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Data collection on kinetic parameters of substances

Pilot phase – A methodological report

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Abstract

Data collection on kinetic parameters of substances
The European Centre for the Validation of Alternative Methods (ECVAM) commissioned the RIVM to develop a pilot database with kinetic parameters of compounds used as reference substances in various *in vitro* toxicity testing (pre)validation programs. The toxicokinetic properties of compounds can form valuable information in human risk assessment. *In vivo* as well as *in vitro*, biological targets are exposed to concentrations of the compounds or their metabolites. Concentrations and their time course, mostly determined in blood or plasma, provide the most direct link between the observed or predicted *in vivo* effects and the effects observed *in vitro*. Accurate quantitative knowledge of the *in vivo* concentration-time relationship is therefore a prerequisite for the correct interpretation of *in vitro* toxicity testing results. Classical compartmental modelling parameters were chosen to describe the *in vivo* kinetic properties as they fulfil the needs for prediction of *in vivo* concentration time profiles under linear conditions. Protein binding parameters were added to facilitate calculation such as unbound substance concentrations.

Next to an input module (storage template) for the database, a retrieval template was developed to be put on the ECVAM website to facilitate further use of kinetic data. The database was filled with human and rat kinetic parameters (mainly based on i.v. and oral administration) for 100 substances following assessment of their reliability. Kinetic data were collected on classical compartmental modelling parameters, which describe the absorption, distribution and elimination (metabolism and excretion) phase. Typical classical compartmental modelling parameters are systemic bioavailability (F), absorption rate constant (k_a), volume of distribution (V_d) and elimination rate constant (k_e).

This pilot database contains kinetic parameters for internal exposure estimation, which may facilitate quantitative *in vitro - in vivo* extrapolation.

Key words: kinetics, parameters, database

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Contents

1	**General introduction**	**7**
2	**Parameter selection**	**11**
2.1	Scope	11
2.2	Kinetic information	11
2.3	Parameter scheme	13
2.4	Conclusions and recommendations	18
3	**Data collection**	**19**
3.1	Scope	19
3.2	Method	19
3.3	Results	19
3.4	Conclusions and recommendations	20
4	**Data assessment**	**21**
4.1	Scope	21
4.2	Method	21
4.2.1	Criteria for research quality	21
4.2.2	Reanalysis	23
4.3	Results	23
4.4	Conclusions and recommendations	24
5	**Data storage**	**25**
5.1	Data model	25
5.1.1	Scope	25
5.1.2	Method	25
5.1.3	Results	25
5.2	Data storage template	27
5.2.1	Scope	27
5.2.2	Method	27
5.2.3	Results	27
5.2.4	Conclusions and recommendations	28
6	**Data retrieval**	**29**
6.1	Scope	29
6.2	Method	29
6.3	Results	29
6.4	Conclusions and recommendations	30

References **31**

Appendix 1. List of substances **45**

Appendix 2. Abbreviations of kinetic parameters **47**

Appendix 3. Codes used in Berkeley Madonna **49**

Appendix 4. Data model **51**

Appendix 5. Storage template **53**

Appendix 6. Retrieval template **55**

Appendix 7. Overview of information in database **61**

1 General introduction

In an organism, exposure to a substance is determined by its concentration and the time it remains at the site of action. Both parameters depend on the rates by which the chemical is absorbed, distributed in organs and tissues, biotransformed to active metabolites or to products of reduced effectiveness and on the rate of excretion from the body. Kinetics describe these processes quantitatively. *In vivo* kinetic parameters may have an important role in predicting the level of pharmaceutical activity or toxicity induced by substances at dose or exposure levels not tested before.

As shown in Figure 1, this basically holds for *in vitro* toxicity experiments too. In *in vitro* experiments, for example, cells are incubated in a culture medium with some nominal concentration of a parent compound, after which the substance may distribute between culture medium and cells, the substance may be metabolised and toxicity may be induced. Taking the culture medium as a surrogate for blood or plasma, this concept enables several strategies for the extrapolation of *in vitro* observed toxicity to the *in vivo* situation. Ideally, this extrapolation should be based on a substance's *in vitro* concentration time-course and its corresponding time-dependent toxicity. This needs a fully integrated *in vitro* - *in vivo* toxicokinetic and toxicodynamic extrapolation model. In most cases, however, the level of toxicity is only measured at the end of the total incubation period and related to the nominal concentration of the culture medium at the start of the experiment. Thus, in practice, the necessary information for such an extrapolation is seldom available.

Whatever extrapolation is performed, quantitative knowledge of the *in vivo* concentration-time relationship or a reliable prediction thereof is needed (upper left part of Figure 1, i.e. translation from external exposure to a blood or plasma concentration-time course). Here, classic (linear) one- or two-compartment modelling may be very helpful. Using known blood or plasma concentration time *C,t*-profiles, classical compartmental modelling analysis may reveal necessary kinetic parameters. Once the compartmental parameters are known, within the range of linear kinetics, predictions can be made for other exposures or doses than the tested ones.

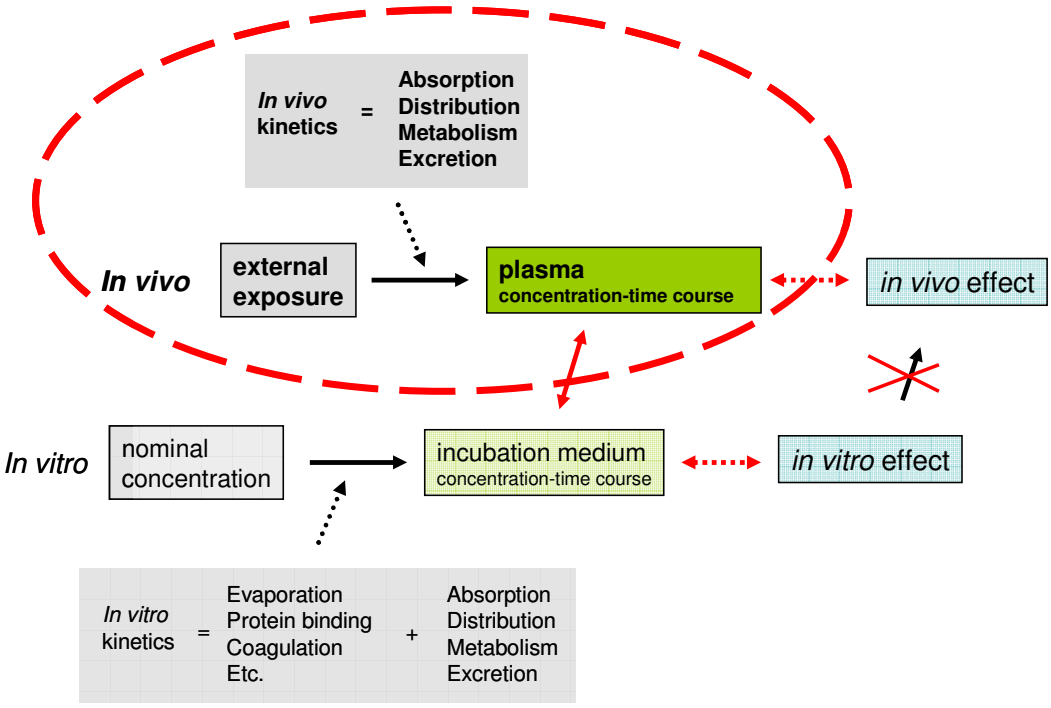

Figure 1. Central paradigm for quantitative *in vitro - in vivo* extrapolation pointing at the central role of kinetic information. This project focuses on *in vivo* kinetics (red circle).

Although the 'quantitative *in vitro - in vivo* extrapolation' (QIVIVE) paradigm seems to be obvious (Figure 1), its actual application is rather complex and not without problems in the current setting of development of *in vitro* toxicity assays. These problems are due to the fact that from an *in vitro* experiment most often concentration-effect relations are obtained that relate a nominal concentration (most often the concentration at the start of the incubation) to an effect observed after some experimental time duration. Such a protocol completely ignores possible loss of the substance from the incubation due to physico-chemical reasons (e.g. evaporation, binding to the wall of incubator cells and physico-chemical breakdown) or biochemical processes (metabolism, binding to protein,) as well as transport processes (delayed distribution in multilayer systems such as tissue slices or sandwich cultures). Moreover, such a protocol may ignore the dynamics of the effect when the effect is only measured at one time point (often at the end of the experiment).

Furthermore, it is questionable whether the time course of concentration in the affected cells *in vitro* is sufficiently similar to that occurring *in vivo*. Even if in an apparently simple example, the applied (nominal) concentration would stay constant during the *in vitro* experiment, the *in vivo* concentration-time course after one oral dosing would certainly not. The question arises how the *in vitro* and *in vivo* exposures should be related. *E.g.* should the *in vivo* C_{max} be related to the *in vitro* C_{max} (= nominal concentration)? Or should the *in vivo AUC* be related to the *in vitro AUC*? These questions urge for a fundamental

change in approach when we aim to quantitatively predict *in vivo* effects based on *in vitro* experiments. At least, awareness should be created among *in vitro* toxicologists that the QIVIVE paradigm implies that *C,t*-curves play a pivotal role **both** *in vitro* and *in vivo*.

Aim of the present project

Aim of the present pilot project is the construction of a web-based database of relevant *in vivo* kinetic parameters and corresponding kinetic models of 100 substances. The selection of these substances is performed by ECVAM and include substances involved in the prevalidation and validation phases of alternative testing methods.

The objectives of this pilot phase are:

- to establish which kinetic information is required
- to generate a template to collect such information
- to determine and test the efficiency of the information sources
- to collect information on 100 compounds

The database should contain the necessary kinetic information to construct *in vivo* plasma concentration-time courses using classical compartmental modelling. This kinetic information is collected for rats and humans, since the majority of the studies are performed in these species. The collected information should include absorption/bioavailability, distribution, metabolism and excretion characteristics. In addition, protein binding characteristics were included from *ex-vivo* experiments.

Outline of the project

This project started with the selection of the kinetic parameters, which was followed by the construction of the data model. A data model describes how data is represented and accessed. This data model defines entities[1] and relationships between entities. The application of the data model includes supporting the development of the database and enabling the exchange of data. Based on the data model, the database is developed. After finishing the outline of the database, a method is developed for data collection and the assessment of the toxicokinetic data. A web-based retrieval templated is constructed to view the information of the database and finally, the toxicokinetic data of 100 compounds is put into the database.

Chapter 2 describes the parameter selection, the kinetic models used and the quotations for the concentration-time curves. In Chapter 3, the method and results of the data collection are mentioned. In Chapter 4, the assessment of the data is addressed, which describes the quality criteria given to the data from public literature references and the performance of the reanalysis that was performed for some papers that provided no complete set of kinetic parameters albeit (a) high quality *C,t*-profile(s). Chapter 5 addresses the construction of the data model and the data storage template. Finally, the web-based retrieval template is described in Chapter 6.

