

## **A MIAME for Toxicogenomics - MIAME/Tox**

DRAFT August 2003 – Based on MIAME/Tox 1.1

With the development of toxicogenomics we believe that it is necessary to move toward harmonization of minimal toxicological data requirements to fully realise the potential of this emerging interdisciplinary field.

Following the very favourable response that the Minimum Information About a Microarray Experiment (MIAME)<sup>1</sup> has received from the microarray community and key scientific journals<sup>2,3</sup> we have initiated the harmonization process as applied to array-based toxicogenomic experiments. MIAME/Tox<sup>4</sup> is a set of guidelines defining the *minimum* information required to interpret unambiguously and potentially reproduce and verify array-based toxicogenomic experiments. Similarly, MIAME/Tox seeks to provide such a conceptual structure in the context of pharmacogenomics and chemogenomics. Therefore, this harmonization effort in toxicogenomics will have broad application in experimental science as well as clinical medicine.

MIAME/Tox supports a number of different objectives, for example: linking data within a study, and linking several studies from one institution and exchanging toxicogenomics datasets among public databases. In fact, the major objective of MIAME/Tox is to guide the development of toxicogenomics databases and data management software. The breadth, depth, and uniformity of the information a database contains are critical to its utility. To address the last issue, MIAME/Tox content areas for experiment descriptions include information that are recommended to be provided by maximum use of controlled vocabularies or ontologies (such as species taxonomy, cell types, anatomy terms, histopathology, toxicology, and chemical compound nomenclature). The use of controlled vocabularies is needed to enable database queries and automated data analysis.

MIAME/Tox guidelines have been adopted to guide the development of toxicogenomics databases underway at the NIEHS National Center for Toxicogenomics<sup>5</sup>, USA and at the EMBL European Bioinformatics Institute (EBI)<sup>6</sup>, UK in conjunction with the International Life Sciences Institute's Health and Environmental Sciences Institute (ILSI HESI)<sup>7</sup>, USA.

MIAME/Tox is continuously developing in accordance with our understanding of microarray technology and its applications to toxicology and pharmacology. Please join the MIAME/Tox discussion list ([mged-toxico@lists.sourceforge.net](mailto:mged-toxico@lists.sourceforge.net)) and contribute with your ideas and comments.

### **On the behalf of EMBL-EBI, NIEHS NCT, NIEHS NTP and ILSI HESI:**

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- 1 EMBL – The European Bioinformatics Institute
- 2 NIEHS National Center for Toxicogenomics
- 3 ILSI Health and Environmental Sciences Institute

- 4 ILSI Health and Environmental Sciences Institute, Genomics Committee
- 5 Pfizer and ILSI Health and Environmental Sciences Institute, Genomics Committee
- 6 NIEHS National Toxicology Program

## References

- [1] Brazma A *et al.* (2001). Minimum information about a microarray experiment (MIAME) - toward standards for microarray data. *Nature Genetics*, 29, 365-371.
- [2] Microarray standards at last. *Nature* 2002 419:323.
- [3] Ball CA *et al.* (2002). An open letter to the scientific journals. *Science*, 298(5593):539. *Bioinformatics*, 18(11):1409. *The Lancet*, 360:1019.
- [4] MIAME/Tox 1.1 draft at: <http://www.mged.org>
- [5] NIEHS NCT: <http://www.niehs.nih.gov/nct/>
- [6] Toxicogenomics at EBI: <http://www.ebi.ac.uk/microarray/Projects/ilsi/index.html>
- [7] ILSI HESI: <http://hesi.ilsil.org/index.cfm?pubentityid=120>

## MIAME/Tox Checklist

Minimum information to be recorded about toxicogenomics experiments is defined in subsequent sections and should include the following data domains:

- Agent description, formulation, purity, solubility, vehicle, separation methods, chemical structure, active moieties, safety and toxicity, storage, half-life.
- Experimental design parameters, genetic background and animal husbandry information or cell line and culture information, exposure parameters, dosing regimen, and dose groups.
- Microarray data, specifying the number and details of replicate array bioassays associated with particular samples, and including PCR transcript analysis if available.
- Biological endpoint data, including animal and organ weights at necropsy or cell counts and doubling times, clinical chemistry and enzyme assays, hematology, urinalysis, other.
- Textual endpoint information such as clinical and gross observations, pathology and microscopy findings.

As with MIAME, MIAME/Tox has two major sections.

- Array design description;
- Gene expression experiment description.

The first section remains identical to the MIAME 1.1 document, and the second section is extended to fulfill the need of this toxicogenomics-specific application of MIAME. The two components of MIAME/Tox are discussed in further detail below.

### Array design description

*This section remains identical to the MIAME 1.1 document.*

## Experiment description

By *experiment*, MIAME refers to a set of one or more hybridizations that are in some way related (e.g., related to the same publication or the same study). The minimum information for a toxicogenomic experiment includes a description of the following five parts.

- 1) Toxicogenomic experimental design
- 2) Biological materials used, extract preparation and labeling, **toxicological assays**.
- 3) Hybridization procedures and parameters
- 4) Gene expression measurement data and Specifications of data processing

MIAME/Tox recommends the following details on each of these sections.

### 1. Toxicogenomic experimental design

The following information is included in the experimental design.

