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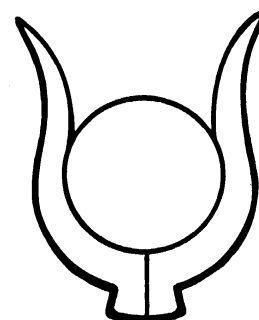
ISIS BioComp

Data Management Systems For Preclinical Research

Reproductive Toxicology



In-life Toxicology



Computing for Bio research

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TFR/Tox Overview

- Comprehensive, integrated system for the collection, management and evaluation of data generated by teratology, fertility, reproductive and general toxicology studies
- Supports observations for reproductive, fertility and teratology studies including mating, littering, pup developmental markers and behavioral indicators, cesarean section and fetal exams (external, skeletal and visceral)
- Supports data collection for routine in-life toxicology examinations and observations including animal body weights, fresh and used feeder/water weights, mortality checks, clinical observations, dosing observations and veterinary examinations.
- Supports data collection for acute, subacute and chronic toxicity/oncogenicity studies
- Supports data collection for special examinations such as Acute Eye Irritation and Draize Skin Test
- System is flexible and can be easily customized to users' requirements
- Data are protected from unauthorized access via a multi-level password security system
- Data can be exported to SAS, RS/1 or to any other statistical analysis or database system
- Extensive data validation and audit trails help comply with regulatory requirements and Good Laboratory Practices (GLP's). Complies with 21CFR11
- Reports are designed for the archival, evaluation, and submission of data to regulatory agencies
- Study data can be simultaneously accessed via a networked database. The database can be a microcomputer or mainframe.
- System constructed with compliance in mind and quality is "built in" from development through release. Complete testing and structural validation documentation is available for review.
- Data entry field requirements are provided for each screen to assist with your internal validation effort
- The system accesses an Oracle database, and the workstations operate with Windows 95, 98, NT, 2000, and XP.

Flexibility

The observations and examinations currently supported by the *TFR/Tox* system cover most standard protocols. In recognition of the fact that laboratories do things differently, we have designed the system to be extremely flexible and easy to customize. The system can be configured to operate the way your laboratory collects data. Several of the exams (i.e., pup developmental indicators, pup physical parameters) can be tailored by the user to collect the specific indicators and measurements used by the installation.

Data in the system is managed with the ORACLE relational database management package. The capabilities inherent in a relational database make it easy to add and drop data collection parameters.

The reports supplied with the system are produced with a very powerful report writing facility. It permits us ... or you ... to customize the appearance of your reports very easily. We can also develop new reports very quickly.

Data can be exported to SAS, RS/1, or to any other statistical analysis or database system.

Integrated Environment

The database management system used by the *TFR/Tox* system can be used by other applications developed in-house or available from other software vendors. Integration would allow the laboratory to capture other pre-clinical and clinical data in one central database. This integrated environment would allow correlation of data from all phases of a compound's development.

Security and Audit Trails

Data collected by the *TFR/Tox* system are protected from unauthorized access via a multi-level, user ID and password-based, security system. Users must identify themselves to the system via a user ID and a password. Authority to access particular exams and data are limited on both a study and a global level. The system complies with the requirements of 21CFR11.

The security system functions hierarchically. Personnel must be identified in the Global User List and be given a specific password to access the system. Associated with this password is a list of basic system modules to which the user has access (data collection, report generation, study management, etc.) During study protocol definition for a specific study, the study administrator assigns each user data collection authority for the exams to which they require access.

The protocol specific exam authorization assignments can be made in a template. Each new study created with that protocol will automatically contain the user authorization list.

All data collected are protected from modification by an audit trail which includes: who made the change, what the change was, and when and why the change was made.

Features

In *TFR/Tox*, all text-oriented examinations (clinical signs, veterinary exam, fetal examinations) utilize the same hierarchical glossary system. This glossary structure allows observations to be collected and reported with as much or as little detail as desired.

Protocols can be easily modified at anytime during a study. Animals can be added to groups, entirely new groups can be added, and schedules can be modified in order to accommodate new study requirements.

Historical control data can be maintained easily. The data is stored in a relational database management system, therefore, transfer to a historical database is routine.

All data collection is controlled via a daily schedule. This schedule is generated prior to the workday and details all exams. The user is presented with a list of animals for each examination. Unscheduled observations may be made, but the user must give a reason for making the observation. All scheduling in the system is driven by the current *phase* of an animal. This is important in a reproductive study where the exams required for a dam are determined by pregnancy status and other reproductive events. The system allows an animal to be *phase shifted* at any time. The schedule is immediately updated to include any observations required for the new phase.

