entimICE® ToxKin

Fact Sheet

Mission

Rapid Reporting for Standard Toxicokinetic and Pharmacokinetic Evaluations

ToxKin is an innovative, server-client software solution for non-compartmental analysis of toxicokinetic and pharmacokinetic studies. With more than 50 TK/PK parameters, 12 built-in descriptive statistics calculated per parameter and 46 configurable report types, ToxKin supports routine evaluations and rapid creation of reports for standard TK/PK studies, while also providing sufficient flexibility for specialized analyses and reporting.

3 reasons for ToxKin

✓ **1. Rapid standard reports:**

More than 50 TK/PK parameters, 12 built-in descriptive statistics calculated per parameter and 46 configurable report types for comprehensive reports in no time.

✓ **2. Reusable designs:**

Centralized (client-server) and validated solution supports collaboration and reusability of evaluation settings and report designs via templates.

✓ **3. Regulatory compliant:**

Fulfils regulatory requirements and is 21 CFR Part 11/GxP compliant with electronic signatures, audit trail, date/time and user stamps

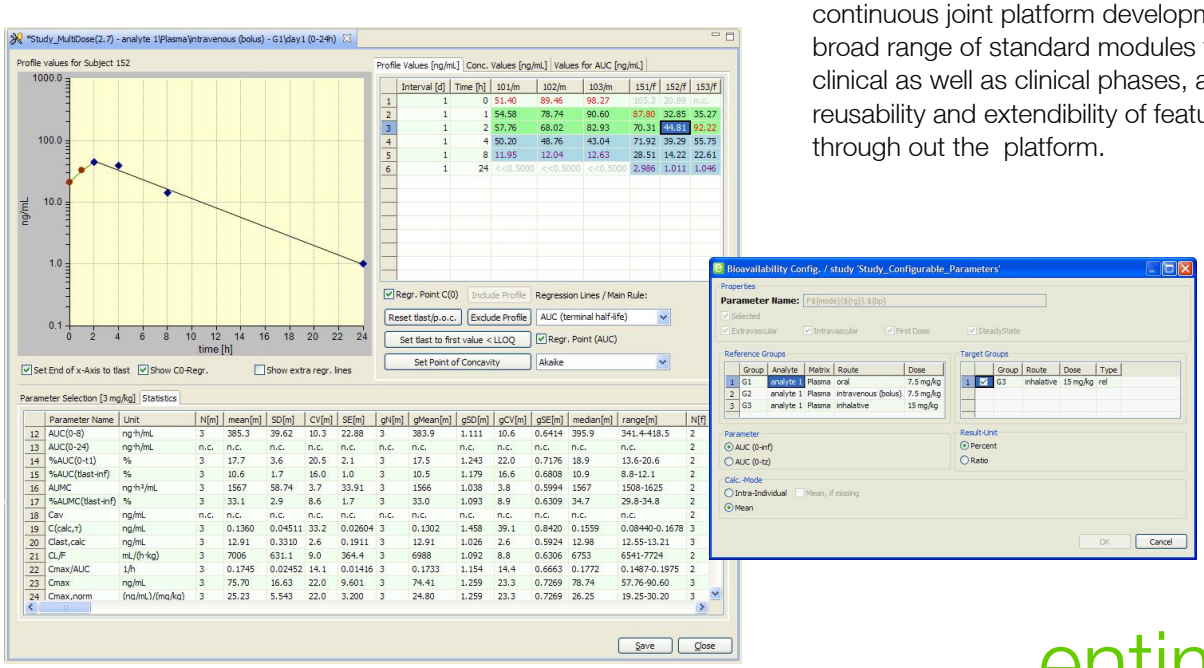
What is new?

ToxKin has been continously developed. In the latest release, feature highlights include:

- Direct import from Watson, KinLIMS, CCW, PhaLIMS and Excel
- Bioavailability, metabolite and accumulation ratios
- Automatic unit conversion
- Extended extrapolation rules for missing values
- Up to 6 regression lines per subject with automatic and interactive point selection
- Improved reporting quality
- Comparison tables for parameters
- Dynamic titles with numerous variables
- Advanced management of evaluation templates

