

## **Appendix G:**

# **Overheads from the Session on Information Exchange and International Cooperation**

Slide 1

**U.S. Endocrine Disruptor Screening Program**

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**U.S. Endocrine Disruptor Screening Program**

- Required by the Food Quality Protection Act of 1996
- Only legally mandated EDC screening program in the world.
- EPA must screen pesticides for estrogenic effects that may affect human health
- EPA can use only validated methods
- Timeline for implementation

Slide 2

**SCOPE OF EPA'S ENDOCRINE DISRUPTOR SCREENING PROGRAM**

- Based on current science and existing EPA testing authorities, the scope of the screening program includes:
  - Estrogen, Androgen and Thyroid hormones
  - Human health and ecological effects
  - Expanded universe of chemicals and mixtures

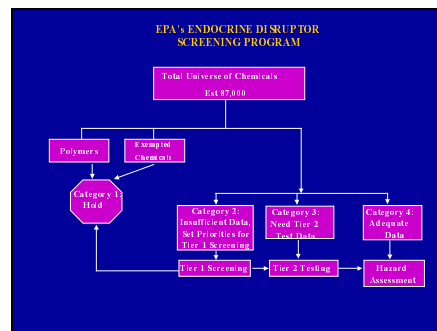
**THE UNIVERSE OF CHEMICALS**

- Chemicals Under EPA's Purview
  - 900 pesticide active ingredients
  - 2500 "inerts" in 20,500 products
  - 75,500 industrial chemicals on the TSCA inventory
  - environmental contaminants (?)
- Chemicals Under Other's Purview
  - cosmetics
  - food additives
  - nutritional supplements

Slide 3

**Framework of the EDSP**

- Initial Sorting
- Priority Setting
- Screening (Tier 1)
  - Identifies substances for further testing
- Testing (Tier 2)
  - Identifies adverse effects and establishes dose-response relationship for hazard assessment



Slide 4

### Screening, Testing and Assessment Strategy

- US focus is on screening
- Current efforts focused on:
  - How to set priorities
  - Validation of Tier 1 and Tier 2 assays
- The first group of chemicals to be screened will be selected from:
  - Pesticide active ingredients
  - HPV chemicals and pesticide formulation inerts
  - Chemicals positive in QSAR

### Implementation Strategy: Commercial Chemicals

- **Goal:** Set priorities for chemicals according to potential exposure and potential endocrine effects
- **How:**
  - Enter data into Priority Setting Database
  - Group chemicals based on common effects and exposure information
  - Compare chemicals within groups and establish priorities within groups
  - Pick highest priority chemicals in each group

Slide 5

### Setting Priorities for Commercial Chemicals in Tier I Screening

- **Problem:** Lack of effects data
- **Solution:** Use Structure Activity Relationship models based on ER, AR binding or HTPS
- EPA is evaluating two different SAR approaches
  - US FDA developed models vary from simple 2-D to complex 3-D models comparing conformations of ligands
  - O. Mekenyan's model is a 3-D model incorporating molecular descriptors
- EPA is evaluating the Japanese HTPS system

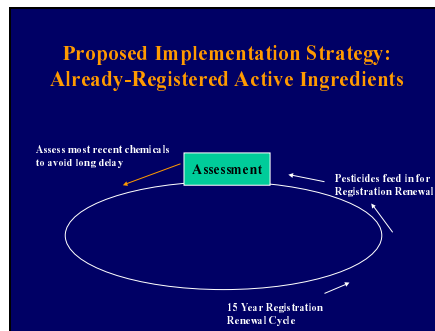
### Proposed Implementation Strategy: Already-Registered Active Ingredients

- Conduct Pilot Program with 25-50 "potentially high EAT hazard concern" substances (Complete in December 2001)
- Pilot will be used to develop criteria for evaluating existing information and sorting pesticides and chemicals into Categories 2, 3 and 4.
- Contractor will conduct literature search and assessment using developed criteria

Slide 6

### Proposed Implementation Strategy: Already-Registered Active Ingredients

- Start with most recent registration /re-registration cases and work backward
- Also assess chemicals as they come in for Registration Renewal (a 15 year cycle)
- Obtain screening or testing data by periodic issuance of testing orders (FFDCA Section 408p) for additional substances
- Take appropriate risk management action under current laws