Data can be changed via the same screens used in data collection. The system is placed in "Edit Mode" and the date the target observations were collected is specified. The user then modifies the specific data using the same data entry screens. Entries are made in the audit log as detailed previously.

"Group based" observations are available for observations such as clinical signs and dosing where start and end times for specific groups are desired. Comments can be made on the group level as well as the individual animal level.

Current development will support direct capture of lesion images from microscopes or the necropsy lab into the study database. These images will be immediately available for display along with the lesion text. Lesion images can be retained with the glossary as an on-line reference library.

Networking

During the course of a normal toxicological and reproductive study, activities that require access to the *TFR/Tox* system may be occurring simultaneously. For example, Cesarean sections may be taking place while other animals are dosed, or observations on pups are made. QA may be checking interim results while F₁ body weights are being entered. More than one workstation may be needed in a busy necropsy room. The *TFR/Tox* system supports simultaneous access to study data via the network support capabilities of the underlying database management system.

The Oracle database can reside on any server accessible via SQL*Net (or Net8). Current clients use Windows NT, DEC Alpha, Unix, and Novell servers. The file service network can be any network accessible from the client PCs.

Hardware and Software Requirements for TFR/Tox

The following hardware is required, recommended or can be optionally used with *TFR/Tox*:

Required or Recommended Hardware

TFR/Tox can be **demonstrated and evaluated** on a stand-alone Windows-based personal computer. About 100Mb of disk space is required.

The **production** system runs on ordinary PC workstations networked to a suitable database and network server. The PCs can run any Windows operating system from Windows 95 forward, and should have at least 128MB of RAM. A local hard disk is recommended but not required.

A modem, or access via Internet, is required for installation and support.

Optional Hardware

- A Microsoft Mouse compatible pointing device (mouse, trackball, etc.)
- A printer. The system currently supports HP LaserJet (PCL) compatible printers. It can also produce PostScript, Adobe PDF, or plain ASCII output. The printers can be attached directly to the workstation or connected to the network.
- Electronic scales (Mettler, Sartorius, Arbor, etc.).
- Barcode reader, Avid or BMDS animal identification scanner

Required or Recommended Software

- The TFR system employs the ORACLE™ relational database, which must be supplied by the user. We require ORACLE Kernel, SQL*Net for each workstation, and at least one copy of SQL*Plus.
- Reports are generated by Brio.Report (formerly SQR), from Brio. One or more copies for the PC are required.
- pcAnywhere is required for the PC used for remote support.

System Customization

Routine customization includes defining the examinations and data collection screens utilized at the user's facility. ISIS BioComp will also assist in setting up template studies for copying for routine studies, as well as your glossaries. Specific customization will be performed on an additional cost basis - cost to be determined depending upon work involved in making the desired changes. Once trained, the user can define and add most new examinations without the assistance of ISIS BioComp.

User Friendly

TFR/Tox is extremely user friendly. The data collection screens are consistent from exam to exam. The user interface utilizes pop-up windows, scrollable menus, and function fields that are selectable via a keyboard or a mouse.

- All modules are accessed via one program through a series of menus. The user does not have to exit one program and enter another (i.e., data collection to report generation). All choices are clearly defined via menu choices and function fields. Memorization of function keys is not required.
- A user is granted privilege to enter the individual modules via their password. In order

to prevent confusion, if a user does not have the privilege for a specific module or a data collection activity, it does not show up as a menu choice.

- All information in the system is entered via screens that follow a format consistent from module to module. Color is used to enhance presentability and highlight information content. All information supplied by the user (control as well as data) can be edited on the screen on which it was entered. Separate edit routines are not required. All edits to the data are protected via an audit trail.
- The system is designed to minimize the entry of required control information. Information that is common to all studies (glossary terms, standard responses, instrumentation in use, etc.) is accessed via global data management functions and needs to be customized only at system installation.
- Study protocol entry is facilitated by the ability to establish *template studies*, which can be used as guides for starting actual studies. Templates can be established for each of the major protocols in use.
- Data entry is controlled via a scheduling system that allows the system to know what animals require what data, what data have been collected and what data are missing. The user is prompted for missing data, data that are out of user defined ranges, inconsistent data, etc. Default responses can be defined for each data element and supplied automatically by the system.
- The user does not need to memorize codes or numeric responses as observations can be entered from glossary listings or pop-up fields containing allowed responses. The system does any necessary numeric conversion.
- The data collected for each exam can be customized for the installation. The user, at the time of collection, can modify the order of presentation for each data collection parameter.
- A series of general and field-specific help screens can be invoked from any screen with TFR/Tox by special function keys. These screens provide specific information about the screen being viewed.

