	3978
Fish Toxicity	4501	4501	5177
In Vitro Genotoxicity	55854	59179	59672
TOTAL	**62242**	**66647**	**69547**

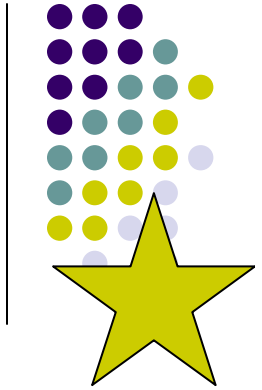
Skin Sensitisation



Alteration of the original data fields

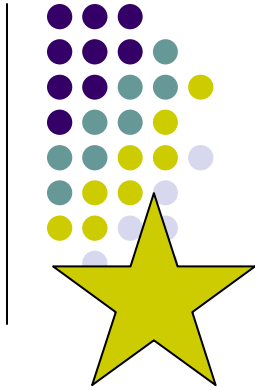
- Based on published literature and regulatory guidelines (e.g. OECD)
- To cater for QSAR needs
- To provide fuller records
- Enable inclusion of details for more assays
- Concise yet complete
- Includes free text additions for method and other comments

CONCLUSIONS



- There are huge amounts of data out there
- Not all of it is easy to obtain nor is it all in the right format
- Some ideas for solving some of the data issues are collaboration, data sharing and the construction of a purpose-built database

ACKNOWLEDGEMENTS



Lhasa staff, in particular:

- Nicole McSweeney – Head of Sales
- Philip Judson – Chief Scientific Officer
- VITIC Database Team