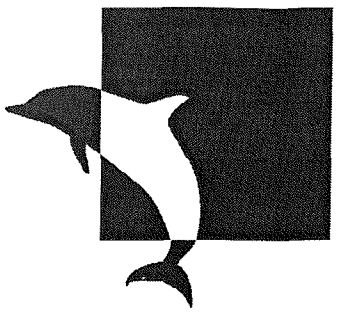

# Human variability in kinetics for the major metabolic pathways - Application to chemical risk assessment

A thesis submitted to the University of Southampton in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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*Cette thèse est dedicatée a ma chère mère Annie Marie Marguerite Gatel qui nous a quitté le 22 décembre 2000 et repose en paix après un combat de titan de trois ans contre une maladie infranchissable.*

*A toi chère mère, chère Nani qui aimait tant le sourire des gens...*

*This thesis is dedicated to my dear mother Annie Marie Marguerite Gatel who left us on December 22 2000 .*

*Look at the stars, look how they shine for you*

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# Foreword

Part of the work presented in this thesis has been published/submitted in international journals:

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Dorne, J.L.C.M., Walton, K., and Renwick, A.G. "Human variability in renal excretion and renal-excretion related uncertainty factors." in preparation.

Papers describing the analysis human variability of the CYP3A4, CYP2C19 and N-acetyltransferases pathways are also in preparation.

# Abstract

This thesis deals with the statistical analysis of human variability in kinetics for the major metabolic pathways (Phase I (CYP isoforms (CYP1A2, CYP2C9, CYP2C19 CYP2D6, CYP2E1, CYP3A4), hydrolysis, Alcohol dehydrogenase), Phase II (N-acetyltransferases, glucuronidation, glycine conjugation, sulphation) and renal excretion) to investigate the appropriateness of the default uncertainty factor ($10^{0.5}$, 3.16) currently in use for the risk assessment of thresholded toxicants and accounting for human variability in kinetics.

Probe substrates were selected on the basis that oral absorption was total and that the metabolic route was the primary route of elimination of the compound (60-100% of an oral). Intravenous data were used for compounds for which absorption was variable.

Human variability in kinetics was quantified for each compound from published pharmacokinetic studies (after oral and intravenous dosing) in healthy adults and other subgroups of the population (effect of ethnicity, age and disease) using parameters relating to chronic exposure (metabolic and total clearances, area under the plasma concentration time-curve (AUC)) and acute exposure (Cmax). All parameters were analysed using the assumptions that data were either normally or log normally distributed and that kinetics were linear.

Three sets of pathway-related uncertainty factors were calculated using the lognormal variability in kinetics to cover 95$^{th}$, 97.5$^{th}$ and 99$^{th}$ centile of the general healthy adult population respectively. These pathway-related uncertainty factors were also calculated for subgroups using the magnitude of the difference in internal dose between each subgroup and healthy adults (ratio of geometric means and the subgroup specific variability).

Low inter-individual variability (about 21-31%) and pathway-related uncertainty factors (1.6- 2.2, 99$^{th}$ centile) were found for all monomorphic pathways with the exception of CYP3A4 metabolism for which variability after oral dosing was 46% (2.8, 99$^{th}$ centile). Polymorphic pathways showed that the current kinetic default would not be adequate to cover healthy adult poor metabolisers for CYP2D6 and CYP2C19 metabolism and slow acetylators for N-acetylation and uncertainty factors of 26, 52 and 5.2 would cover these

subgroups to the 99$^{th}$ centile respectively.

Comparisons between subgroups and healthy adults showed that neonates would be the most susceptible subgroup for compounds handled via CYP1A2, glucuronidation, glycine conjugation and renal excretion. No reliable data were available for polymorphic pathways in neonates. Pathway-related uncertainty factors for interethnic differences were above the 3.16 kinetic default for CYP2C19 and CYP3A4 metabolism. The 3.16 would not be adequate for CYP2D6, CYP2C19, CYP3A4 metabolism, N-acetylation and renal excretion in the elderly and both polymorphic CYP isoforms in children.