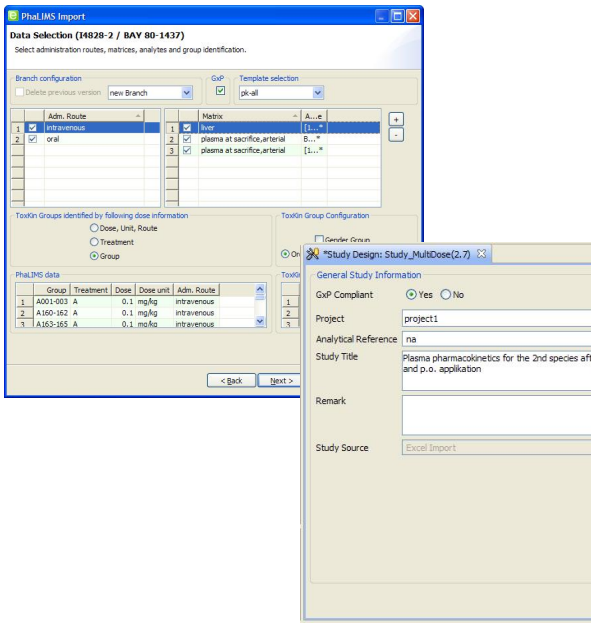
entimICE®

ToxKin is based on entimo's solution platform entimICE®. Through the modular approach and the flexible combination of included features, the solutions efficiently and effectively meet every customer's needs. Our customers benefit from continuous joint platform development, a broad range of standard modules for pre-clinical as well as clinical phases, and reusability and extendibility of features through out the platform.



entimo®

Feature Highlights



Direct data import

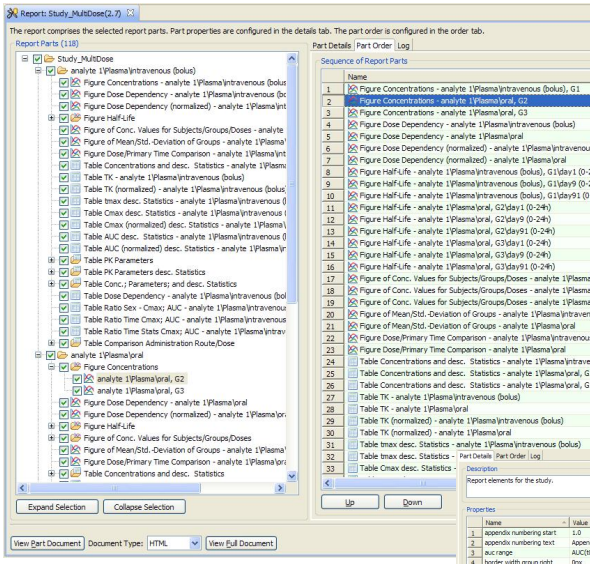
ToxKin connects to external data sources and allows seamless data transfer into ToxKin directly from LIMS systems like Watson, KinLIMS, CCW or PhaLIMS and from Excel files.
A dedicated import wizard leads you through the necessary import steps including the mapping of configuration data, grouping criteria and study branch.

Study Templates

By using a dedicated template editor, study templates can be created and made available to users, saving configuration effort and supporting customer-specific SOPs. Every study setting can be pre-configured in a template. The user simply needs to load the template in the evaluation design to apply all pre-configured study and report settings.