Slide 7

**Proposed Implementation Strategy:  
New Pesticides**

- Amend registration testing requirements (40 CFR 158) to include EDSP components
- Requirements may vary with class and use pattern, *e.g.*,
  - Requirements may or may not apply at all
  - Requirements may be required prospectively or triggered

**Modes of Action to Incorporate in  
Screening and Testing**

- Hormone synthesis and clearance
- Hormone storage and release
- Hormone transport
- Receptor binding
- Altered post-receptor activation

Slide 8

**PROPOSED SCREENING  
BATTERY (Tier 1)**

- *In vitro* Screens
  - ER Binding / Reporter Gene Assay
  - AR Binding / Reporter Gene Assay
  - Steroidogenesis Assay
- *In vivo* Screens
  - Rodent Uterotrophic Assay
  - Rodent Pubertal Female Assay with Thyroid
  - Rodent Hershberger Assay
  - Frog Metamorphosis Assay
  - Fish Reproduction Screening Assay

**ALTERNATE SCREENING ASSAYS**

- Rodent Pubertal Male Assay with Thyroid
- Aromatase
- Rodent *in utero* through lactation Assay

Slide 9

**PROPOSED TIER 2  
TESTING BATTERY**

- Multigeneration reproduction and development studies
  - Mammalian
  - Fish
  - Avian
  - Amphibian
  - Invertebrate

**Test Method Validation**

1. Background Review and Method Development
2. Pre-validation in one laboratory
  - Demonstration of relevance
  - Standardization of protocol
3. Validation in multiple laboratories
  - Reliability and performance standard
4. Scientific Peer Review
5. Regulatory acceptance and implementation

Slide 10

### Test Method Validation

- Stakeholder involvement in validation process through Endocrine Disruptor Methods Validation Subcommittee
- EPA to work with OECD to develop and validate methods of international interest
- OECD observer status on EDMVS
- Peer review by ICCVAM, EPA's SAP or international peer review panel
- Final screening battery depends on validation results

### Validation Studies Started or Completed

Tier 1 <i>In Vitro</i> Screens	Lit Review	Initial Demo	Pre-Valid	Valid
ER/AR Binding	•	•	•	
Steroidogenesis	•			
Aromatase	•			

Slide 11

### Validation Studies Started or Completed

Tier 1 <i>In Vivo</i> Screens	Lit Review	Initial Demo	Pre-valid	Valid
Uterotrophic (OECD)	•	•	•	•
Hershberger (OECD)	•	•	•	
Pubertal female	•	•		
Pubertal male	•	•		
Fish repro screen (OECD)		•		

### Validation Studies Started or Completed

Tier 2 Tests	Lit Review	Initial Demo	Pre-valid	Valid
Mammalian 2-Gen (OECD)		•		
Fish 2-Gen (OECD)				
Avian 2-Gen (OECD)		•		
Amphibian (OECD)				
Invertebrate (OECD)		•		

Slide 12


### US Timeline

2000 2001 2002 2003 2004 2005

Priority Setting  
Tier I Validation  
Tier II Validation  
Screen 1<sup>st</sup> Group Chemicals

Slide 1

THE WORK OF OECD ON  
TESTING AND ASSESSMENT  
OF  
ENDOCRINE DISRUPTERS




**OECD**  
**(Organisation for Economic Co-operation and Development)**  
International Organisation grouping 30 industrialised countries:

Australia	Hungary	Poland
Austria	Iceland	Portugal
Belgium	Ireland	Slovak Republic
Canada	Italy	South Korea
Czech Republic	Japan	Spain
Denmark	Luxembourg	Sweden
Finland	Mexico	Switzerland
France	The Netherlands	Turkey
Germany	New Zealand	United Kingdom
Greece	Norway	United States



Slide 2

Our Stolen Future .....?  
Certainly not for  
Toxicologists!



"Our Stolen Future provides a vivid and readable account of emerging scientific research about how a wide range of manmade chemicals disrupt delicate hormone systems."