[1] An entity is a general concept about which information is kept.

2 Parameter selection

2.1 Scope

The database should provide the necessary, basic, kinetic information to construct the *in vivo* plasma concentration-time curve after exposure to a single oral dose of a substance. The database is intended for ease of use for *in vitro* toxicologists, *i.e.* its use should not require advanced modelling expertise. In fact only basic calculus is needed to construct plasma concentration-time curves. In some cases only information after administration by an alternative route, i.e. intravenous, dermal or via inhalation was available. In these cases this information is used instead.

2.2 Kinetic information

Within toxicokinetics, various processes can be distinguished, i.e. extent and rate of absorption, distribution, metabolism and excretion. This commonly referred to as the ADME scheme:

- Absorption is the process of a substance entering the body across the gut (alternatively, the lung or dermal) wall.
- Distribution from blood to the tissues is caused by both the difference of physicochemical and biochemical properties of different tissues and the central blood compartment and the physicochemical properties of a substance.
- Metabolism is the elimination via irreversible transformation of parent compounds into metabolites. As metabolites can act as the toxic agent instead of or together with the parent compound, this kind of elimination is considered separately of elimination by excretion.
- Excretion is the elimination of the parent compound from the body, e.g. through urine or sweat.

Toxicokinetics is the integrated description of these ADME processes. The kinetic information that is of primary interest in classical compartmental modelling are the classical toxicokinetic parameters such as volume of distribution[2], elimination half-life time[3], systemic bioavailability and absorption rate. Note that both the non-intravenous and intravenous administration route is required for determining the systemic bioavailability, i.e. the fraction of the absorbed dose which surpasses first-pass hepatic metabolism upon entering the systemic circulation.

[2] Volume of distribution is the volume into which the substance distributes in the body at equilibrium.

[3] The elimination half-life is the time taken for the plasma concentration, as well as the amount of substance in the body, to fall by one-half. The elimination half-life is related to the constant k_e by $t_{½} = 0.693/ k_e$.

In this report kinetic modelling is limited to one- or two-compartment modelling. In two-compartment *p.o.* modelling three distinct, successive, dominant phases can be distinguished: absorption, distribution, and elimination through metabolism or excretion. During the absorption phase the absorption of the orally administered substance dominates over the concomitantly occurring distribution and elimination, and likewise for the other phases. Ideally, all three phases are visible in the experimental data of the plasma concentration-time curve of an orally administered substance. This ideal case is depicted with the blue concentration-time curve in Figure 2. Note, in order to become discernible, the sampling of plasma should comprise all three of these phases. However, in practice, this may not always be the case. As a consequence only part of the experimental information related to two-compartmental kinetics is available. For example, starting plasma sampling well after absorption has almost been completed will not provide any information of this process, such as absorption rate. On the other hand, when plasma sampling is stopped too early, elimination phase characteristics cannot be derived from the experiment. Figure 2 shows some examples of such insufficient sampling strategies: fast absorption where sampling during the absorption phase is not really feasible or the rate of absorption is limiting with respect to distribution and the two different processes cannot be discriminated (green curve and, even worse, purple curve). The red concentration-time curve at last shows poor sampling strategy tests where only modelling of the elimination phase is feasible. In this case two of the three characteristic phases of two compartmental *p.o.* kinetics, i.e. absorption and distribution, are not reflected in the data. In this case two-compartmental modelling in fact has passed into an orally administered dose which has been absorbed and distributed almost instantly, resulting in one-compartment modelling in which elimination is the only experimental observable left.

So, depending on the ADME characteristics, experimental feasibility and experimental sampling scheme, only partial kinetic information may be available. If that is the case and if no additional *i.v.* experiment is performed, the systemic bioavailability[4] cannot be determined. That implies that initial volume of dilution and volume of distribution cannot be determined in absolute value, but only related to the systemic fraction available.

[4] Systemic bioavailability measures the availability of the active drug in systemic circulation after non-intravenous administration (i.e. after oral, rectal, transdermal, subcutaneous, *etc* administration). In order to determine systemic bioavailability of a drug, a kinetic study must be performed to obtain a plasma drug concentration vs time plot for the drug after both intravenous and extravascular administration. The systemic bioavailability is the dose-corrected area under curve (AUC) extravascular divided by AUC intravenous.

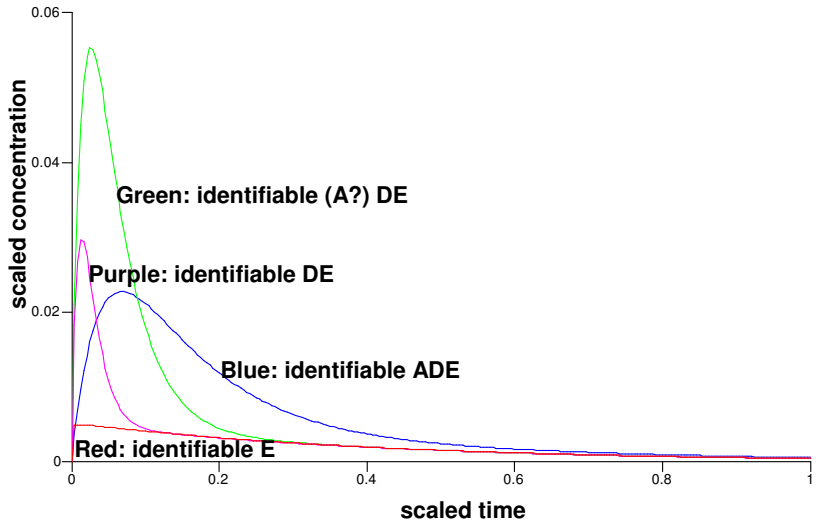

Figure 2. Hypothetical concentration-time curves after oral administration with different characteristics of absorption (A), distribution (D) and elimination (E) kinetics. These differences, together with an insufficient experimental sampling scheme, may lead to a limited set of parameters stored in the database, i.e. a parameter set which only allows the construction of only part of the plasma time-concentration of a full two-compartment model.

2.3 Parameter scheme

Table 1 shows which parameters can be stored in the database in dependence of the available experimental information. In this scheme, V_d is the volume of distribution, V_i the initial volume of dilution, F is the fraction that is systemically available, k_e is the terminal elimination rate constant, k_i is the distribution rate constant and k_a is the absorption rate constant (Table 2). When no additional *i.v.* experiments were performed, the volumes of initial dilution and of distribution cannot be estimated independently, i.e. be mathematically identified. Hence, in that case, only the ratios (V_i / F) and (V_d / F) can be derived from experimental data. To stress the fact that in this case actually these ratios are the model parameters, these will be denoted as (V_i / F) and (V_d / F).

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Table 1. Identifiability of parameters derived from different experimental outcomes. Single parameters can either be derived directly or indirectly as a combination, depending on whether or not information on the processes of absorption/distribution is available and whether or not an additional independent *i.v.* administration experiment was performed

Modelling: One-compartment **Phases determined:** Elimination						**Formulas**
Intravenous administration?						
	(V_d/F)	F	k_a	k_e	V_d	$C(t) = \frac{D}{(V_d/F)} \exp(-k_e t)$ $AUC = \frac{D}{k_e \cdot (V_d/F)}$
no	+			+		
	(V_d/F)	F	k_a	k_e	V_d	$C(t) = \frac{FD}{V_d} \exp(-k_e t)$ $AUC = \frac{FD}{k_e V_d}$
yes		+		+	+	

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<table>
<tr><td colspan="6">Modelling: One-compartment
Phases determined: Absorption, Elimination</td><td>Formulas</td></tr>
<tr><td colspan="6">Intravenous administration?</td><td rowspan="3">$$C(t) = \frac{D}{(V_d/F)}\left(\frac{\exp(-k_e t) - \exp(-k_a t)}{1 - k_e/k_a}\right)$$
$$AUC = \frac{D}{k_e \cdot (V_d/F)}$$</td></tr>
<tr><td rowspan="2">no</td><td>(V_d / F)</td><td>F</td><td>k_a</td><td>k_e</td><td>V_d</td></tr>
<tr><td>+</td><td></td><td>+</td><td>+</td><td></td></tr>
<tr><td rowspan="2">yes</td><td>(V_d / F)</td><td>F</td><td>k_a</td><td>k_e</td><td>V_d</td><td rowspan="2">$$C(t) = \frac{FD}{V_d}\left(\frac{\exp(-k_e t) - \exp(-k_a t)}{1 - k_e/k_a}\right)$$
$$AUC = \frac{FD}{k_e V_d}$$</td></tr>
<tr><td></td><td>+</td><td>+</td><td>+</td><td>+</td></tr>
</table>

Modelling: Two-compartment
Phases determined: Distribution, Elimination

Formulas

Intravenous administration?

	(V_i/F)	(V_d/F)	F	k_a	k_i	V_i	k_e	V_d
no	+	+			+		+	

$$C(t) = \frac{D}{(V_i/F)} \cdot \left(\left(1 - \frac{(V_i/F)}{(V_d/F)} \right) \exp(-k_i t) + \frac{(V_i/F)}{(V_d/F)} \cdot \exp(-k_e t) \right)$$

$$AUC = D \left(\frac{1}{k_i} \left(\frac{1}{(V_i/F)} - \frac{1}{(V_d/F)} \right) + \frac{1}{k_e \cdot (V_d/F)} \right)$$

	(V_i/F)	(V_d/F)	F	k_a	k_i	V_i	k_e	V_d
yes			+		+	+	+	+

$$C(t) = \frac{FD}{V_i} \cdot \left(\left(1 - \frac{V_i}{V_d} \right) \exp(-k_i t) + \frac{V_i}{V_d} \cdot \exp(-k_e t) \right)$$

$$AUC = FD \left(\frac{1}{k_i} \left(\frac{1}{V_i} - \frac{1}{V_d} \right) + \frac{1}{k_e V_d} \right)$$

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Modelling: Two-compartment **Phases determined:** Absorption, Distribution, Elimination									**Formulas**
Intravenous administration?									
	(V_i / F)	(V_d / F)	F	k_a	k_i	V_i	k_e	V_d	$C(t) = \frac{D}{(V_i/F)} \cdot \left(\frac{1-(V_i/F)/(V_d/F)}{1-k_i/k_a} \cdot (\exp(-k_i t) - \exp(-k_a t)) + \frac{(V_i/F)/(V_d/F)}{1-k_e/k_a} \cdot \exp(-k_e t) - \exp(-k_a t)) \right)$ $AUC = D\left(\frac{1}{k_i} \left(\frac{1}{(V_i/F)} - \frac{1}{(V_d/F)} \right) + \frac{1}{k_e \cdot (V_d/F)} \right)$
no	+	+		+	+		+		
	(V_i / F)	(V_d / F)	F	k_a	k_i	V_i	k_e	V_d	$C(t) = \frac{FD}{V_i} \cdot \left(\frac{1-V_i/V_d}{1-k_i/k_a} \cdot (\exp(-k_i t) - \exp(-k_a t)) + \frac{V_i/V_d}{1-k_e/k_a} \cdot (\exp(-k_e t) - \exp(-k_a t)) \right)$ $AUC = FD\left(\frac{1}{k_i} \left(\frac{1}{V_i} - \frac{1}{V_d} \right) + \frac{1}{k_e V_d} \right)$
yes			+	+	+	+	+	+	

Table 2. Definition of parameters

Parameter		Definition
Analysis		
One-compartment	Two-compartement	
F	F	Systemic bioavailability
	V_i	Initial volume of distribution
V_d	V_d	Volume of distribution
k_a	k_a	Absorption rate constant
	k_i	Initial rate constant
k_e	k_e	Elimination rate constant

Using these parameters, new *C,t*-curves can be constructed and corresponding AUCs can be calculated using the formulas provided in Table 1. For example, in the most simple case for a substance where only one-compartment analysis could be performed and there was no information on absorption and distribution, neither an i.v. administration, only (V_d / F) and k_e are available to reconstruct new *C,t*-curves and corresponding AUCs (Table 1 first example). In case an additional i.v. administration was performed, F and V_d are both available as well as k_a in addition to k_e.