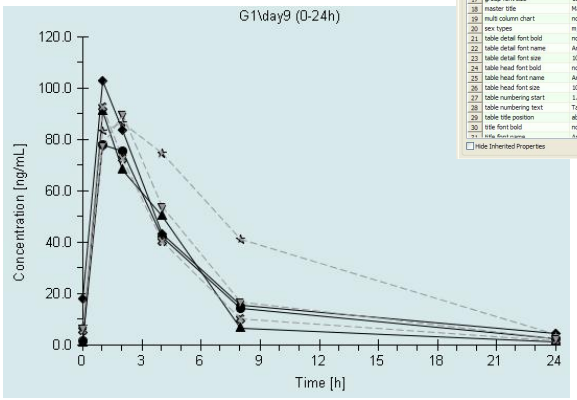
Configurable study design

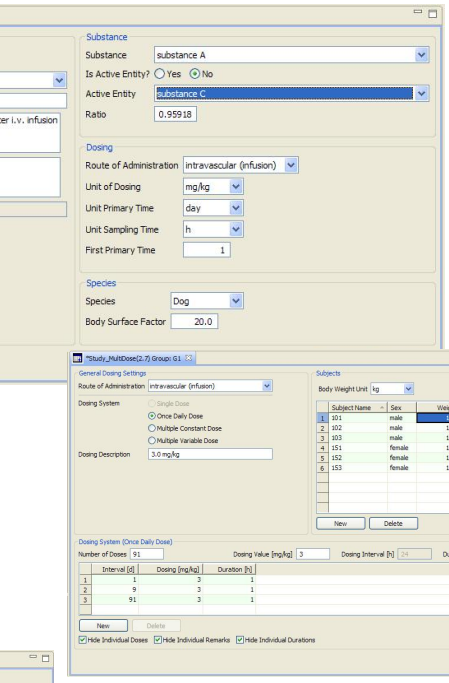
ToxKin is highly configurable and supports various study designs. On one side, users can control general settings of master data including administration routes, species with their properties such as body surface factor, unit categories and unit conversion factors. GxP and non-GxP modes are supported for studies with active or silent audit accordingly.
Single dose, multiple constant and multiple variable dosing as well as clock-time studies are supported. The system allows flexible grouping of databatches. Different analytes, matrices, extra- and intravascular routes with or without duration can be investigated within one study.
The solution allows selection of LLOQ rules at the beginning, in the middle and at the end of the time intervals selected for analysis. In addition, LLOQ rules for AUC parameters can be managed separately.
For each evaluation design, user can select parameters from a large set of predefined TK/PK parameters, statistics to be calculated and reports to be created.
ToxKin has a built-in workflow for studies from draft through input data accepted to finalized and obsolete. Workflow changes trigger different system actions such as, for example, audit trail for accepted data or creation of a final report for the status finalized.
A study can contain branches for different evaluations and different versions within one branch as independent instances of the study.

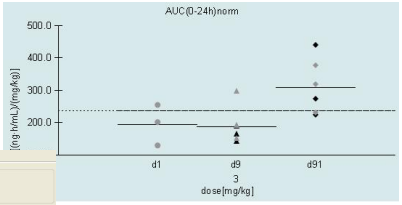


Guarantee of the regulatory compliance

ToxKin supports existing and emerging government regulations including 21 CFR Part 11 and Good Practices (GxP). The solution includes audit trails, history recording, versioning, time, date and user stamps as well as electronic signatures, thus automatically guaranteeing compliance with regulatory requirements.
All critical user activities are logged and can be retrieved from the repository using dedicated views with search functionality.
For each study human readable audit trail reports can be generated which provide details on the changes to study data. All historical information is accessible for investigation and reporting.
In addition, the system supports a status-based workflow for studies.







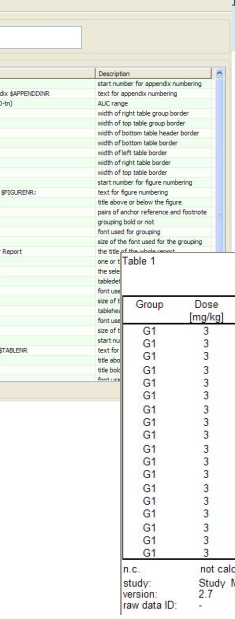


Table 1 Individual toxicokinetic parameters of analyte 1 in Plasma after daily intravenous (bolus) administration of substance A to dogs

Group	Dose [mg/kg]	day	Sex	Subject	Tmax [h]	Cmax [ng/mL]	AUC(0-24h) [ng·h/mL]
G1	3	1	m	101	2	57.76	n.c.
G1	3	1	m	102	1	78.74	n.c.
G1	3	1	m	103	1	90.60	n.c.
G1	3	1	f	151	1	87.80	770.7
G1	3	1	f	152	2	44.81	378.7
G1	3	1	f	153	2	92.22	n.c.
G1	3	9	m	101	1	77.90	483.2
G1	3	9	m	102	1	90.84	421.0
G1	3	9	m	103	1	102.8	561.4
G1	3	9	f	151	2	86.44	883.5
G1	3	9	f	152	1	92.60	442.9
G1	3	9	f	153	2	89.50	564.9
G1	3	91	m	101	2	94.63	666.0
G1	3	91	m	102	2	107.7	818.5
G1	3	91	m	103	1	135.4	1315
G1	3	91	f	151	2	134.2	1123
G1	3	91	f	152	1	92.75	685.2
G1	3	91	f	153	1	178.0	948.6

n.c. not calculated
study: Study MultiDose
version: 2.7
raw data ID: -

Explorative Evaluation

A distinguishing feature is ToxKin's interactive user interface for explorative evaluation of ongoing studies.
A great number of evaluation options is available:
Exclusions can be defined for single values and complete profiles. In the latter case, manual or automatic exclusions are supported reflecting the current state of regulatory guidelines (e.g. if a defined share of data points is missing).
Common extrapolation rules are available for missing values including C(0) regression with linear or logarithmice extrapolation.
Users can choose between nominal and individual time and dosing.
For the determination of the terminal half-life and calculation of regression parameters, points are automatically selected according to the Akaike information criterion. In addition, user can interactively select or deselect values to be used in the regression on the chart view.
Composite profiles can be created based on individual subjects with a single mouse click. In this case profiles for males, females and both sexes are automatically calculated to enable detection of gender effects.
AUC parameters can be calculated based on different trapezoidal rules (logarithmic, linear, linlog).
A highlight of the solution is easy unit conversion (e.g. for source data as a basis for parameter and statistic calculation). Units defined in master data can be comfortably selected in the GUI and automatically apply. For many parameters, values normalized by dose, subject weight or body surface factor are automatically calculated.