Since many environmental contaminants are eliminated by several pathways, a preliminary study focusing on multiple pathways for compounds partially metabolised by polymorphic enzymes (propranolol and diazepam) was undertaken to test the validity of a Monte Carlo model to predict varability in kinetics. The variability for the different pathways (CYP1A2, CYP2D6, glucuronidation for propranolol and CYP2C19, CYP3A4 for diazepam) has been combined in the Monte Carlo model and compared to variability in propranolol and diazepam kinetics from individual *in vivo* studies. Results showed that the Monte Carlo model could be of potential use to predict human varability in kinetics for compounds handled by multiple pathways. However, a full validation of the model including more compounds would be required.

Applications of pathway-related uncertainty factors for chemical risk assessment are discussed and a knowledge–based framework to predict human variability in kinetics for thresholded toxicants is proposed to move away from default assumptions.

# Chapter I Introduction

In the modern world, humans are exposed to a wide range of natural and synthetic chemicals, and a number of questions have been raised as to whether these substances could potentiate adverse health effects through the adulteration of food, beverages and the environment[1]. As early as the first century AD, Pliny the elder wrote "So many poisons are employed to force wine to suit our taste and we are surprised that it is not wholesome!". During the 16th century, the physician and alchemist Paracelsus observed silicosis in miners as an example of chronic occupational exposure and was one of the first to consider the relationship between the dose of a chemical and a toxic response with its famous aphorism "Sola dosis fecit venenum-it is only the dose which makes a chemical a poison". Later, Sir Percival Pott conducted one of the first epidemiological study and correlated occupational exposure with scrotal cancer in young British chimney sweeps (Beck *et al.,* 1994). During the 20th century, the complex process of chemically induced toxicity has been classified to consist of five stages: (1) exposure and penetration of the chemical into the target organism; (2) delivery of the toxicant to its site of action; (3) interaction of the toxicant with the target (cell and molecular components); (4) early toxic response after the initiating interaction which can be described in histopathological, physiological, biochemical ... terms; (5) clinical symptoms of the intoxication (Aldridge, 1995).

From a regulatory point of view, the multidisciplinary framework of risk assessment has provided a basis to identify health and environmental outcomes related to chemical exposure and, to establish safe levels (for cancer and non-cancer effects) in humans. For non-cancer effects, such safe levels have been determined assuming the presence of a threshold dose or exposure below which no adverse effect will arise. Surrogates for the threshold for non-cancer endpoints (such as the no-observed-adverse-effect-level and the benchmark dose) have been derived from animal toxicity studies and extrapolated to humans using uncertainty factors. The scientific validity of this traditional approach has been questioned (Dourson and Stara.,1983; Dourson,1996; Hattis, 1987; Calabrese *et al.,* 1985; Renwick, 1991; Renwick, 1993; Renwick and Lazarus., 1998) and refined to take

[1] Over 100,000 natural substances have been identified (with many more for which the structures have not been determined) and more than five million man-made chemicals of which 70,000 are in commercial use.

into account interspecies differences and human variability to allow for differences in the movement of the chemical (toxicokinetics) and differences in mechanisms of toxicity (toxidynamics) for both aspects of uncertainty (Renwick, 1991; Renwick, 1993; Renwick and Lazarus., 1998).

This introductory chapter will define the different approaches/steps specific to non-cancer risk assessment together with the concept of toxicological threshold and the history of uncertainty factors. New strategies for the risk assessment of non-cancer effects incorporating science-based uncertainty factors will be described and applied to human variability in toxicokinetics for the main metabolic pathways (phase I and phase II enzymes) in order to develop pathway-related default uncertainty factors.