- Authors, laboratory or clinic, contact
- A brief description of the experiment and its goal and a link to a publication if one exists (Links (URL), citations).
- Indicate the Experiment Design Type  
Instances could be:
  - **compound\_treatment\_design**
  - **dose\_response\_design**
  - **injury\_design**
  - **stimulus\_or\_stress\_design**
  - **other.**

Note that use of multiple entries if of course possible to specify the type of the experiment. One can also propose a term: e.g. **Acute, pre-chronic or chronic treatment, or clinical trial**

- Experimental factors, i.e. organisms, parameters or conditions tested, for instance:
  - species, strain, genotype, genetic variation
  - age and weight, developmental stage
  - dose(s) in standard units
  - route of exposure, vehicle, time of treatments and observations
- Indicate the total number of hybridizations in the experiment
- Quality control steps taken:
  - Replicates done (yes/no), type of replicates (biological, technical) description
  - if pools of extracts (yes/no) were used versus extracts from individual samples, description
  - whether dye swap is used (only for two channel platforms)
  - other.

## 2. Biological materials used, extract preparation and labeling, toxicological assays.

By *biological material*, MIAME/Tox refers to the material (sample) used in toxicological, pharmacological or clinical investigations and from which nucleic acids were extracted for subsequent labelling and hybridisation. In this section all steps that precede the hybridization are described. We can usually distinguish between:

- Assessment of the source of the sample (biosource properties);
- **Treatments applied to the samples (manipulations);**
- **Toxicological assessments;**
- Extract preparation;
- Extract labelling; and
- Hybridization controls.

### Biosource properties

- organism (NCBI taxonomy)
- sample source provider
- descriptors relevant to the particular sample, such as
  - strain
  - sex
  - genetic background
  - genetic modifications
  - age
  - weights
  - development stage
  - organism part (tissue) of the organism's anatomy from which the biological material is derived (if samples are cells)
  - cell type
  - animal/plant strain or line
  - genetic variation (e.g., gene knockout, transgenic variation)
  - individual genetic characteristics (e.g., disease alleles, polymorphisms)
  - disease state or normal
  - additional clinical information available an individual identifier (for interrelation of the biological materials in the experiment)

**Sample manipulations:** laboratory protocols and relevant parameters, such as:

- **facilities details**
- **animal husbandry and housing details**
- **cell culture conditions**
- **growth conditions (passage level and frequency)**
- **metabolic competency of cell strains**
- **treatment (stressor), *in vivo*, *in vitro***
- **treatment type (e.g., compound, small molecule, heat shock, cold shock, food deprivation, diet)**
- **treatment compound name and grade formulation, including manufacturer**
- **type of compound (e.g. chemical, drug or solvent)**
- **CASRN, chemical structure/molecular formula**
- **vehicle for chemical treatment**

- **exposure method (route of administration, e.g. oral, gavage, mucular, medium, intraperitoneal, intramuscular, intravenous, topical)**
- **duration**
- **dose (and unit)**
- **date/time at death or at sacrifice**
- **sacrifice method**

**Toxicological assessments:** laboratory protocols and relevant parameters measured and data files e.g.,

#### **Clinical observations**

- **weight**
- **survival (yes/no)**
- **signs (e.g., general, behavior)**
- **site of application**
- **lesions**
- **color effects**
- **other**

#### **Gross necropsy examination**

- **organs and tissues examination list**
- **organs and tissues collection list**
- **organs and tissues weight list**
- **organs and tissues storage method and location**

#### **Histopathology evaluation**

- **which biological materials (control and experimental)**
- **slide preparation, storage method and location**
- **topography (definite anatomical region)**
- **system**
- **organ**
- **sites**
- **cell type(s)**
- **morphology(s)**
- **qualifier(s) for the morphology(s)**

#### **Clinical pathology**

- **hematology (e.g., erythrocyte count, mean corpuscular volume, hemoglobin)**
- **clinical chemistry (e.g., sorbitol dehydrogenase (SDH), alkaline phosphatase (ALP), creatine kinase (CK))**
- **other parameters measured, e.g., sperm morphology and vaginal cytology evaluation (SMVCE)**
- **estrous cycle length**
- **micronucleated erythrocytes determination**
- **functional observation battery**
- **other.**

Nucleic acid extraction protocol applied to the biological material

- Type of nucleic acid RNA, mRNA, or genomic DNA is extracted
- extraction method
- amplification methods if any.

Labeling protocol for each labeling prepared from the extract, including

- amount of nucleic acids labeled
- label used (e.g., A-Cy3, G-Cy5, 33P, ....)
- label incorporation method
- Facility details (if this part of the experiments has been carried out in facility different from the sample treatment and toxicological assessments steps above, e.g. consortium, contracting out).

External controls added to hybridization extract(s) (spiking controls)

- element on array expected to hybridize to spiking control
- spike type (e.g., oligonucleotide, plasmid DNA, transcript)
- spike qualifier (e.g., concentration, expected ratio, labelling methods if different than that of the extract)

### **3. Hybridization procedures and parameters**

*This section remains identical to the MIAME 1.1 document*

### **4. Measurement data and specifications of data processing**

*This section remains identical to the MIAME 1.1 document*