2.4 Conclusions and recommendations

In conclusion, in order to facilitate prediction of external doses or exposure that provide *in vivo C,t*-curves, classical compartmental modelling parameters were concluded to provide the best, if not the only, option. Therefore it was decided to search for classical compartmental modelling parameters to be put into the pilot database.

3 Data collection

3.1 Scope

In vivo kinetic parameters of 100 substances have been collected, which have been part of ECVAM's prevalidation and validation phases of alternative testing methods.

3.2 Method

The compounds of interest were selected and provided by ECVAM (Appendix 1). Kinetic properties of compounds are collected from public available scientific literature. The literature search was performed using Pubmed and was restricted to English literature. Kinetic parameters are collected of the species rat and human. The literature search included the following terms: (toxico/pharmaco)kinetic(s), absorption, bioavailability, distribution, metabolism, excretion, clearance, protein binding, plasma binding and blood plasma ratio.

The results of the literature search were primarily sorted for possible relevance based on the title. For decision on actual inclusion into the database the complete paper was read by an assessor. As this is a pilot project, the publication with the most complete kinetic parameter data set was selected and the parameters were included in the database.

Besides toxicokinetic parameters (called dynamic parameters in the data model), static parameters are also presented in the database. Static parameters which are included in this project are blood to plasma ratio and plasma protein binding.

The routes of administration included mainly intravenous and per oral, and occasionally intraperitoneally, intra-arterial, intramuscular, dermal, inhalation, intra-tracheal, sublingual and subcutaneous. From these information was collected on absorption, bioavailability, distribution, metabolism and excretion. The kinetic parameters which are collected and stored in the database are described in Appendix 2.

3.3 Results

Within the constraints of the project, kinetic parameters of 100 substances had to be collected. In order to collect kinetics for 100 compounds, 122 compounds had to be investigated. For 22 compounds no reliable information regarding kinetic parameters could be obtained from the literature at all. These compounds were stored in the database with clear reference for the user that no information is available.

3.4 Conclusions and recommendations

When no parameters are available, the relevant compound will be mentioned in the database and it is indicated that no parameters were found. Both complete and incomplete data sets were stored in the database.

More kinetic information can be collected from public available literature when there is no restriction to one publication for each compound. We recommend collecting all information for the compounds selected to build a more complete database. In this case, the user can choose and compare between different publications describing kinetic parameters.

More toxicokinetic properties can be found using other literature databases. For more species and toxicological information, data from the pharmaceutical industry should be included.

4 Data assessment

4.1 Scope

For the assessment of the data, criteria for research quality had to be developed. This would facilitate additional filling of the database with new parameter values without having to assess 'old' parameters over and over each time as assignment of a quality rating should be independent of the moment and independent of any other information already present.

4.2 Method

4.2.1 Criteria for research quality

The evaluation of the publications is based on the criteria for research quality, especially designed for this project. Criteria for research quality were developed based on guidelines of the Environmental Protection Agency[5] and Klimisch et al., 1997[6].

The reliability code is explicitly mentioned in the data base, to give information on the reliability of a study. The research study is evaluated on reliability and four categories are used to describe the research quality.

Categories of reliability:

Code	Category
1	Reliable without restrictions
2	Reliable with restrictions
3	Not reliable
4	Unusable

[5] Health effects test guidelines, metabolism and pharmacokinetics. United States Environmental Protection Agency, EPA 712-C-95-244, 1995.

[6] Klimisch HJ, Andreae M, Tillmann U. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Toxicol Pharmacol 1997; 25: 1-5.

Criteria for reliability categories
The study should include information on:

1. ***Test substance***
   This should include information on the identification of the test substance, such as substance name, molecular structure, qualitative and quantitative determination of its composition and purity.

2. ***Test animals***
   This should include information on the animals used; species, strain, age or body weight, sex, health status (e.g. diabetic), housing and feeding conditions.

3. ***Methods***
   This should include details of the study design and methodology used, including a description of:

- Preparation of the test substance
- Number of individuals, i.e. animals or humans
  a. Animals: preferably $n \geq 2$, if not, then reliability category 2 or 3
  b. Humans: preferably $n > 1$, if not, then reliability category 2 or 3
- Number of treatment groups
- Dosage levels and volume
- Route of administration
- Frequency of dosing
- Sample collection and handling
- Experimental measurements and procedures
- Data analysis: methodological description (non-compartmental, two-compartmental, PBPK etc)
- Statistical analysis: statistical method used to calculate mean ± SD or mean ± SEM and significant difference

Reliability code 1 (Reliable without restrictions):
This includes studies which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (ICH, OPPTS, OECD TG 417). The information on the test substance and test animals is available and the method used is appropriate.

Reliability code 2 (Reliable with restrictions):
This includes studies of which the information on test substance and/or test animals is incomplete, but the method used is appropriate and correct. This also includes studies in which the test parameters documented (e.g. number of test animals) do not totally comply with the testing guideline, but are nevertheless well documented and scientifically acceptable, i.e. appeared in a peer reviewed journal. Furthermore, data analysis could be unclear or ambiguous (e.g. kinetic model does not describe the concentration time curve).

Reliability code 3 (Not reliable):
This includes studies in which the method used is not appropriate or correct and/or the information on test substance and/or test animals is incomplete.

Reliability code 4 (Unusable):
This includes studies in which incorrect species or no kinetic data is demonstrated.

4.2.2 Reanalysis

In this pilot project, for a few compounds, a kinetic (re)analysis was performed on studies which provided unanalyzed, but clear plasma time-course data. Reanalysis was performed using the plasma time-course as published in a graph, which was scanned and digitized using the DigitizeIt 1.5.8 software. Subsequently, the digitized data were analysed using i.v. and p.o. kinetic models (for the source code, see Appendix 3) in the Berkeley Madonna™ software platform.

4.3 Results

In total, 158 publications were investigated on their quality (see overview Table 3). In 56 cases (27 compounds), data was reliable and complete data sets were found (quality rate 1), meaning that the parameter set published was sufficient to reconstruct a *C,t*-curve from zero time on. In 92 cases (55 compounds), the data set was not complete or not reliable. When the parameter set given is not complete, a complete *C,t*-curve can not be reconstructed by the user (quality rate 2). In 10 cases (10 compounds), no reliable information could be obtained from the literature within the constraints of this project (quality rate 3). No quality rate was given to 53 publications (42 compounds) which have investigated protein binding or blood-plasma ratio

Table 3. Overview of the number of publication and compounds per quality code

Quality rate	Number of publications	Number of compounds	Remark
1	56	27	Complete data set
2	92	55	Incomplete or no reliable data
3	10	10	No reliable data
Not given*	53	42	

* No quality rate is given to refences describing protein binding or blood-plasma ratio

For 15 substances, when no parameters were found, but a complete graph (*C,t*-curve) was found in a paper, a reanalysis was performed. When successful, a complete parameter set was stored in the database. In addition, the compartment model used is mentioned in the database.

4.4 Conclusions and recommendations

Only 56 of 158 publications presented a complete data set to construct a *C,t*-curve. Most of the publications (92) describe a limited data set, with quality code 2.

For a limited number of substances (15), when no parameters were found, but a complete graph (*C,t*-curve) was found in a paper, we performed a reanalysis using the published graph. At succeeding in the reanalysis, a complete parameter set was stored in the database.

For a uniform and larger data set, we recommend to perform a reanalysis when a *C,t*-curve is given in the paper and when the quality rate is at least 3.

5 Data storage

5.1 Data model

5.1.1 Scope

A data model had to be developed to support the construction of the database and enabling the exchange of data. A data model describes how data is represented and accessed, and defines entities[7] and relationships between entities.

5.1.2 Method

The development of a data model is a combined effort of domain experts and information analysts. The process of building a data model can be seen as an iterative process between the following activities:

- generating domain knowledge in discussions with domain experts, i.e. kineticists, toxicologists, kinetic modeller
- recording the information in a concise manner: schemes in UML (Unified Modelling Language) and plain text
- verifying the recorded information

The relationships of the toxicokinetic parameters were investigated and a concept of the data model was developed. This concept was optimized after collecting information from kineticists and toxicologists. Finally, a data model was constructed and used for the development of the database (see Appendix 4).

5.1.3 Results

Information on the data model was collected using a preliminary data model as presented in the project proposal by RIVM, dd. October 2006. In this concept model it was assumed that there was a clear distinction between all collected parameter values and a preferred set of values. This assumption was not correct and the decision was made that all values should be presented marked with a quality rating. Based on the given quality rate, the user can make an own judgement on the data of interest.

The following entities and data objects were important during the development of the data model: publication, substance, organism, route, dose, kinetic model, quality, administration protocol and parameter.

Both the entities ‘experiment’ and ‘test’ were introduced in the data model. The entity ‘experiment’ describes the general information of a study, such as the substance and

[7] An entity is a general concept about which information is kept.

(sub)species used, age and/or weight, gender, feed regimen and information on administration. The entity ‘test’ describes the quantity of the administered dose is.

It appeared that a parameter ‘value’ could not always regarded as a single value. Also ranges of values are reported in literature and had to be dealt with in the data model. Therefore, the attributes ‘lower’ and ‘upper’ values were introduced. In some cases, a value is reported as an open interval, therefore, the attribute ‘open interval sign’ was introduced (containing ‘<’ or ‘>’ characters). A parameter value can be reported as a mean value combined with either a coefficient of variation, or a standard deviation. When a mean value is reported, information on the number of observations has to be given. Conceptually the unit also belongs to the value. In conclusion, the ‘value’ consists of the following attributes: mean value, coefficient of variation, standard deviation, open interval sign, lower value, upper value, number of observations and unit.