(Vice President Al Gore, January 1996 in his Foreword to *Our Stolen Future*)



Slide 3


The research should be driven by the need to answer a small number of crucial questions:

- How much are we exposed?
- How much is the human body really responding to hormone-disrupting chemicals?
- What is the impact on ecosystems?
- When and how should the government act?  
- (Colborn, Dumanoski and Myers, in "Our Stolen Future", 1996)



IFCS II (February 1997) recommended that IOMC should:


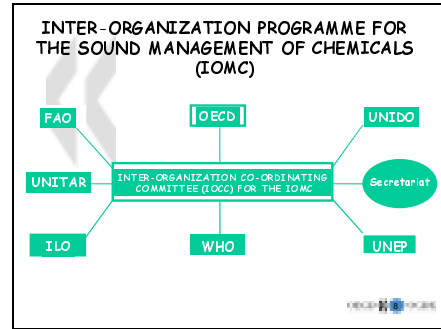
- compile and harmonise definitions and terms;
- promote coordinated research, identify gaps and priorities;



Slide 4

**IFCS II (February 1997) recommended that IOMC should:**


- C. identify testing priorities, gaps, develop and harmonise testing guidelines;
- D. adopt and maintain an inventory of research activities;
- E. facilitate information exchange.

Slide 5


**EDTA - OBJECTIVES**

- Provide information and co-ordinate activities
- Develop new and revise existing Test Guidelines to detect endocrine disrupters
- Harmonise hazard characterisation and assessment approaches for endocrine disrupters among Member countries



**EDTA - TASKS**

- Enhancements and modifications of existing Test Guidelines
- Development of new Test Guidelines
- Management of validation work, as appropriate
- Development of harmonised strategy for the screening and testing of endocrine disrupters



Slide 6


**The work in OECD is**

- directed by Member countries' priorities and preferences;
- based on consensus;
- driven by scientific/technical/policy inputs (e.g. EDSTAC, CSTE, SCP, International workshops/meetings).



**"The CSTE acknowledges the role played by other international bodies, in particular in OECD, as the focal point under which the most significant developments on EDCs knowledge are taking place."**

(8th Plenary Meeting of the EC Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTE), March 1999)



Slide 7

### Recommendations of the CSTEE (on testing):

- the development of in vitro pre-screening test methods is not recommended; instead major emphasis should be on in vivo assays;
- current test guidelines have to be enhanced and new guidelines developed.

### Recommendations of the CSTEE on test priorities:

- for **mammals**: enhancements of Guidelines 407 and 416;
- for **fish**: enhancement of Guideline 210 and the development of both the partial and full life-cycle tests;
- for **birds**: enhancement of Guideline 206;
- for **invertebrates**: addition of relevant endpoints to existing tests.

Slide 8

### Conclusions of the CSTEE:

- at present Test Guidelines cannot detect all endocrine disrupting effects;
- reliance on in vitro assays for predicting in vitro endocrine disrupter effects may generate false results (both positive and negative).

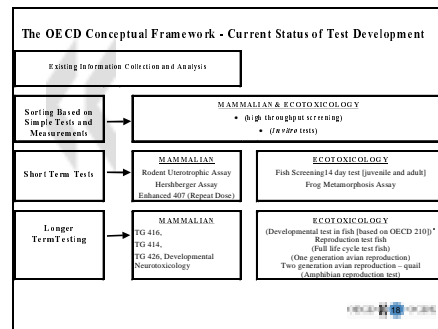
"The SCP does not consider the endocrine disrupters (ED) problem to be of great concern for the assessment of plant protection products [...] because the current process of evaluation, if conducted with special attention to this issue, already permits a rather comprehensive appreciation of the ED-related toxicological risk for mammals and man."

(Opinion expressed by the EC Scientific Committee on Plants (SCP) on 2 December 1999)

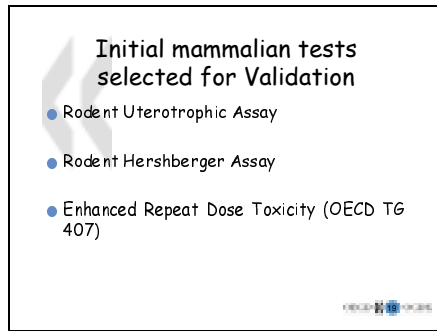
Slide 9

"... Ecotoxicological risks arising from EDs generally can be captured by the current assessment scheme, although for some species the test programme is not yet satisfactory."