Evaluation parameters

ToxKin automatically calculates numerous descriptive statistics for study data and parameters. The following arithmetic and geometric statistics are available: N, mean, CV, SD, SE, median, range; gN, gmean, gSD, gSE, gCV.
More than 50 predefined toxicokinetic and pharmacokinetic parameters are available for selection including:

- Concentration based parameters and their ratios (e.g. Cmin, Cmax, Cmin/Cmax, C(tn)/Cmax)
- Time parameters
- AUC and their ratios (e.g. AUC(tz, rest-inf))
- AUMC and their ratios (e.g. AUMC(tz, rest-inf)
- Mean residence time for first dose and steady state
- Clearance (first dose and steady state, extra- and intravascular)
- Central volume of distribution
- Volume of distribution at steady state and in pseudo distribution equilibrium, extra- and intravascular
- Peak-trough fluctuation
- Regression parameters
- Half-Life
- Bioavailability (absolute and relative)
- Metabolite ratio
- Accumulation ratio (including day combinations after the first interval)
- Linearity ratio...

Additionally, male to female and day N to day 1 ratios can be computed in reports.

Powerful and flexible reporting

Based on the study design and selected evaluation settings, standard reports can be created with several mouse clicks in the reporting module.
ToxKin provides numerous predefined sub-reports, visual elements and variables which build the reporting base. A study report is created as a sequence of report parts. The report generator allows individual selection of sub-reports, tables and figures for each report. The arrangement and properties of the report parts can be easily configured. A ready-to-publish report can be exported in different formats such as PDF, MS Word, HTML. The following report parts are available

Figures for study evaluation:

- Analyte comparison with standard deviation
- Dose dependency
- Dose dependency (normalized)
- Dose/primary time comparison
- Half-life
- Mean/standard deviation of groups
- Concentration values for subjects/groups/doses
- Concentrations
- Ct – dose comparison
- Ct – primary time comparison

Tables for study evaluation:

- Dose Comparison / Dose dependency
- Comparison Dose/Analyte
- Comparison Route/Dose/Matrix
- Comparison Route/Dose
- Comparison Route/Dose/Analyte
- AUC (normalized) descriptive statistics
- AUC descriptive statistics
- Cmax (normalized) descriptive statistics
- Cmax descriptive statistics
- Concentrations and descriptive statistics
- Concentrations, parameters and descriptive statistics
- Ct / Ct (normalized)
- PK Parameters
- PK Parameters descriptive statistics
- Ratio sex - Cmax, AUC
- Ratio sex – Ct
- Ratio time
- Ratio time statistics
- Ratio time Ct
- Ratio time Ct statistics
- TK / TK (normalized) Parameters
- Tmax descriptive statistics

Tables for study design:

- Study
- Group
- Evaluation
- Exclusions
- All PK parameters
- Data Batch
- Chart Data
- Calculation Data
- Audit
- Import Protocol

Technical Requirements

Client Hardware:

- Processor >= 2 GHz
- Main memory >= 256 MB
- Free hard disk space >= 300MB

Client operating system:

- Microsoft® Windows 2000 Professional
- Microsoft Windows XP, Vista, Windows 7

Additional software:

- Microsoft Office 97 or higher
- PDF Viewer (Acrobat Reader)

Optional Server Hardware (in case of Citrix installation):

- Recommended ToxKin server: HP 9000
- Main memory >= 2 GB
- Free hard disk space: 2 disks 36 GB each

Server operating system:

- Any OS supported by Oracle 9i.x or higher (10,11)
- HP/UX 11.0 (recommended)

Database software:

- Oracle 9i R2 (9.2.0.8) or higher (10,11)

entimo®

About

Entimo is an ISO 9001:2008 certified life sciences and regulatory informatics company which provides high quality software products and services to pharmaceutical, biotechnology and crop science companies, contract research organizations and medical device manufacturers as well as to the relevant regulatory authorities.

Entimo AG | Stralauer Platz 33 – 34
10243 Berlin | Germany
T: +49 (0) 30 520 024 100
F: +49 (0) 30 520 024 101
www.entimo.com