Occasionally, published studies investigated parameter values of both the parent substance and of the metabolite. Therefore, information on the metabolite had to be introduced into the data model. It would be useful when the values of the parent and the metabolite are connected, but at the same time the information on the metabolite must be stored separately from the information on the parent. When the chemical name of the metabolite is unknown, the metabolite is reported as ‘metabolite of x (name of parent)’. In the data model, the entity ‘metabolite’ was extended with the attribute ‘label in publication, ‘thereby creating an optional relationship between ‘metabolite’ and ‘substance’.

During the course of the modelling process, the entity ‘kinetic model’ was related to the entity ‘experiment’, meaning that only one kinetic model was permitted within an experiment. When a re-analysis is performed on the published data, a different kinetic model could be used and this information has to be stored also in the database. Therefore, the data model was altered to contain two relationships between (kinetic) test and (kinetic) parameter value; one labelled PP (= primary publication) and the other labelled RA (= re-analysis). Because the ‘PP’-data and the ‘RA’-data are not necessarily based on the same kinetic model, the entity ‘kinetic model’ was replaced from ‘experiment’ to ‘test’.

Some parameter values have a certain validity period, for example, an AUC with a validity period of 0-24 h. The validity period is reported in the published studies or can be assessed by the reviewer. Therefore attributes to score information on the validity period were introduced in the entity (kinetic) parameter value.

Next to kinetic parameters, the database also contains parameters of protein binding and blood-plasma ratio. Kinetic parameters are referred to ‘dynamic parameters’ in the database and protein binding/blood-plasma ratio are referred to ‘static parameters’. A parallel set of ‘static’ entities was introduced next to the ‘kinetic’ entities: Static Experiment, Static Test and Static Parameter Value.

The data model is presented in Appendix 4.

5.2 Data storage template

5.2.1 Scope

A database had to be build, according to the data model, and an input module (storage template) had to be constructed. Conditions of the data storage template are that entered data is validated and/or checked and that structural integrity is guaranteed.

5.2.2 Method

The following considerations were of importance in choosing the technical platform and techniques:

- Use one platform/technique to build both database and input module, in this case alterations in the data model can be easily performed
- Use a platform which is easily portable (i.e. usable by others)
- The input module does not need to be made user friendly
- The platform should be without a license, since there is a limited budget for this deliverable

This product was realised via the RAD-method (Rapid Application Development). This method is commonly used in similar projects where close cooperation between expert users and technicians is necessary. At first, the user interface was built roughly and presented to a group of expert users in the project team. Although not all functionalities were available at that point, it gave the expert users a good idea of what they could expect after further development of the data storage template. Their feedback at this point assures that the development fits their needs. This process (in RAD-method terms: a cycle) was repeated until the functional requirements were achieved.

5.2.3 Results

The database and input module were realised in Microsoft Excel 2002 SP 3. The usage of Visual Basic Forms and code assured that the data entered is structurally sound. Each table used is located on its own worksheet and ID's are used to refer to rows in other tables (on other worksheets) as one would normally see in regular database solutions.

The method (RAD) used had the following result:

- Intermediate results could be delivered easily, since ECVAM could use the Excel-files immediately.
- Short communication lines between the users and developers were assured.
- It took a short time to develop (new) functionalities, which implies little interruptions between the primary process of finding and entering data.

Functional aspects of the storage template:

- It is a single-user application.
- The first worksheet has 3 buttons: start application, manage picklists and export data to storage template (Appendix 5, A).

- After starting the application, the user can choose between selecting an existing reference or importing a new reference (Appendix 5, B)
- The user can search for references. Found references are shown with all its linked test data.
- A new reference starts with importing publication information, followed by the choice of a static or kinetic experiment (Appendix 5, C).
- Test data-items consist (at least) of compound, species, subspecies, age, gender, feed regimen, route, parameter and dose.
- All input is validated; no empty fields are allowed and numerical fields must contain valid numbers. Other validation (ranges, pick-list, etc.) is performed where possible.
- Error messages and warnings are understandable for the average user.
- References can exist in the database, without linked parameters. Parameters cannot exist without a link to a reference.
- The reference can be deleted (if there is no linked test data) or modified. A test data-item can be selected in order to be deleted or modified.
- The user can add test data to a reference.
- When a reference is selected, the following information is presented: publication, experiment details, list of experiments, list of formed metabolites, list of tests, publication parameters and reanalysis parameters (5, D).

5.2.4 Conclusions and recommendations

The storage template was build in Excel and proved to be workable (database are usually build in typical relational databases). For future database development, the following should be considered:

- Separate the database from the input module, so both retrieval template and storage template work with the same database
- Allow multi-user usage on the storage side, so more users can store data simultaneously

The RAD-method for development of the input module proved to be very applicable and can be used in similar developments where complex matter has to be broken down into comprehensible structures.

6 Data retrieval

6.1 Scope

Create the possibility to web-based retrieval of data from the kinetic database.

6.2 Method

The retrieval template is build based on the following principals:

- The retrieval template facilitates the search for kinetic data by an user, i.e. *in vitro* toxicologist
- The database can be downloaded from the website of ECVAM in a retrieval template format using Excel
- The kinetic data can be found easily
- The first determining entity is the substance
- Substances can be filtered and/or searched
- Updates of retrieval template and/or database must be easy to implement

In close consultation with ECVAM it was decided to keep the retrieval template as simple as possible.

6.3 Results

The technique chosen to build the retrieval template fits the technique used for the storage template; Microsoft Excel 2002 SP 3 (using Visual Basic Forms and code). This has the advantage that the database contents from the storage template is easily transferred to the retrieval template and there was no need for a separate database. Also various code developed for the storage template could be reused for the retrieval template. The final result is a retrieval template in a single file which can be placed in the website of ECVAM.

The information from the storage template becomes available in the retrieval template format, when the database is copied to the retrieval database. The start page of the retrieval database is presented in Appendix 6A. The first page of the retrieval database presents the substance, CAS number and the number of experiments in human and/or rat. The number of experiments in human and/or rat are divided into *in vivo* (kinetic data) or *ex vivo* (static data) experiments. Using the button, substances can be filtered and/or searched. The search/filter can be used for (a part of) the CAS number or (a part of) the substance. Experiments can be viewed by double clicking the cell or by using the button ‘go to selected experiments’ beneath the table. In the new page (Appendix 6B), the experiments of the selected compound can be viewed and the user can choose a specific experiment (e.g. specific dose or specific dosing route) to view the publication details, ex-

periment details or test details (Appendix 6C). Publication details include author(s), title, publication year and journal information. Experiment details include substance administered, (sub)species, age and/or weight, gender, species conditions, feed regimen, route of administration, vehicle information, frequency and duration of administration and the quality rate. Test details show the substance related to the parameter value, the model used in the specific experiment and/or in the reanalysis, the parameters, the values (mean ± SD and/or range) and the number of observations. In this way a user-friendly interface is created in which the user can specify their queries, browse through the results and get detailed information.

The information of each compound is summarised in the table in Appendix 7. The table can be placed in the website of ECVAM. In this way, the user can see which information is available in the database. The table presents compound, species, gender, plasma protein binding, blood-plasma ratio, route of administration, quality of the publication (see second interim report), reanalysis, first author of the reference and information on the parameters of a non-, 1-, 2- or 3-compartmental analysis. The parameters in the table are necessary for the construction of a concentration-time curve.

6.4 Conclusions and recommendations

The storage template, database and retrieval template being realised, the following recommendations can be made:

- The initial ECVAM call did not contain an explicit description of the desired functionality of the storage and retrieval template. For a follow up project, currently developed templates can be used to determine what functionality works fine, what functionality is missing and what would be 'nice to have'.
- Although Excel proved to be very useful to get results fast and relatively cheap, it is not a robust system for further data base development. It is best to choose technical solutions where storage template, database and retrieval template are separated, thereby enabling their independent and therefore more efficient development.

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Appendix 1. List of substances

1,2,3,4-tetrachlorobenzene	ethanol	RU-486/mifepristone
17a-ethynylestradiol	diethylene glycol	sodium fluoride
2,4 dinitrophenol	diethylphtalate	phenanthrene
3-nitropropionic acid	digoxin	phenobarbital
5,5-diphenylhydantoin	diphenhydramine	physostigmine
5-fluorouracil	diquat	potassium cyanide
Acetaminophen	fipronil (carbamate)	procainamide hydrochloride
acetylsalicylic acid	flutamide	propranolol hydrochloride
acrylaldehyde (acrolein)	genistein	propylparaben
AlCl3 (hexahydrate)	glufosinate-ammonium	pyrene
amiodarone	glutethimide	quinidine sulfate dihydrate
amitriptyline hydrochloride	haloperidol	rifampicine
amphetamine	hexachlorobenzene	sodium lauryl sulfate (= dodecyl)
arsenic trioxide	hexachlorophene	strychnine
atropine	Isopropanol	tert-butylhydroperoxide
B,B'-iminodipropionitrile (IDPN)	ketoconazole	tetracycline
benz(a)anthracene	lead acetate	thalidomide
benzene	L-glutamate	thallium sulphate
bisphenol A	lindane (organochlorate)	theophylline
cadmium (II) chloride	malathion	thioridazine hydrochloride
caffeine	maprotiline	toluene
carbamazepine	mercury (II) chloride	trimethadione
carbendazim (ISO)	methadone	trimethyltin
chloramphenicol	methanol	valproic acid
chloroquine diphosphate/sulphate	methyl mercury chloride	verapamil
chlorpyrifos (organophosphate)	methylindole (organophosphate)	warfarin
cis-diammineplatinum dichloride	mipafox (organophosphate)	disulfoton
colchicine	nicotine	endosulfan
cycloheximide	nocodazole	dextropropoxyphene
cyclosporine A	ochratoxin A	antipyrine
deltamethrin (pyrethroid type II)	orphenadrine	gossypol
DES (diethylstilbestrol)	paraben (butyl paraben)	busulfan
diazepam	paraquat dichloride	2,5-hexanedione
dibutylphtalate	parathion	cyclophosphamide
dichlorvos	pentachlorobenzene	acrylamide
disopyramide	pentachlorophenol	methanol
domoic acid	rotenone	