## I.Traditional approaches to risk assessment

The risk assessment approaches, whether applied to non-cancer or cancer endpoints, reflect the complex process of critical analyses of the scientific evidences behind the potential harmful effects of (a) particular substance(s) in humans (WHO, 1999). Two main approaches have been used : quantitative risk assessment and safety assurance.

### I.1 Quantitative risk assessment and safety assurance

Quantitative risk assessment is a procedure undertaken for non threshold (cancer) effects that uses the dose-response relationship gathered usually from experimental animal data, and low dose extrapolation to quantify the risk for human health associated with estimated levels of exposure or, to estimate the exposure associated with a particular degree of human risk. In contrast, safety assurance is the assessment of the dose-response relationship which characterises a dose/level of exposure below which no deleterious effect is measurable (threshold) and an exposure associated with negligible health risk. From this exposure level, a standard setting can be calculated for the compound under review whether it is a food contaminant (Acceptable daily Intake (ADI), Reference dose (RfD)) or an occupational hazard (occupational exposure standard) (Renwick, 2000).

### I.2 Steps in Human Risk Assessment

Human risk assessment, for both quantitative risk assessment and safety assurance, has been divided into four sequential steps: hazard identification, dose response assessment, exposure assessment and risk characterization (IPCS, 1987; WHO,1999).

### I.2.1 Hazard identification

The first step in the risk assessment procedure is to identify the substance of concern and address whether it would be a hazard to human health (adverse effects) and under what circumstances it might express its toxicity (target populations, conditions of exposure, etc...) (WHO, 1999).

Hazard identification is usually based on the results of available epidemiological studies and/or toxicological data (mechanisms of toxicity for various toxicological endpoints and target organs) and/or structure–activity relationship analyses.

Ideally, human data from ethical epidemiological studies would provide the most relevant health effect related to the presence of the hazard in the environment as well as associated risk factors (diet, smoking etc ...) and would avoid extrapolation from animals to man.

However, there is a major lack of human data and toxicological studies on animals (mainly mice, rat, rabbit and dog), using standard guidelines and good laboratory practices (GLPs), play a critical role in hazard identification. From these studies, several categories of toxicity end-points can be described (IPCS, 1987): (1) functional manifestations (weight loss, laxative effects...); (2) lesions (non-neoplastic) with morphological manifestations/target organ; (3) neoplastic/carcinogenic manifestations.

Increasing ethical concerns about animal experimentation have brought about efforts to possibly replace the use of animals, or refine protocols to minimise the number of animals and stress/pain inflicted to them. *In vitro* systems from human or animal tissues (cell culture, isolated tissues and organs) have been developed as alternative methods and have provided useful data but their validation and reproductibility still remain a problem and constitute a present challenge to toxicologists.

Finally, in the absence of human and animal toxicological data, structure-activity relationship data based on the chemical properties of the hazard would provide useful insights into the prediction of the movement of the toxicant in the body (toxicokinetics) for groups of structurally related chemicals such as the flavouring compounds (WHO, 1999).

### I.2.2 Dose response Assessment (Hazard Characterisation)

This second step in the risk assessment process involves the characterization of the dose-response relationship for a given chemical agent and the quantification of the incidence of adverse health effects after exposure to the agent. The dose response assessment will depend on the aim of the procedure and can be divided into two main categories: non neoplastic (non-cancer) and neoplastic effects. However and similarly to the hazard identification step, the lack of human data does not allow direct establishment of the dose response and usually requires the use of dose response data from animal studies (IPCS, 1987; WHO, 1999).

For non-neoplastic effects, surrogates for the threshold and uncertainty factors to extrapolate from experimental animals to humans (section II and III) have traditionally been used to generate a safe level of exposure, ie the tolerable /acceptable daily intake (TDI/ADI) in Europe or the Reference Dose/concentration (RfD/RFC) in the USA (IPCS, 1994; WHO, 1999).