Animal Numbering System

The animal numbering system for TFR/Tox is extremely flexible. The basic number is composed of a numeric portion with optional user-defined prefix and suffix if needed. Group and sex can be automatically incorporated in animal IDs. Quarantine animal numbers can be retained for study numbers or new numbers can be assigned with the system keeping track of the previous number. Pup numbers can be automatically based on dam IDs. The maximum length is ordinarily 20 characters due to space requirements on reports, but even this can be changed if necessary.

User's Manual

The User's guide includes a total of eight chapters (User Management, Global Management, Study Management, Schedule Generation, Data Collection, Report Generation, Drug and Diet Preparation, and System Administration) and exceeds 500 pages in length. It includes a Table of Contents, an Index and an Appendix containing error messages, warnings and database messages.

Documentation and Compliance

ISIS BioComp's personnel have backgrounds in regulatory compliant toxicology systems. This results in software that is designed and constructed with compliance in mind. Quality is "built-in" to the software at every stage, development through release. Complete documentation for every element in the system's development life cycle is available for review. System documentation that details the components of the software and their relationships is provided. Modules are structurally validated as they are developed and all related testing is documented. Data entry field requirements for each screen are provided to assist with your laboratories internal validation effort.

Reports Produced by TFR/Tox

TFR/Tox provides reports designed for the archival, evaluation and submission of data to the regulatory agencies. *Individual Animal Reports* present all raw data for the study. *Incidence Summary Reports*, and *Group Summary Reports* provide a group level summation (including means and standard error or deviation). Special statistics can be added on a customer basis or external statistical routines can be utilized. Because the standard reports are generated by an advanced reporting system, their specific appearance can easily be tailored to the user's needs. The standard reports available with *TFR/Tox* are divided into **Global, Study Management, Scheduling, Drug and Diet Prep, Individual Animal, Group Summary, Teratology, Pup, Export Routines, Customer Specific and System Management**. Reports are continually being updated and new reports are being added. Reports currently include the following:

Global Data

• GLBLAUDT	TFR990	Global Audit Log
• DOCEXAM	TFR030	Global Exam Definitions
• INSTR	TFR904	Global Instrument Listing
• DOCOBS	TFR031	Global Observation Definitions
• CLINSIGN	TFR911	Global Observation Listing
• DOCPARAM	TFR032	Global Parameter Definitions
• GLBLSCLG	TFR918	Global Scale Calibration Log
• SCHED4	TFR804	Global Scheduled C-Sections and Deliv...
• TEAM	TFR902	Global Team Listing
• TOPOGRAF	TFR910	Global Topography Listing
• GLBLUSER	TFR901	Global User Listing
• HELPTXT	TFR920	Help Text
• TABLES	TFR905	Lookup Table Contents
• GLBLMISC	TFR903	Miscellaneous Global Items
• COMPSKGL	TFR805	Scheduled Activity Completion
• DAYSKGL	TFR805	Scheduled Daily Activity
• EXAMGLOS	TFR913	Standard Observation Glossaries
• GLBLSTUD	TFR923	Studies in the Database

Study Management

• ALLOC	TFR925	Allocation Report
• EXAMLIST	TFR919	Animal Selection Lists
• CAGECHNG	TFR812	Cage Change Report
• CENSLIST	TFR918	Census Listing
• FETLASGN	TFR931	Fetal Exam Assignment
• PHASCHNG	TFR810	Phase Change Report