Appendix 2. Abbreviations of kinetic parameters

Abbreviation	Description	Synonyms
AUC	area under the (plasma) concentration - time curve	
$AUC_{0-\infty}$	area under the (plasma) concentration - time curve 0 to infinity	AUC_0^∞ AUC_{inf}
AUC_{0-t}	area under the (plasma) concentration - time curve 0 to time t	AUC_0^t AUC_t
AUC/D	area under the (plasma) concentration per dose	
C	concentration	
C_{max}	maximum (plasma) concentration	
T_{max}	time of maximum (plasma) concentration	
F	systemic bioavailability	F_{sys}
F_{abs}	fraction absorbed	F_a
k_a	absorption rate constant	k_{abs}
k_i	initial (absorption + distribution) phase rate constant	k_α
k_e	elimination rate constant	k k_β
V_i	volume of distribution, initial phase	$V_{d,\alpha}$ V_α
V_d	volume of distribution, elimination phase	V $V_{d,\beta}$ V_β
V_γ	volume of distribution, second elimination phase in case of 3-compartment model	$V_{d,\lambda}$
V_{ss}	volume of distribution at steady state	$V_{d,ss}$
V_c	volume of central compartment	
V_p	volume of peripheral compartment	V_1
$t_{1/2,abs}$	half-life, absorption phase	
$t_{1/2,\alpha}$	half-life, initial phase	
$t_{1/2,\beta}$	half-life, elimination phase	
$t_{1/2,\gamma}$	half-life, second elimination phase in case of 3-compartment model	$t_{1/2,\lambda}$
CL_{total}	total clearance	CL CL_t
CL_h	hepatic clearance	$CL_{hepatic}$ CL_{metab}
$CL_{h,int}$	intrinsic hepatic clearance	$CL_{hepatic,int}$ $CL_{metab,int}$
CL_r	renal clearance	CL_{renal}
$CL_{r,int}$	intrinsic renal clearance	$CL_{renal,int}$
MRT	mean residence time	

Appendix 3. Codes used in Berkeley Madonna

IV administration/1-compartment model used for reanalysis of data

C = D * EXP(- ke * time) / Vd ; concentration (dose unit / volume unit)

D = 1 ; dose (dose unit)
Vd = 1 ; distribution volume (volume unit)
ke = 1 ; exponential elimination rate (1 / time unit)

PO administration/1-compartment model used for reanalysis of data

C = IF (ke <> ka)
THEN Fsys * D * (EXP(- ke * time) - EXP(-ka * time)) / ((1 - ke / ka) * Vd)
ELSE Fsys * D * ka * time * EXP(-ka * time) / Vd ; concentration (dose unit / volume unit)

D = 1 ; dose (dose unit)
Vd = 1 ; distribution volume (volume unit)
ke = 1 ; exponential elimination rate (1 / time unit)
Fsys = 1.0 ; systemic availability (unitless)
ka = 3 ; absorption rate (1 / time unit)

AUC = Fsys * D / (ke * Vd) ; concentration (dose unit / volume unit) x time (time unit)
t_beta = LOGN(2) / ke ; half-life time elimination phase (time unit)

IV administration/2-compartment model used for reanalysis of data

C = D * ((1 - Vi/Vd) * EXP(- ki * time) + Vi/Vd * EXP(- ke * time)) / Vi ; concentration (dose unit / volume unit)

D = 1 ; dose (dose unit)
Vi = 0.1 ; initial volume of dilution (volume unit)
Vd = 1 ; terminal volume of distribution (volume unit)
ki = 10. ; exponential distribution rate (1 / time unit)
ke = 1.; exponential terminal rate (1 / time unit)

ta = LOGN(2) / ki
tb = LOGN(2) / ke
AUC = (D / Vi) * ((1 - Vi / Vd) / ki + (Vi / Vd) / ke)

PO administration/2-compartment model used for reanalysis of data

C = Ci + Ce ; total concentration (dose unit / volume unit)

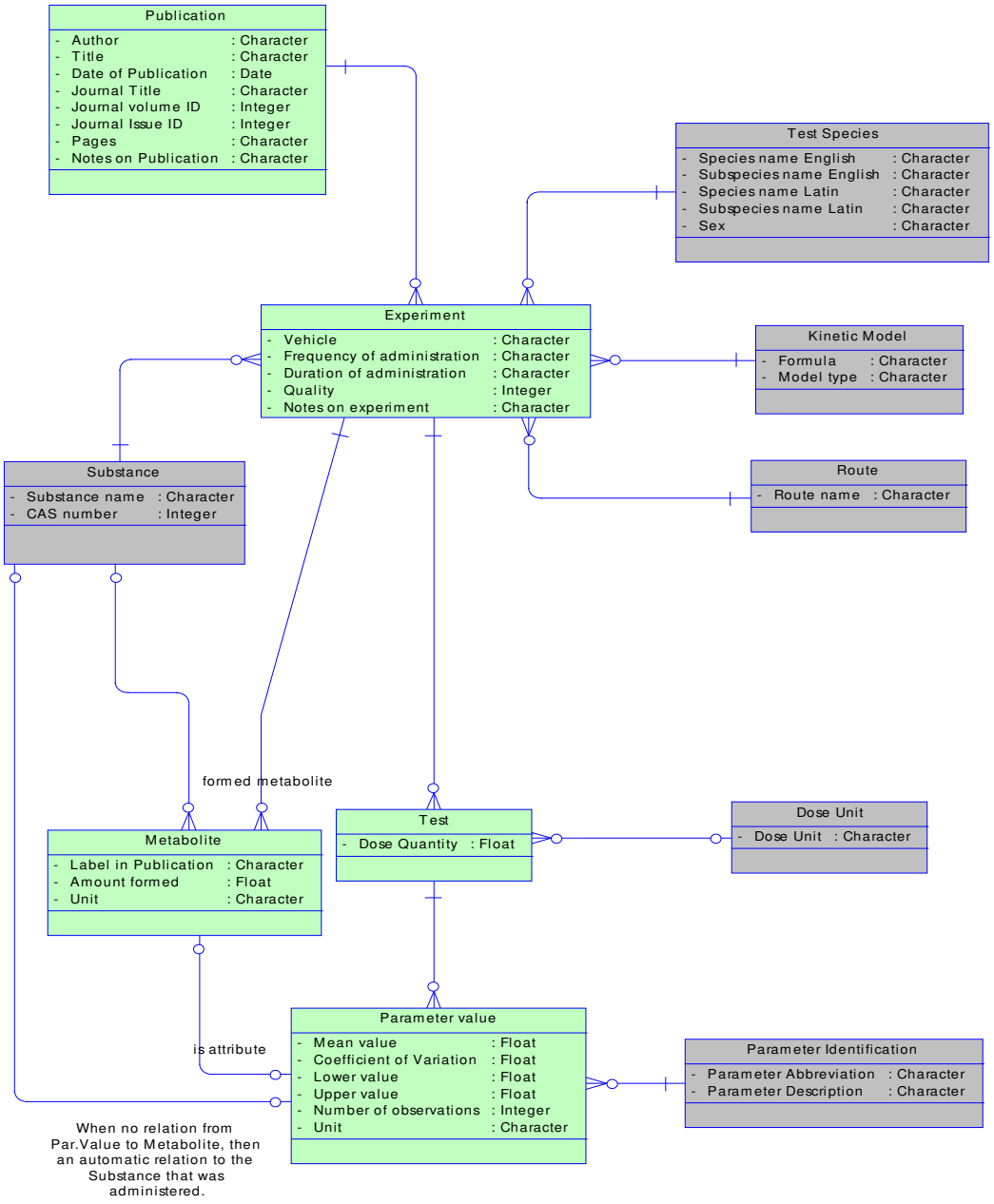
Ci = IF (ki <> ka)
THEN Fsys * D * (1 - Vi/Vd) * (EXP(- ki * time) - EXP(-ka * time))/ ((1 - ki / ka) * Vi)
ELSE Fsys * D * (1 - Vi/Vd) * ka * time * EXP(-ka * time) / Vi ; concentration of initial phase (dose unit / volume unit)

Ce = IF (ke <> ka)
THEN Fsys * D * Vi/Vd * (EXP(- ke * time) - EXP(-ka * time)) / ((1 - ke / ka) * Vi)
ELSE Fsys * D * Vi/Vd * ka* time * EXP(-ka * time) / Vi ; concentration of terminal phase (dose unit / volume unit)

D = 1 ; dose (dose unit)
Vi = 0.1 ; initial volume of dilution (volume unit)
Vd = 1 ; terminal volume of distribution (volume unit)
ki = 10. ; exponential distribution rate (1 / time unit)
ke = 1 ; exponential terminal rate (1 / time unit)
Fsys = 1.0 ; systemic availability (unitless)
ka = 3 ; absorption rate (1 / time unit)

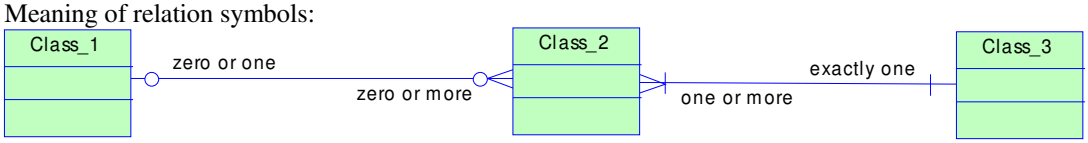
AUC = Fsys * D * ((1 - Vi/Vd) / ki + (Vi/Vd) / ke) / Vi ; concentration (dose unit / volume unit) x time (time unit)
t_alpha = LOGN(2) / ki ; half-life time distribution phase (time unit)
t_beta = LOGN(2) / ke ; half-life time elimination phase (time unit)

Appendix 4. Data model



UML model

Meaning of relation symbols:



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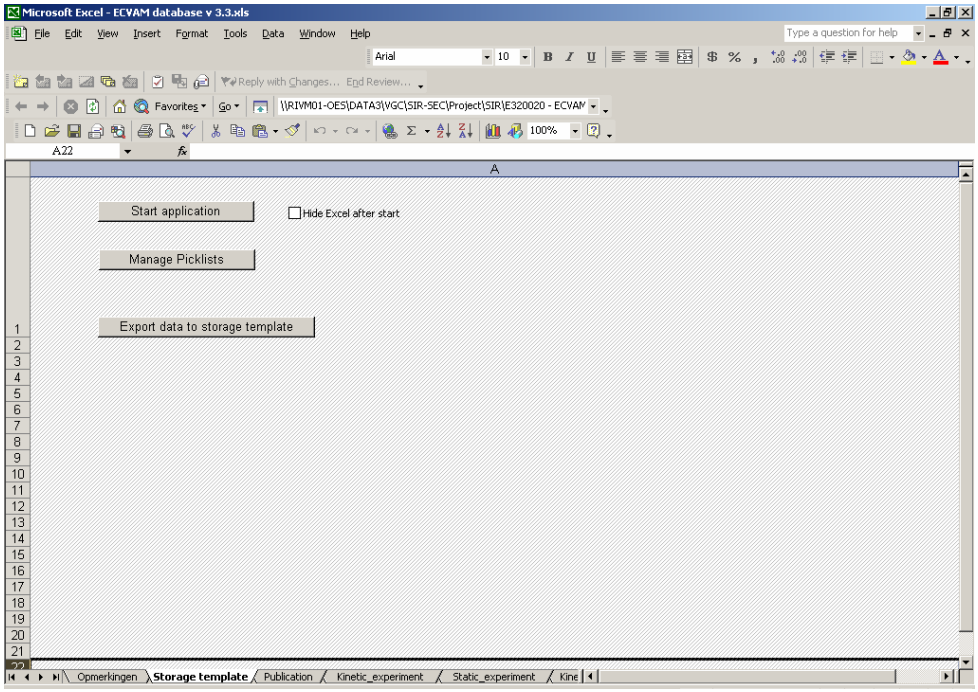
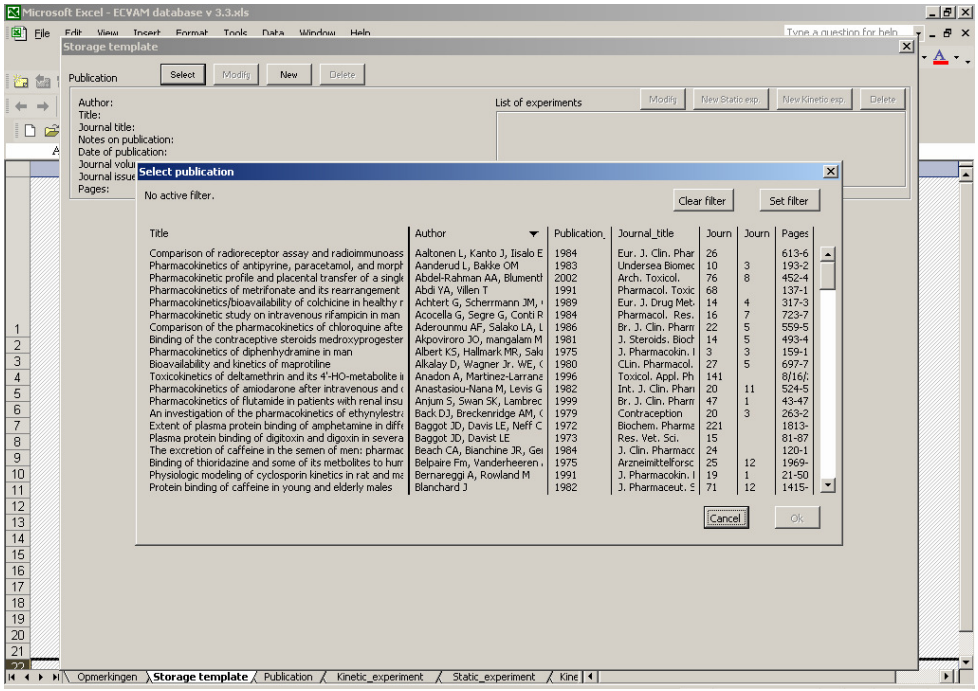
Appendix 5. Storage template

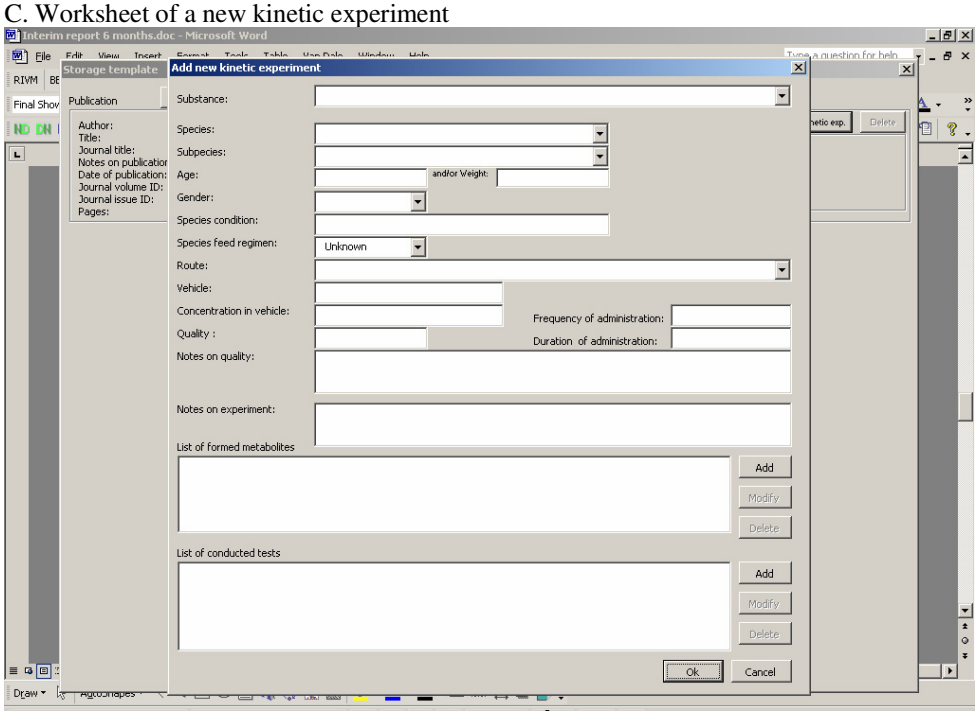
A. Start worksheet



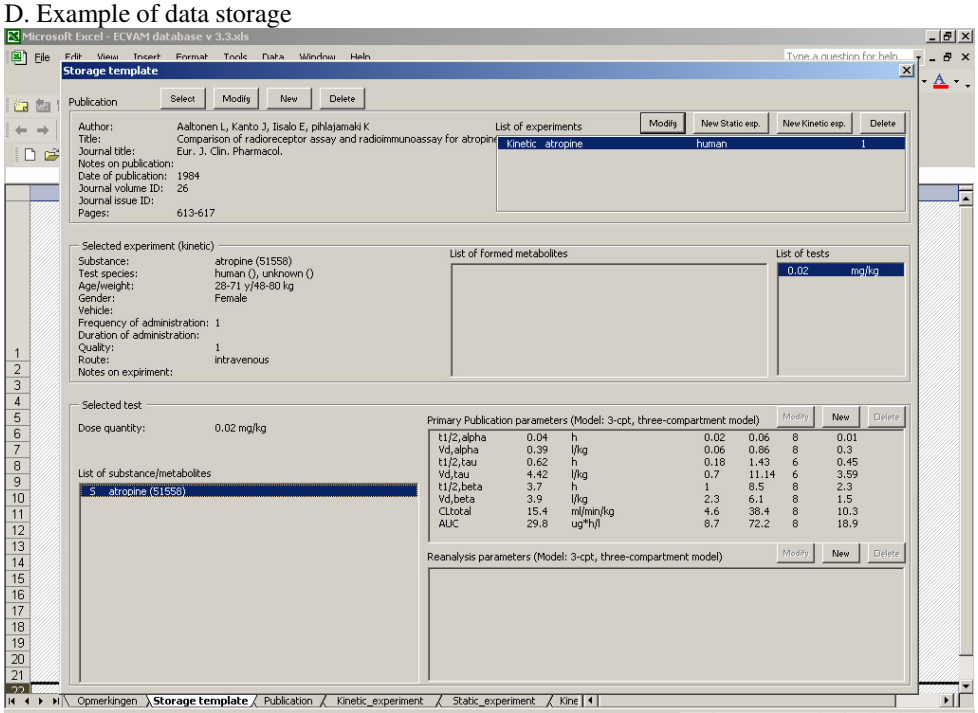
B. Worksheet for reference selection



C. Worksheet of a new kinetic experiment



D. Example of data storage



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Appendix 6. Retrieval template

A. Start page of the retrieval template

Search / filter substance

Double click a cell (if it contains a number) to view the experiments, or select a number and press the 'Go to selected experiments' button.

No. Experiments per species and substance					
Substance	Cas-number	human		rat	
		In vivo	Ex vivo	In vivo	Ex vivo
1,2,3,4-tetrachlorobenzene	634662				
2,4-dinitrophenol	51285				
2,5-hexanedione	110134			1	
3,3'-iminodipropionitrile	111944				
3-methylindole	83341				
3-nitropropionic acid	504881				
4-hydroxy-2-ethyl-2-phenyl glutarimide		1			
5,5-diphenylhydantoin	57410	2	2		1
5-fluorouracil	51218	1	1		1
L-glutamate	1676739				
R-methadone	76993		1		
R-thalidomide	50351		1		
R-warfarin	81812	1			
RU 486	84371653	1	1		
S-methadone	76993		1		
S-thalidomide	50351		1		
S-warfarin	81812	1			
acetaminophen	103902	2	1		
acetylsalicylic acid	50782	1	1	3	
acrolein	107028				
acrylamide	79061			4	
amiodarone	1951253	2	1		
amitriptyline	50486	1	2		
amphetamine	300629	1	1		1
antipyrine	60800			1	
arsenic trioxide	1327533	1	1		
atropine	51558	8			
benz(a)anthracene	56553			1	
benzene	71432			2	
bisphenol A	80057			1	
busulfan	55981	1			
cadmium chloride	10108642				
caffeine	58082	1	1		
carbamazepine	298464	1	1		

carbendazim	10605217			2	1
chloramphenicol	56757	1			
chloroquine	54057	2	1		
chlorpyrifos	2921882			1	
cis-diammineplatinum dichloride	15663271				2
colchicine	64868	2			
cotinine	486566			1	
cycloheximide	66819				
cyclophosphamide	50180	1			
cyclosporine A	59865133	2	1		1
deltamethrin	52918635			2	1
desmethyldiazepam	1088115		1		1
dextropropoxyphene	469625	1			
diazepam	439145	1	1		1
dibutylphtalate	84742				
dichlorvos	62737	1			
diethylene glycol	111466			1	
diethylphtalate	84662				
diethylstilbestrol	56531	1			
digoxin	20830755	2	1		1
dimethadione	695534	1			
diphenhydramine	58731	3	2		
diquat	2764729			1	
disopyramide	3737095	3	1		
disulfoton	298044	1			
domoic acid	14277975			2	
endosulfan	115297			1	
ethanol	64175	3			
ethynylestradiol	57636	2	1		1
fipronil	120068373	1			
flutamide	13311847	1		2	
genistein	446720	1		4	
glufosinate ammonium	77182822	1			
glutethimide	77214	1			
glycidamide	5694008			4	
gossypol	303457			2	
haloperidol	52868	2	2		
hexachlorobenzene	118741			1	
hexachlorophene	70304			1	
hexahydrate	7791186				
hydroxy flutamide	52806538				
isopropanol	67630			4	
ketoconazole	65277421	3	1	1	1
lead acetate	6080564			1	
lindane	58899			2	
malathion	121755	1			
maprotinline	10262698	3	2		
mercury chloride	7487947				

methadone	76993	1			
methanol	67561	2			
methyl mercury	22967926	1			
mipafox	371868				
nicotine	54115			1	1
nocodazole	872504				
norpropoxyphene	3376941	1			
ochratoxin A	303479		1	2	1
orphenadrine	83987	2			
paraben	120478			1	
paraquat dichloride	1910425	1			
parathion	56382	1		1	
pentachlorobenzene	608935				
pentachlorophenol	87865		1	4	1
phenanthrene	85018			1	
phenobarbital	50066	3			1
physostigmine	57476	2	1		1
potassium cyanide	151508			1	
procainamide hydrochloride	51069	1			
propanolol hydrochloride	525666	1			
propylparaben	94133				
pyrene	129000			2	
quinidine	56542	1	1		1
rifampicine	13292461	1	1		
rotenone	83794				
sodium fluoride	7681494	2			
sodium lauryl sulfate	151213				
strychnine	57249	2			
tert-butylhydroperoxide	75912				
tetracycline	60548	1	1		
thalidomide	50351	1			
thallium sulfate	7446186				
theophylline	58559	1	1		
thioridazine	50522	1	2		
toluene	108883			1	
trimethadione	127480	1		2	
trimethyltin	1066451			1	
valproic acid	99661	1	1		
verapamil	52539	2	2		1
warfarin	81812	1			1

B. Example of selected experiments of a compound

⇦ Back

Selected experiments	
Type experiment:	In vivo
Substance:	pentachlorophenol
CAS-number:	87865
Species:	rat

Double click a cell to view the experiments tests (light gray columns), double click to view the specific test (light yellow columns), or select a row and press the 'Refine exp. tests' or the 'Refine test' button.