For most carcinogens, dose response assessment relies upon the characterisation of the dose-response relationship obtained from animal experimental data and the low dose risk extrapolation to humans using mathematical modelling techniques. Various models, which are beyond the scope of this work, are available to the risk assessor such as stochastic models (one hit, multi stage), time to tumour models (eg Weibull) and biologically-based models (Moolgavkar-Venzon-Knudson model) (Renwick, 2000; WHO, 1999).

### I.2.3 Exposure Assessment

Exposure assessment aims to quantify the amount of an agent that has reached the individual (external dose) or has been absorbed into the individual (internal dose, absorbed dose). The European community commission defined exposure assessment as "the determination of the emission pathways and rates of movement of a substance and its transformation or degradation, to estimate the concentrations/doses to which human populations or environmental spheres (water, soil, air) are or may be exposed" (EC, 1996). Three main approaches have been published in the exposure estimate guideline and have provided a basis to predict chemical exposure in humans and quantify the uncertainty/variability inherent in this process (US EPA, 1986; US EPA, 1992; WHO, 1999):

-*Point of contact or personal assessment*: The exposure can be quantified from the contact point(s) of the body (outer boundaries ie skin, mouth, nostrils or exchange boundaries (absorption) skin, lung, gastro-intestinal tract) and both the quantity/concentration and time of exposure can be measured and integrated. This type of estimate constitutes the ideal case where the exposure can be estimated precisely and does not rely on a mathematical model. Typical examples of this technique are the use of a badge for radiation exposure or studies using skin patches (WHO, 1999).

-*Scenario evaluation*: the concentration of the chemical is measured or modelled in the media (soil, water, food...) where contact would occur. Exposure scenarios are then modelled, and combined with the concentration data using different mathematical models (WHO, 1999). A typical example of a statistical exposure model (STEM) was developed by Slob (1993) using the 1991 national food consumption survey for the Dutch population and estimations of exposure to dioxin and cadmium. The log-normally distributed data were fitted to a polynomial function using regression analysis and differences between real data, fitted values (uncertainty) and intersubject variability were calculated to provide estimations of intakes in the tails of the distribution ($90^{th}$, $95^{th}$ and $99^{th}$ centiles) in different age categories (Slob, 1993). However useful, these population estimates are subject to a number of biases related to the sampling process (sampling individuals from the population of interest) and the extrapolation process (short term exposure to long term exposure) and Monte Carlo simulations have been used to reduce the biases and compare the distributions of the observed data with the generated model (Slob and Pieters., 1998).

-*Biological monitoring* using internal markers (biomarkers) of exposure (blood levels, urinary levels...) provides an evaluation of the intake and uptake rates of a substance of concern to estimate the dose after the exposure has taken place. Biomarkers have been used to detect the exposures to contaminants in the air, water, food (aromatic amines, polycyclic aromatic hydrocarbons, aflatoxins), and medicines (alkylating agents etc...) (WHO, 1999).

These three models demonstrate that the combination of real data and statistical techniques can prove very useful in establishing exposure assessments, bearing in mind the biological relevance of a model.

### I.2.4 Risk characterisation

The final risk characterisation step constitutes the synthesis of critically evaluated information and data from hazard identification, dose response assessment and exposure assessment, and is applied to a specific use or occurrence of an environmental health hazard (eg a chemical compound) (IPCS, 1987; WHO, 1999). The assessment requires quantitative data on the human exposure in the specific situation and the end product is a quantitative risk estimation about the proportion of people that could be affected by the hazard in a target population (IPCS, 1987; WHO, 1999). In conjunction with risk assessors, risk managers will consider socio-economic and political aspects to formulate a final decision. Quantitative risk assessment and safety assurance approaches differ, in this particular final step, since a risk will be estimated with a particular exposure for the former (cancer effects) whereas a maximum level of exposure associated with a negligible risk will be determined for the latter (non cancer effects) (Renwick, 2000).