(Opinion expressed by the EC Scientific Committee on Plants (SCP) on 2 December 1999)



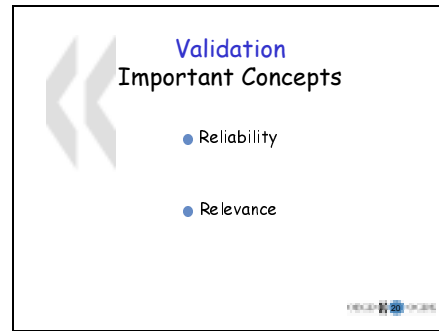
Slide 10



**Initial mammalian tests selected for Validation**

- Rodent Uterotrophic Assay
- Rodent Hershberger Assay
- Enhanced Repeat Dose Toxicity (OECD TG 407)

OECD ECVAM

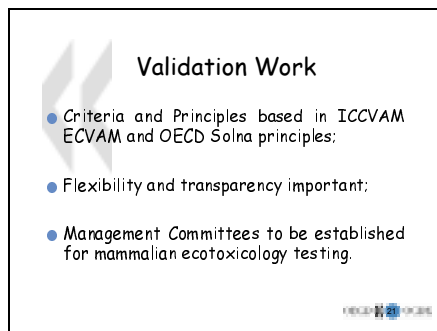


**Validation Important Concepts**

- Reliability
- Relevance

OECD ECVAM

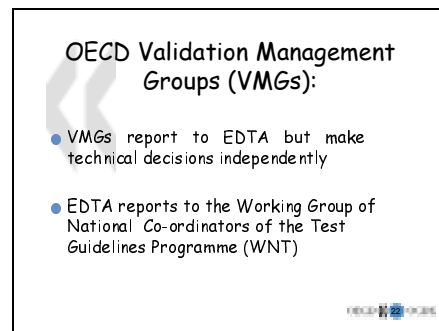
Slide 11



**Validation Work**

- Criteria and Principles based in ICCVAM, ECVAM and OECD Solna principles;
- Flexibility and transparency important;
- Management Committees to be established for mammalian ecotoxicology testing.

OECD ECVAM

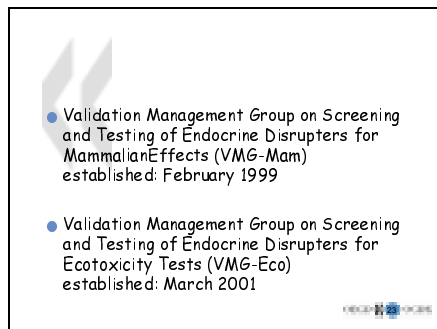


**OECD Validation Management Groups (VMGs):**

- VMGs report to EDTA but make technical decisions independently
- EDTA reports to the Working Group of National Co-ordinators of the Test Guidelines Programme (WNT)

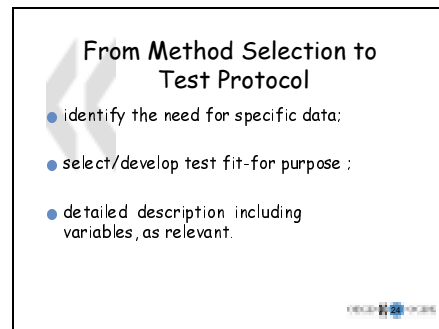
OECD ECVAM

Slide 12



- Validation Management Group on Screening and Testing of Endocrine Disrupters for Mammalian Effects (VMG-Mam) established: February 1999
- Validation Management Group on Screening and Testing of Endocrine Disrupters for Ecotoxicity Tests (VMG-Eco) established: March 2001

OECD ECVAM



**From Method Selection to Test Protocol**


- identify the need for specific data;
- select/develop test fit-for purpose ;
- detailed description including variables, as relevant.

OECD ECVAM

Slide 13


The structure, management and approach of the validation work is strongly supported by:

- Member countries,
- the European Commission,
- industry (through BIAC),
- workers unions (through TUAC).



Enhancement of Repeat Dose Toxicity (OECD 407)


- To evaluate suitability of sub-acute tests as screening;
- Examine suitability and sensitivity of additional (endocrine related parameters);
- Routinely done.