• ROOMCHNG	TFR811	Room Change Report
• SCHED3	TFR803	Scheduled C-Sections and Deliveries
• SESSION	TFR926	Session Listing
• STDYAUDT	TFR991	Study Audit Log
• DESIGN	TFR916	Study Design Description
• STDYJRNL	TFR920	Study Journal Log
• SCALELOG	TFR915	Study Scale Log
• TEAMLOG	TFR917	Study Team Log
• STDYUSER	TFR914	Study User Listing
• VERIFY	TFR927	Unverified Data Report
Scheduling Reports		
• SCHED2	TFR802	Schedule Details
• SCHED1	TFR801	Scheduled Activity Completion Summary
• SCHED1	TFR801	Scheduled Daily Activities
Drug and Diet Prep Reports		
• DOSEVOL	TFR641	Dose Volume Calculation and Manual Re...
Individual Animal Reports		
• INDAG	TFR622	Adult Glossary Exams
• SACRIFIC	TFR100	Animal Sacrifice Information
• BODYWT	TFR601	Body Weight Data for Females during G...
• BODYWT	TFR100	Body Weights Parameters
• WTGAIN	TFR501	Body-Weight Changes, Gravid Uterine W...
• DELIVERY	TFR693	Delivery Observations
• DOSEHIST	TFR100	Dosing History
• ESTROUS	TFR100	Estrous Observations
• ESTROUS	TFR691	Estrous Record
• INDOPEN	TFR612	In-life Glossary Exam Positive Findings
• INDORGWT	TFR631	Individual Organ Weight Report
• OSSIF	TFR113	Individual Ossification Data
• ROTOR	TFR111	Individual Rotor Treadmill Data
• SCHEDBW	TFR602	Individual Scheduled Body Weights
• SCHEDFC	TFR603	Individual Scheduled Food Consumption
• SCHEDGL	TFR610	Individual Scheduled Glossary Observa...
• PMORPH	TFR115	Individual Sperm Morphology Data
• WMAZE	TFR112	Individual Water Maze Data
• MFEP	TFR114	Male Fertility Endpoints
• MFEPW	TFR11W	Male Fertility Endpoints
• MATING	TFR692	Mating Record
• INDGLOS	TFR613	One-Time Glossary Exam Positive Find.....
• PREGLEN	TFR680	Pregnancy Length
• LITTERWT	TFR696	Pup Litter Weights during Lactation
• RAWDATA	TFR690	Raw Data Report
• TUMORWT	TFR100	Tumor Weight
Group Summary Reports		
• GENERAL	TFR710	General Observation Summary
• CLINOBSM	TFR611	Glossary Exam Summary of Incidence
• INDORGXR	TFR632	Organ Weights Crossreference Report
• SMORGWT	TFR711	Summary of Absolute and Relative Organ..
• SMFETSTB	TFR729	Summary of C-sectioning Observations ...

• SMPUPDEV	TFR731	Summary of Developmental Signs
• SMFETSTA	TFR728	Summary of Fetal Observations at Cesa...
• SMFETSTC	TFR730	Summary of Fetal Observations in Cesa...
• SMGSTPRT	TFR723	Summary of Gestation Length and Partu...
• SMFETMAL	TFR726	Summary of Incidence of Fetal Malform...
• SMPREG	TFR722	Summary of Maternal Survival and Preg...
• SMPUPGRO	TFR727	Summary of Offspring Growth
• SMVIA	TFR725	Summary of Offspring Viability
• SMRI2	TFR732	Summary of Reproductive Indices
• SMRI	TFR724	Summary of Reproductive Indices
• HEMATOLS	TFR710	Summary: Hematology Data

Teratology Reports

• IMPLANTS	TFR502	Status of Implants at C-Section
• INDFETGL	TFR512	Fetal Glossary Exams
• INDFETPA	TFR511	Individual Fetal Parameters
• FETUS	TFR503	Parameters of Live Fetuses Delivered ...
• FETLPOS1	TFR515	Positive Findings in Fetal Exams
• FETLPOS2	TFR516	Summary of Positive Findings in Fetal...

Pup Reports

• CULLING	TFR694	Culling Report
• PUPWT	TFR660	Mean Pup Weights during Lactation
• PUPWTI	TFR661	Individual Pup Weight Report
• PUPDEV	TFR662	Pup Developmental Signs
• PUPDEV D	TFR663	Pup Developmental Signs: Day of Appea...
• PUPPOS2	TFR616	Summary of Positive Findings in Pups
• VIABILITY	TFR695	Pup Viability Individual Animal Report

Export Routines

• EXPPARAM	TFR851	Export of Parametric Data
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Customer-Specific Reports

• HEMATOLI	TFR101	Hematology Detail by Parameter
• SPERMTOX	TFR100	Sperm Toxicity Report

System Management

• GLBLCONT	TFR052	Contents of Data Collection Tables
• DBSTATO	TFR056	Oracle Statistics
• INSTREPT	TFR051	Report Installation
• DOCINDEX	TFR042	TFR/Tox Index Documentation
• REPORTS	TFR050	TFR/Tox Report Documentation
• DOCTAB	TFR040	TFR/Tox Table Documentation

Advantages of TFR/Tox

- ISIS BioComp offers a completely integrated system for the collection of data from reproductive and general toxicology studies.
- TFR/Tox is a mature system, in daily use at multiple sites.
- It's complete: it handles every kind of data, including all fetal and pup exams. And it's easily extended by the user.
- It was designed to FDA requirements, and is fully documented. It's vendor-verified and user-validated, and it complies with 21CFR11.
- Our systems are competitively priced, and we offer a substantial discount for a secondary installation.
- Complimentary PowerPoint demonstrations are available and TFR/Tox is available for evaluation.
- We offer a variety of ways to license, including leasing

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