## II.The Threshold approach

### II.1 Definition of a toxicological threshold

A toxicological threshold has been defined as the maximum exposure/dose below which homeostatis and cytoprotective mechanisms are maintained and no adverse/toxic effects will occur. Threshold toxicity (non cancer) has been shown to be triggered via a diverse range of mechanisms of toxicity (non genotoxic substances, immunotoxicity, reproductive or developmental toxicity, neurotoxicity...)(WHO, 1999). A classification of thresholded chemicals relative to their toxicity has been established and recognized three distinct classes (Kroes *et al.,* 2000): (1) chemicals of simple structure and metabolised rapidly suggesting a low oral toxicity, (2) intermediate substances with chemical structures less innocuous than class I but with no structural features suggesting high toxicity, (3) substances with chemical structures that may suggest the presence of reactive functional groups and significant toxicity.

## II.2 Existence of a toxicological threshold

In theory, the distinction, between threshold and non-threshold toxicity lies, in the fact that a single molecule (or any level of exposure) of a genotoxic carcinogen could irreversibly bind, mutate or damage DNA and increase the probability of the target cell(s) becoming malignant (Slob, 1999; WHO, 1999). In reality, this distinction is difficult to measure since thresholds have not been observed in any animal experimental settings and both threshold and non-threshold toxicity could not show any quantifiable or statistically significant response in a low dose linear dose-response relationship (Slob and Pieters, 1998; Vermeire *et al.,* 1999; Slob, 1999; Renwick, 2000).

## II.3 Measuring thresholds in experimental settings: the Critical Effect Size

Slob (1999) argued that thresholds cannot exist in a strict quantitative sense and that the key to their biological basis is not to look at the dose-threshold in a mathematical sense but the effect–threshold in a biological sense. It involves the identification and quantification of the adverse effect for a particular toxicological endpoint and measurement of its size in relation to the dose: the critical-effect-size (Slob, 1999). Moreover, toxicological endpoints have been traditionally described by ordinal, quantal or continous variables. Ordinal data have been used, for instance, to depict lesions obtained from histological data using a scale of severity (slight, moderate, marked, severe...) where as quantal data referred to the presence or the absence of a toxic response (*in vitro* or *in vivo*). Both of these variables actually reflect a more quantitative continous response and the critical-effect-size could be quantified in this fashion i.e, how much of a change (increase or decrease) in liver weight in experimental animals would constitute an adverse effect ? In practice, the weight would be considered as a continous variable and the effect size (using expert judgement for example 10-20% change) would be quantified and compared between the test and the control groups of animals (Slob,1999).

## II.4 Hormesis

Recently, the concept of hormesis, described more than a century ago by Schulz and known as the Arndt-Schulz law, has been widely supported: a low dose of chemical can have a beneficial effect (stimulation of growth for a growth supressor, anticarcinogenic properties for a carcinogen) followed by a high-dose adverse effect (Calabrese and Baldwin., 1998a). During the XVI$^{th}$ century, Paracelsus also noticed that toxic substances may be beneficial in small doses and this observation is consistent with his aphorism "the

dose makes the poison". The most common form of hormesis has been shown to follow a typical low dose stimulation-high dose inhibition β curve (or a U-shape relevant to toxicological end-points) and many chemicals have been shown to exhibit hormesis properties, including environmental contaminants (non carcinogens and carcinogens), in a wide range of taxa (Calabrese and Baldwin., 1998a; Calabrese and Baldwin., 1998b). Calabrese and Baldwin (1998a) assessed the scientific basis behind hormesis to determine whether it was a common biological phenomenon with respect to chemical class, animal model, gender and biological end point and 10% of toxicological studies (out of 4000) demonstrated chemical hormesis (Calabrese and Baldwin, 1997; Calabrese and Baldwin, 1998a). However, no long term mechanistic data provided a satisfactory explanation for the observable fact and authors speculated that the hormetic paradigm might not be nessecarily associated with low dose protection and it may instead trigger cellular promotional processes responsible for the stimulation of growth (Calabrese and Baldwin, 1998b).