Slide 14


Rodent Uterotrophic Assay

- Test in use since 1930's in pharmaceutical industry;
- Evaluates ability of a chemical to mimic estrogen activity in intact animal.



Hershberger Assay


- Assay developed in the 1950's;
- Looks at the effect of chemicals to restore the weight of prostate gland and seminal vesicles in castrated rodents.



Slide 15


14-day Fish Assay

- Based on existing OECD 204 and 215 using adult and juvenile animals;
- Applicable to different fish species;
- Intended to detect activity of oestrogen and androgen (anti-)agonists.



Fish Reproduction Test


- 42-day test (21-d exposure) using adult reproductively-active animals;
- Uses the fathead minnow;
- Identifies oestrogens/anti-oestrogens and androgens/anti-androgens.



Slide 16


### Avian Two-generation Test

- Two-generation reproduction test in the Japanese quail;
- Assesses reproductive toxicity and endocrine disrupting effects.



### Frog Metamorphosis Assay


- Based on assessment of tail absorption in *Xenopus laevis*;
- Evaluates ability of a chemical to interfere with thyroid axis in vertebrates.



Slide 17


### SHARING THE BURDEN OF TESTING AND ASSESSMENT

- vast number of chemicals
- number of screens/tests for each chemical
- time pressure
- costs of testing are very high
- different philosophies in Member countries



### SHARING THE BURDEN OF TESTING AND ASSESSMENT


- Hazard Assessment
  - Differences in assessment approaches
  - Underlying science and principles
  - Exchange information on emerging scientific developments
  - Agreement on essential elements of E.D. assessment reports
  - Develop generic guidance for the assessment of EDs



Slide 18


### SHARING THE BURDEN OF TESTING AND ASSESSMENT

- Grouping of Chemicals
  - Tools for Screening and Testing
  - Co-ordination of Testing
  - Hazard Assessment



### SHARING THE BURDEN OF TESTING AND ASSESSMENT


- Grouping of chemicals
  - Individual chemicals that have triggered a regulatory interest;
  - Priority lists of chemicals of concern;
  - Other groupings of chemicals;
  - Criteria for selection of chemicals;
  - Details of planned action, including scheduled screening/testing.



Slide 19


SHARING THE BURDEN OF TESTING AND ASSESSMENT

- Grouping of chemicals
- Tools for Screening and Testing
- Co-ordination of Testing
- Hazard Assessment



SHARING THE BURDEN OF TESTING AND ASSESSMENT


- Tools for Screening and Testing
  - High Throughput Pre-Screen (HTPS)
  - DNA micro-assay
  - QSAR models
  - Prepubertal assay
  - Mammalian two-generation study
  - Reproduction tests in birds
  - Reproduction tests in fish



Slide 20


SHARING THE BURDEN OF TESTING AND ASSESSMENT

- Grouping of chemicals
- Tools for Screening and Testing
- Co-ordination of Testing
- Hazard Assessment



SHARING THE BURDEN OF TESTING AND ASSESSMENT


- Co-ordination of Testing
  - early notice of testing plans
  - use of internationally agreed protocols
  - share results



Slide 21


SHARING THE BURDEN OF TESTING AND ASSESSMENT

- Grouping of chemicals
- Tools for Screening and Testing
- Co-ordination of Testing
- Hazard Assessment



SHARING THE BURDEN OF TESTING AND ASSESSMENT

- Hazard Assessment
  - Differences in assessment approaches
  - Underlying science and principles
  - Exchange information on emerging scientific developments
  - Agreement on essential elements of E.D. assessment reports
  - Develop generic guidance for the assessment of EDs



Slide 22



Slide 1

European Commission - DG ENV

European Workshop on Endocrine Disruptors, Aronsborg, (Balsta), Sweden, 18-20 June 2001

**“European Community Strategy for Endocrine Disruptors: Implementation to date”**

Kathryn Tierney,  
European Commission, Environment DG

European Commission - DG ENV

**Contents of presentation**

1. Community Strategy COM(1999)706
2. Implementation to date COM(2001)262
  - Establishment of a priority list of substances for further evaluation
  - Legislative Action
3. Conclusions