Experiments				Tests	
Author	***Pub. year***	***Subspecies***	***Route***	***Dose***	***Unit***
Reigner BG, Gungon RA, Hoag MK, Tozer TN	1991	Sprague-Dawley	intravenous	2.5	mg/kg
Reigner BG, Gungon RA, Hoag MK, Tozer TN	1991	Sprague-Dawley	per oral	2.5	mg/kg
Braun WH, Young JD, Blau GE, Gehring PJ	1977	Sprague-Dawley	per oral	10	mg/kg
				100	mg/kg
Braun WH, Young JD, Blau GE, Gehring PJ	1977	Sprague-Dawley	per oral	10	mg/kg
				100	mg/kg

C. Example of publication details, experiment details and test results

Publication details	
Author:	Reigner BG, Gungon RA, Hoag MK, Tozer TN
Title:	Pentachlorophenol toxicokinetics after intravenous and oral administration to rat
Publication year:	1991
Journal title:	Xenobiotica
Journal volume ID:	21
Journal issue ID:	12
Pages:	1547-1558
Notes on publication:	

Experiment details	
Substance:	pentachlorophenol (87865)
Species:	rat
Subspecies:	Sprague-Dawley
Age:	
Weight:	302-443 g
Gender:	Male
Species condition:	
Species feed regimen:	Fed
Route:	intravenous
Vehicle:	NaOH/phosphate buffer
Concentration in vehicle:	1.5 mg/ml
Frequency:	1
Duration:	bolus
Notes on experiment:	
Quality:	1
Notes on quality:	

Test dose: 2.5 mg/kg

Data from primary publication, model: two-compartment model

P	*Substance*	*Parm.*	*Parameter*	*Value*	*No of observ.*
X	pentachlorophenol	AUC	area under the plasma concentration - time curve	96.2 +/- 12.2 ug*h/ml	5
X	pentachlorophenol	CLtotal	clearance	0.0263 +/- 0.0034 l/h/kg	5
X	pentachlorophenol	CLrenal	renal clearance	1.41 +/- 0.23 ml/h/kg	5
X	pentachlorophenol	Vd,beta	volume of distribution, terminal phase	0.268 +/- 0.03 l/kg	5
X	pentachlorophenol	Vd,ss	volume of distribution, steady state	0.251 +/- 0.021 l/kg	5
X	pentachlorophenol	t1/2,alpha	half-life, initial phase	0.67 +/- 0.46 h	5
X	pentachlorophenol	t1/2,beta	half-life, terminal phase	7.11 +/- 0.87 h	5
X	pentachlorophenol	Vd,alpha	volume of distribution, initial phase	0.155 +/- 0.042 l/kg	5

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Appendix 7. Overview of information in database

A. Information on 1- and 2-compartment model analysis

Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
2,5-hexanedione	rat	male			sl	2									+			+		Misumi et al., 1997
4-hydroxy-2-ethyl-2-phenyl-glutarimide	human	male			po	3												+		Rotschafer et al., 1980
5,5-diphenylhydantoin	rat	n.m.	+																	Bowdle et al., 1980
5,5-diphenylhydantoin	human	n.m.		+																Schulz et al., 1983
5-fluorouracil	rat	n.m.	+																	Celio et al., 1983
5-fluorouracil	human	n.m.		+																Schaaf et al., 1987
acetaminophen	human	n.m.	+																	Milligan et al., 1994
acetaminophen	human	male			iv	1										+	+	+	+	Rawlins et al., 1977
acetaminophen	human	male			po	1								+				+		Rawlins et al., 1977
acetylsalicylic acid	rat	male			iv	1										+		+	+	Fu et al., 1991
acetylsalicylic acid	rat	male			po	1								+	+			+		Fu et al., 1991
acetylsalicylic acid	human	n.m.	+																	Ghahramani et al., 1998
acetylsalicylic acid	human	male			po	1			+	+	+									Yoovathaworn et al., 1986
acrylamide	rat	both			iv	1				+	+									Doerge et al., 2005
acrylamide	rat	both			po	1		+	+	+										Doerge et al., 2005
amiodarone	human	female			iv	1				+	+									Anastasiou-Nana et al., 1982
amiodarone	human	both			po	1				+	+									Anastasiou-Nana et al., 1982
amiodarone	human	n.m.	+																	Veronese et al., 1988
amitriptyline	human	n.m.	+																	Brinkschulte et al., 1982
amitriptyline	human	n.m.		+																Fisar et al., 2006

Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
amphetamine	rat / human	n.m.	+																	Baggot et al., 1972
amphetamine*	human	both			po	2	+		+	+										Schepers et al., 2003
arsenic trioxide	human	n.m.		+																Kumana et al., 2002
atropine	human	male			iv	2										+		+		Hinderling et al., 1985
atropine	human	male			im	1			+	+	+									Kamimori et al., 1990
atropine	human	female			iv	1										+		+	+	Kanto et al., 1981
atropine	human	both			iv	1										+		+	+	Pihlajamaki et al., 1986
benz(a)anthracene*	rat	female			po	2	+		+	+										Modica et al., 1983
bisphenol A	rat	male	+		iv	2														Yoo et al., 2000
caffeine	human	n.m.	+																	Blanchard, 1982
carbamazepine	human	n.m.	+																	Hooper et al., 1975
carbamazepine	human	male			po	1			+	+	+									Pynnonen, 1977
carbendazim	rat	n.m.	+																	Jia et al., 2003
carbendazim	rat	male			iv	1										+		+		Krechniak, Klosowska, 1986
chloramphenicol	human	both			iv	2				+	+									Narang et al., 1981
chloroquine	human	male			iv	2												+		Aderounmu et al., 1986
chloroquine	human	male			im	3												+		Aderounmu et al., 1986
chloroquine	human	n.m.	+																	Walker et al., 1983
chlorpyrifos	rat	female			iv	1										+		+	+	Abdel-Rahman et al., 2002
cis-diammineplatinum dichloride	rat	n.m.	+																	Manaka and Wolf, 1978
cyclosporine A	rat	n.m.	+	+																Bernareggi, Rowland, 1991
cyclosporine A	human	both			po	1								+	+	+		+	+	Galla et al., 1995
cyclosporine A	human	both			iv	1										+		+	+	Galla et al., 1995
cyclosporine A	human	n.m.	+																	Legg and Rowland, 1987
deltamethrin	rat	male			po	1								+		+		+	+	Anadon et al., 1996

Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
deltamethrin	rat	n.m.		+																Kim et al., 2008
desmethyldiazepam	rat / human	n.m.	+																	Klotz et al., 1976
diazepam	rat / human	n.m.	+	+																Klotz et al., 1976
dichlorovos*	human	male			po	2	+			+										Abdi and Villen, 1991
diethylstilbestrol*	human	male			iv	3										+	+	+	+	Nakamura, 1986
digoxin	rat / human	n.m.	+																	Baggot and Davist, 1973
dimethadione	human	male			po	1				+	+									Kobayashi et al., 1984
diphenhydramine	human	n.m.	+																	Albert et al., 1975
diphenhydramine	human	both			iv	2												+	+	Scavone et al., 1990
diphenhydramine	human	both			po	2								+				+		Scavone et al., 1990
diphenhydramine	human	both			sl	2								+				+		Scavone et al., 1990
diquat	rat	female			it	2										+		+		Charles et al., 1978
disopyramide	human	n.m.	+																	Bredesen et al., 1982
disopyramide	human	male			iv	1										+		+	+	Bryson et al., 1978
disopyramide (phosphate)	human	male			po	1		+	+	+										Bryson et al., 1978
disopyramide (rythmodan)	human	male			po	1		+	+	+										Bryson et al., 1978
domoic acid	rat	female			iv	2												+	+	Truelove and Iverson, 1994
endosulfan	rat	male			po	2									+	+		+	+	Chan et al., 2005
ethanol	human	male			iv	2													+	Rangno et al., 1981
ethanol	human	male			po	2									+				+	Rangno et al., 1981

Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
ethynylestradiol	rat / human	n.m.	+																	Akpoviroro et al., 1981
ethynylestradiol	human	female			po	1								+				+		Back et al., 1979
ethynylestradiol	human	female			iv	2										+		+	+	Back et al., 1979
fipronil*	human	male			po	3	+		+	+										Mohamed et al., 2004
glufosinate ammonium	human	male			po	2										+		+	+	Hirose et al., 1999
glutethimide*	human	male			po	3	+			+										Rotschafer et al., 1980
glycidamide	rat	both			po	1			+	+										Doerge et al., 2005
glysidamide	rat	both			iv	1				+	+									Doerge et al., 2005
gossypol	rat	male			iv	2										+		+	+	Othman, Abou-Donia, 1988
gossypol	rat	male			po	2										+		+		Othman, Abou-Donia, 1988
haloperidol	human	n.m.	+																	Forsman and Ohman, 1977
haloperidol	human	male			po	1								+	+	+		+		Holley et al., 1983
hexachlorobenzene	rat	male			iv	2										+		+	+	Scheufler and Rozman, 1984
hexachlorophene*	rat	male			iv	2						+	+		+	+		+		Klaassen, 1979
isopropanol	rat	both			iv	2				+										Slauter et al., 1994
isopropanol	rat	both			po	2				+										Slauter et al., 1994
ketoconazole	human	n.m.	+																	Johnson et al., 1985
ketoconazole	rat	n.m.		+																Matthew et al., 1993
lead acetate*	rat	male			po	2	+		+	+										Timschalk et al., 2006
lindane	rat	male			ip	2				+										Tusell et al., 1987
lindane	rat	male			po	2		+		+										Tusell et al., 1987
malathion	human	both			d	3								+						Guy et al., 1985
maprotinline	human	male			po	2							+	+		+			+	Alkalay et al., 1980
maprotinline	human	n.m.	+																	Lynn et al., 1981
maprotinline	human	n.m.		+																Maguire et al., 1980