The non-linearity in some low dose extrapolation is supportive of the hormesis hypothesis (Calabrese and Baldwin., 1998b) but further investigations, into the underlying biochemical and cellular mechanisms involved in this conceivable biological process, are required since it could potentially affect the perception of a toxicological threshold and the whole field of toxicology and risk assessment.

## II.5 Surrogates for the threshold

### II.5.1 The No-Observed-Adverse-Effect-Level (NOAEL)

The NOAEL has been defined as "the greatest concentration or amount of an agent, found by study or observation, that causes no detectable, usually adverse, alteration of morphology, functional capacity, growth, development or lifespan of the target" (IPCS, 1987). For food additives, it is usually calculated from chronic (90 days) or subchronic animal studies (28 days) using the most sensitive species (mouse, rat, rabbit or dog) and the dose-response-relationship from a level producing statistically significant adverse effects between treated animals and controls (IPCS, 1987). Historically, the NOAEL has been the foundation for the calculation of safe levels of exposure in humans (such as the ADI and the reference dose). It has been expressed in mg/kg of diet per day in relation to oral exposure in humans and divided by a safety/uncertainty factor of a 100-fold (see section III for the evolution of the 100-fold)(IPCS, 1987; WHO, 1999).

A theoretical analysis of the statistical properties of the NOAEL, performed on three different sample sizes (10, 20, 50) and dose groups, demonstrated that the calculated probabilistic distributions for the NOAEL were associated with high uncertainty and errors in its determination ranged between 3 and 21% (Leisenring and Ryan., 1992). In agreement with Leisenring and Ryan, other authors have discussed the main drawbacks of the NOAEL and concluded that the sensitivity of the end point, the number of animals and the dosing intervals can greatly influence its determination (Renwick and Walker, 1993; Slob, 1999). Moreover, they argued that the most critical points in the extrapolation process were related to the increments between doses during chronic toxicity studies and the slope of the response. These conclusions demonstrate that the NOAEL can potentially underestimate the threshold and as an example a dose toxicity study in animals with a 10-fold increment between doses (10, 100, 1000 mg/kg), a true threshold of 80 mg/kg and a NOAEL of 10 mg/kg would result in an 8-fold underestimation of the threshold (Renwick and Walker, 1993; Renwick, 2000).

### II.5.2 The Lowest-Observed-Adverse-Effect-Level (LOAEL)

The LOAEL has been defined as the lowest dose for which there is an increase in the frequency of adverse effects during chronic/subchronic studies in animals. It is used as a surrogate for the threshold when a NOAEL cannot be determined from experimental data and an uncertainty factor has been introduced to extrapolate from a LOAEL to a NOAEL (using usually a value of 3). Since the LOAEL, like the NOAEL, is totally dependent on the study design including dose spacing, the extrapolation from a LOAEL to a NOAEL using any factor is not scientifically credible and expert judgement in which the whole of the response curve would be taken into account, on a case by case basis, could only assign a particular uncertainty factor (Renwick, 2000; Vermeire *et al.*, 1999).

Thus, this body of evidence gave rise to a general consensus that the NOAEL and the LOAEL, although still used in the majority of non-cancer risk assessment, were not ideal surrogates for the toxicity threshold and another measure that considered the whole of the dose-reponse curve has been proposed: the benchmark dose (Crump, 1984; Renwick and Walker, 1993; Vermeire *et al.*, 1999; Slob, 1999).

### II.5.3 The Benchmark Dose (BMD)

The BMD concept was originally proposed as an alternative option to the NOAEL by Crump (1984) and defined as a lower statistical confidence limit (e.g 95 $^{th}$ centile) for the dose, corresponding to an increase in adverse effects over the background level (lower limit of the experimental range). At typical experimental sample size, it was estimated to correspond to a 10% change, for instance in body weight, compared to control level. For a particular substance, the benchmark dose is calculated using the whole of the dose response relationship and a regression function is fitted to the data to determine the threshold. The main advantage of the BMD, compared to the NOAEL, is that it takes into account the whole of the dose-response curve and renders the need to extrapolate from a LOAEL (using an uncertainty factor) to a NOAEL unnecessary. This quantitative dose-response methodology also allows the use of continous or quantal data (Crump, 1984; Crump, 1995; Slob, 1999).