Slide 2

European Commission - DG ENV

**1. Community Strategy (1)**

- Need for further research
- Need for international cooperation
- Need for communication to the public
- Need for appropriate policy action

European Commission - DG ENV

**1. Community Strategy (2)**

**Short-term actions**

- ▷ Establishment of priority list of substances for further evaluation of their role in endocrine disruption
- ▷ Use of existing legislative instruments
- ▷ Establishment of monitoring programmes
- ▷ Identification of specific cases of consumer use
- ▷ Information exchange/international cooperation
- ▷ Communication to the public
- ▷ Consultation with stakeholders

Slide 3

European Commission - DG ENV

**1. Community Strategy (3)**

**Medium-term action**

- ▷ Identification and assessment of EDs
- ▷ R&D
- ▷ Identification of substitutes

**Long-term action**

- ▷ Overall chemicals policy
- ▷ Water Framework Directive
- ▷ Other legislative actions/proposals

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**2. Implementation to date (1)**

*Establishment of a priority list of substances for further evaluation of their role in ED*

**Procedure :**

- Step 1 : Production of candidate list
- Step 2 : Consultation and Priority-setting

↓

**Priority list of actions**

Slide 4

2. Implementation to date (2)

European Commission - DG ENV

**Results of Steps 1 and 2:**

- BKH Report a reasonable starting point
- Focus on man-made chemicals plus synthetic/natural hormones present in the environment
- All 553 candidate substances retained for further evaluation plus 9 natural/synthetic hormones
- Need to address scientific shortcomings identified by SCTEE/stakeholders in further evaluation
- Need to set up iterative mechanism for updating

2. Implementation to date (3)

European Commission - DG ENV

- No duplication of work with ongoing risk assessments under existing Community legislation
- Of 118 substances with evidence of endocrine disruption or potential ED in BKH Report, 109 are already subject to regulatory measures:
  - 16 obsolete plant protection products
  - 14 banned in EU
  - 22 with marketing restrictions in EU
  - 11 subject to emission controls
  - 46 currently on priority lists for risk assessment

Slide 5

2. Implementation to date (4)

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**Next steps: Priority list of actions:**

- Study to conduct in-depth evaluation of 12 substances not currently addressed (12-18 months)
- Study to gather information on 435 substances with insufficient data in BKH Report (12-18 months)
- Invite MS Competent Authorities (CA) to take ED into account during RA of 46 substances (1-4 years)
- Invite MS CA to carry out classification on 2 substances (1-2 years)

2. Implementation to date (5)

European Commission - DG ENV

**Legislative action**

**Overall chemicals policy**

- White Paper, 13 February 2001
  - Authorisation procedure for CMR/POPs
  - Highlights need for further research on EDs -- on test methods, low dose effects, QSARs
  - Rigorous testing for long-term effects for >100t

Slide 6

2. Implementation to date (6)

European Commission - DG ENV

**Legislative action**

**Overall chemicals policy cont'd**

- Council Conclusions, 7 June 2001
  - Known EDs should be subject to authorisation when agreed scientifically valid test methods and criteria are established

2. Implementation to date (7)

European Commission - DG ENV

**Legislative action**

**Water Framework Directive**

- Proposal for establishing the list of priority substances in the field of Water Policy
  - Of the 33 priority substances, 11 are candidate ED substances
  - Measures to be proposed within 2 years aimed at ending or phasing out emissions, discharges and losses within 20 years.

Slide 7

2. Implementation to date (8)  
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*Legislative action*

**General Product Safety Directive**

- Key risk management instrument in short-term
- Under revision, trilogue discussions
- Will allow simplification of procedures and conditions for urgent measures at Community level

15 Author: RT June 2001

3. Conclusions  
European Commission - DG ENV

**1999 Preparation of Community Strategy**

**2000-2001 Preparatory activities**  
*identification of substances,  
planning of dedicated call for research proposals  
planning of European workshop*

**2001-2002 Implementation**  
*launch of studies research projects  
revision and preparation of legislative proposals  
Launch of new activities e.g. monitoring*

16 Author: RT June 2001

Slide 8

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**Website address:**

<http://www.europa.eu.int/comm/environment/docum/99706sm.htm>

16 Author: RT June 2001