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Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
methadone	human	both			iv	1										+		+	+	Meresaar et al., 1981
methyl mercury	human	male			iv	3												+		Smith et al., 1994
nicotine	rat	n.m.	+																	Miller et al., 1977
ochratoxin A	rat	male			iv	2												+	+	Hagelberg et al., 1989
ochratoxin A	rat	male			po	2								+				+	+	Hagelberg et al., 1989
ochratoxin A	rat / human	n.m.	+																	Hagelberg et al., 1989
paraquat dichloride	human	both			po	3													+	Houze et al., 1990
parathion*	human	male			po	2						+	+		+	+		+		Hoffmann, Papendorf, 2006
pentachlorophenol	rat	male			po	2										+		+		Braun et al., 1977
pentachlorophenol	rat	female			po	1										+		+		Braun et al., 1977
pentachlorophenol	rat	male			iv	1										+	+	+	+	Reigner et al., 1991
pentachlorophenol	rat	male			po	1							+					+		Reigner et al., 1991
pentachlorophenol	rat	n.m.	+																	Schmieder and Henry, 1988
pentachlorophenol	human	n.m.	+																	Uhl et al., 1986
phenanthrene*	rat	female			po	2	+		+	+										Kadry et al., 1995
phenobarbital	rat	n.m.	+																	Leppik and Sherwin, 1979
phenobarbital	human	both			im	2								+	+			+		Wilensky et al., 1982
phenobarbital	human	both			iv	2										+		+		Wilensky et al., 1982
phenobarbital	human	both			po	2								+	+			+		Wilensky et al., 1982
physostigmine	rat / human	n.m.	+																	Unni and Somani, 1985
procainamide hydroclo-ric	human	male			iv	2										+		+	+	Manion et al., 1977
pyrene	rat	male			iv	2										+		+	+	Withey et al., 1991

Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
pyrene	rat	male			iv	2								+	+	+		+	+	Withey et al., 1991
quinidine	rat	n.m.		+																Fremstad, 1977
quinidine	human	both	+																	Fremstad et al., 1979
rifampicine	human	male			iv	2				+	+									Acocella et al., 1984
rifampicine	human	n.m.	+																	Boman, Ringberger, 1974
R-methadone	human	n.m.	+																	Boulton and Devane, 2000
R-Thalidomide	human	n.m.	+	+																Eriksson et al., 1998
RU 486	human	female			po	1									+	+		+	+	He et al., 1989
RU 486	human	n.m.	+																	Heikinheimo et al., 1987
R-warfarin*	human	male			po	2						+	+		+	+		+		Johansson et al., 2005
S-methadone	human	n.m.	+																	Boulton and Devane, 2000
sodium fluoride	human	male			po	1									+	+		+	+	Ekstrand et al., 1977
S-Thalidomide	human	n.m.	+	+																Eriksson et al., 1998
strychnine	human	male			po	2			+		+									Heiser et al., 1992
strychnine	human	female			po	2									+			+		Tegtmeyer et al.,1995
S-warfarin*	human	male			po	2						+	+		+	+		+		Johansson et al., 2005
tetracycline	human	male			iv	2										+		+	+	Raghuram and Krishnas-wamy, 1981
tetracycline	human	n.m.	+																	Wozniak , 1960
theophylline	human	n.m.	+																	Gundert-Remy and Hildebrandt, 1983
theophylline*	human	both			iv	2										+	+	+	+	Lacarelle et al., 1994
thioridazine	human	n.m.	+																	Belpaire et al., 1975
thioridazine	human	male			po	2									+	+		+		Chakraborty et al., 1989
thioridazine	human	n.m.		+																Dinovo et al., 1984
trimethadione	human	male			po	1				+	+									Kobayashi et al., 1984
valproic acid	human	n.m.	+																	Gugler and Mueller, 1978

Compound	Species	Gender	Protein binding	Blood-plasma ratio	Route	Quality	1-compartment model analysis					2-compartment model analysis								Reference
							V_d /F	F	ka	ke	V_d	Vi /F	V_d /F	F	ka	ki	Vi	ke	V_d	
valproic acid	human	both			iv	1										+		+	+	Nitsche and Mascher, 1982
verapamil	human	n.m.	+																	Giacomini et al., 1984
verapamil	human	n.m.	+																	Keefe et al., 1981
verapamil	rat	n.m.		+																Manitpisitkul and Chiou, 1993
verapamil	human	male			iv	2										+		+	+	McAllister and Edward, 1982
verapamil	human	male			po	2								+				+	+	McAllister and Edward, 1982

* Reanalysis performed. Abbreviations: n.m.=not mentioned, d=dermal, im=intramuscular, it=intratracheal, iv=intravenous, po=per oral, sl=sublingual; V_d=volume of distribution (elimination phase), F=systemic bioavailability, ke=elimination rate constant, ka=absorption rate constant, Vi=volume of distribution (initial phase)

B. Information on non- and 3-compartment model analysis

Compound	Species	Gender	Protein-binding	Blood-plasma ratio	Route	Quality	Non-compartment analysis				3-compartment model analysis							Reference
							V_d/F	F	ke	V_d	ka	ki	Vi	ke	V_d	k_γ	V_γ	
5-fluorouracil	human	both			iv	1			+	+								Schaaf et al., 1987
5-fluorouracil	human	n.m.		+														Schaaf et al., 1987
antipyrine	rat	male			iv	2			+	+								Aanderud et al., 1983
atropine	human	female			iv	1						+	+	+	+	+	+	Aaltonen et al., 1984
domoic acid	rat	male			iv	2			+									Suzuki et al., 1993
flutamide	rat	male			po	2			+									Zuo et al., 2002
flutamide	rat	male			iv	2			+	+								Zuo et al., 2002
genistein	human	male			po	1			+	+								Busby et al., 2002
genistein	rat	male			po	1		+	+	+								Coldham et al., 2002
genistein	rat	male			iv	1			+									Coldham et al., 2002
haloperidol	human	male			iv	1						+		+		+		Holley et al., 1983
haloperidol	human	male			po	1						+		+		+		Holley et al., 1983
hydroxy flutamide	rat	male			po	2			+									Zuo et al., 2002
hydroxy flutamide	rat	male			iv	2			+	+								Zuo et al., 2002
paraquat dichloride	human	both			po	3					+							Houze et al., 1990
physostigmine	human	male			po	1		+	+									Walter et al., 1995
physostigmine	human	male			iv	1			+	+								Walter et al., 1995
quinidine	rat	n.m.		+														Fremstad, 1977
quinidine	human	both	+															Fremstad et al., 1979
quinidine	human	both			iv	1			+	+								Fremstad et al., 1979
sodium fluoride	human	male			po	1					+	+		+		+	+	Ekstrand et al., 1977
thalidomide	human	both			po	2	+		+									Teo et al., 2001

Abbreviations: n.m.=not mentioned, iv=intravenous, po=per oral; V_d=volume of distribution (elimination phase), F=systemic bioavailability, ke=elimination rate constant, ka=absorption rate constant, Vi=volume of distribution (initial phase), k_γ=elimination rate constant (second phase), V_γ = volume of distribution (second phase)

C. Information on compounds when no model analysis is mentioned

Compound	Species	Gender	Route	Quality	Parameters											Reference
					F	Vi	V_d	ka	ki	ke	AUC	C_{max}	T_{max}	Cl	V_{ss}	
5,5-diphenylhydantoin	human	male	iv	2			+			+	+	+		+		Kromann et al., 1981
amitriptyline	human	male	po	1			+			+	+		+			Garland et al., 1978
arsenic trioxide	human	both	iv	2			+		+	+	+	+		+		Shen et al., 1997
atropine	human	n.d.	iv	2						+					+	Hayden et al., 1979
atropine	human	male	im	2			+			+	+	+	+	+		Kentala et al., 1990
benzene	rat	male	ih	3		+	+		+	+	+					Haddad et al., 2000
bisphenol A	rat	male	iv	2					+	+	+			+	+	Yoo et al., 2000
busulfan	human	both	iv	2						+	+			+		Schuler et al., 1998
carbendazim	rat	both	po	2						+	+	+	+	+		Jia et al., 2003
cotinine	rat	male	ia	2						+	+					Plowchalk et al., 1992
cyclophosphamide	human	both	po	2						+	+	+	+			Stewart et al., 1995
diethylene glycol	rat	male	po	2			+	+			+			+		Heilmair et al., 1993
digoxin	human	male	po	2	+		+		+	+	+			+		Santostasi et al., 1987
digoxin	human	male	iv	2			+		+	+	+			+		Santostasi et al., 1987
disolfoton	human	female	po	3								+	+			Futagami et al., 1995
ketoconazole	human	male	po	2	+					+	+	+	+			Huang et al., 1986
ketoconazole	rat	male	iv	2			+			+	+					Matthew et al., 1993
maprotinline	human	female	po	2			+			+	+	+	+	+		Hrdina et al., 1980
methanol	human	male	iv	2						+						Haffner et al., 1997
methanol	human	male	po	2						+						Haffner et al., 1997
nicotine	rat	male	ia	2			+			+	+			+		Plowchalk et al., 1992
orphenadrine	human	both	po	2						+	+	+	+			Lee et al., 2006
paraoxon	rat	male	iv	2			+			+				+		Eigenberg et al., 1983

Compound	Species	Gender	Route	Quality	Parameters											Reference
					F	Vi	V_d	ka	ki	ke	AUC	C_{max}	T_{max}	Cl	V_{ss}	
parathion	rat	male	iv	2			+			+				+		Eigenberg et al., 1983
potassium cyanide	rat	male	po	2			+			+	+	+	+	+		Sousa et al., 2003
propanolol	human	both	po	2						+	+	+	+			Roscoe et al., 1982
sodium fluoride	human	male	po	1			+			+	+			+		Ekstrand et al., 1977
toluene	rat	male	po	2				+		+						Turkall et al., 1991
trimethadione	rat	male	po	2			+			+	+	+	+			Tanaka et al., 1981
trimethadione	rat	male	iv	2			+			+	+					Tanaka et al., 1984
trimethyltin	rat	female	ip	3						+		+				Lipscomb et al., 1989

Abbreviations: ia=intra-arterial, ih=inhalatoir, im=intramuscular, ip=intraperitoneal, iv=intravenous, po=per oral; F=systemic bioavailability, Vi=volume of distribution (initial phase), V_d=volume of distribution (elimination phase), ka=absorption rate constant, ki=initial rate constant, ke=elimination rate constant, AUC= area under the (plasma) concentration - time curve, C_{max}= maximum (plasma) concentration, T_{max}= time of maximum (plasma) concentration, Cl= total clearance, V_{ss}= volume of distribution at steady state

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