### II.5.4 The Critical Effect Dose (CED)

A recent probabilistic approach, defined as an extension of the benchmark dose concept, has been proposed to generate a CED from a combination of experimental dose-response data and Monte Carlo analysis (Slob and Pieters,1998). Once a regression model has been fitted to the whole of the experimental dose-response curve, the critical-effect-size can be modelled and a large number of new data sets can be generated using Monte Carlo analysis to provide an uncertainty distribution. A true no-adverse-effect-level (NAEL) in animals can then be calculated from the uncertainty distribution (Slob and Pieters., 1998; Vermeire *et al.*, 1999).

## III. Evolution and future refinements of uncertainty factors

The derivation of safe levels for thresholded chemicals in humans has relied upon the use of uncertainty factors to extrapolate from the surrogates for the threshold (NOAEL/ LOAEL/ BMD/ CED) in animals to humans and many authors have described their evolution and possible refinements (Dourson and Stara., 1983; Dourson,1996; Renwick,1999; Vermeire *et al.*, 1999).

### III.1 Safe levels of chemicals in humans and the 100-fold approach

The uncertainty factor approach has been introduced in the United States, since the mid 1950s according to the Food and Drug Administration (FDA), in response to the need to define legislative guidelines for food additives and environmental contaminants. It was

originally proposed that a human safe level "without appreciable health risk" could be derived from a NOAEL by dividing it with a safety /uncertainty factor of a 100-fold. This safe level was expressed in mg/kg of diet per day to relate it to human oral exposure (Lehman and Fitzhugh, 1954). The original investigators, Lehman and Fitzhugh, defined the 100-fold default factor and reasoned that it allowed for several areas of uncertainty (Vermeire *et al.,* 1999) :

-*Interspecies variability* (allowing extrapolation from the experimental animal to man).
-*Human variability* (taking into account sensitive individuals of the population)
-*Possible synergistic effects* (with eventual toxic outcome) of the many food additives and contaminants which man is exposed to, would be prevented.

In Europe, this scheme was adopted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and by the Joint FAO/WHO Expert on Pesticides Residues (JMPR) in 1961 and the safe level was defined as the Acceptable Daily Intake (ADI). The ADI has been defined under the instigation of Pr Rene Truhaut as "the daily intake of chemical which, during the entire life time, appears to be without appreciable risk on the basis of all known facts at the time" (Truhaut, 1991). Alternative nomenclature around the world includes the minimal risk level (MRL), the tolerable daily intake/concentration (TDI/TC), the Estimated-Concentration-of-No-Concern (ECNC), the reference dose/concentration (RfD/RfC) depending on the regulatory agency (Table 1) (IPCS, 1987; Truhaut, 1991; Rademaker and Linders, 1994; IPCS, 1994; Pohl and Abadin, 1995; Dourson, 1994; Jarabek, 1994; Meek *et al*, 1994).

**Table 1. Nomenclature for the human safe levels of exposure**

| Regulatory agency | Subthreshold dose | Reference |
|---|---|---|
| World Health Organisation (WHO) | Acceptable Daily Intake (ADI)<br>Provisional Tolerable Weekly Intake (PTWI) | IPCS, 1987<br>Truhaut, 1991 |
| Netherlands National Institute of Public Health and Environmental Protection (RIVM) | Estimated-Concentration-of-No-Concern (ECNC) | Rademaker and Linders., 1994 |
| International Programme on Chemical Safety (IPCS) | Tolerable daily Intake (TDI) | IPCS, 1994 |
| U.S Agency for toxic substances and Disease Registry (ATSDR) | Minimal Risk Level (MRL) | Pohl and Abadin., 1995 |
| U.S environmental Protection Agency (EPA) | Reference Dose (RfD)<br>Reference Concentration (RfC) | Dourson, 1994<br>Jarabek, 1994 |
| Health Canada | Tolerable Daily Intake (TDI)<br>Tolerable concentration (TC) | Meek *et al*, 1994 |

Despite these differences in nomenclature the different agencies have relied for the last forty years, upon the original 100-fold default factor approach considered to comprise two 10-fold uncertainty factors. The first ten-fold factor is considered to allow for the extrapolation between the NOAEL from a group of test animals and the NOAEL in an "average human": ***interspecies differences***. The second 10-fold factor would take into account potential sensitive subgroups of the human population and therefore shift the exposure from an average human NOAEL to a sensitive human NOAEL: ***human variability*** (IPCS, 1987; Dourson, 1996; Renwick and Lazarus., 1998). Over the last two decades a number of analyses have been performed to investigate the validity of uncertainty factors and refine them (Dourson and Stara., 1983; Hattis., 1987; Calabrese, 1985; Renwick., 1991; Renwick., 1993; Abdel-Rahman and Kadry., 1995; Naumann and Weideman., 1995; Renwick and Lazarus., 1998; Burin and Saunders., 1999).

## III.2 Refinements of the uncertainty factors

### III.2.1 Scientific basis for the refinements of the uncertainty factors

The rationale behind the refinements of the default factor approach was brought about with the evolution of the science of biochemistry and toxicology which led scientists and regulators to realise that a single default factor would not cover the differences and the complexity of the wide range of metabolic fates and mechanisms of toxicity in test laboratory species or/and in humans. A number of studies and reviews provided a basis to replace either the inter-species factor or the human variability factor to move away from default assumptions and ideally incorporate scientific data on the chemical under assessment (Hattis *et al.*, 1987; Lewis *et al.*, 1990 Renwick, 1991; Calabrese *et al.*, 1992; Renwick., 1993; Renwick., 1995; Naumann and Weidman., 1995; Dourson, 1996; Hattis, 1996; Naumann *et al.*, 1997; Renwick and Lazarus., 1998; Renwick, 1999).

### III.2.2 Early studies on interspecies differences

Dourson and Stara (1983) reviewed an analysis from Weil (1972) of acute lethality data in experimental animals after oral exposure on 490 different chemicals and concluded that for 92% of the chemicals, the 10-fold factor was adequate to allow for interspecies differences (based on a median response). This analysis also provided an indirect evidence that the 10-fold human variability was not necessarily covering the whole of the human population (including sensitive subgroups) because experimental animals are known to be less variable than humans although it did not provide a direct comparison between animals and humans (Dourson and Stara, 1983; Dourson, 1996). A comparison

of $LD_{50}$ ratios between adult and newborn mammals for 238 chemicals demonstrated that the median ratio was 2.6 and that 86% of the ratios were below 10-fold (Sheeman and Gaylor; 1990; Dourson, 1996).

### III.2.3 Early studies on human variability

Calabrese (1985) investigated human differences in capacity to metabolise xenobiotics and found that the 10-fold safety factor would protect 80-95% of the human population but the author assumed that the 10-fold accounted for the total range of human variability (Calabrese, 1985; Dourson, 1996). Hattis *et al.* (1987) examined a set of 101 individual toxicokinetic parameters for 49 compounds and concluded that 96% of the observed human variability was covered by the human default factor (Hattis *et al.,* 1987). A major criticism was that subgroups of the population were not included in the analysis (influence of genetic polymorphism, age, etc ...) and the authors speculated that a greater number of potentially sensitive individuals would probably be at risk compared to the "average healthy adult" (Hattis *et al.,* 1987; Dourson, 1996).

### III.2.4 Subdivision of the interspecies and human variability uncertainty factors

#### *III.2.4.1 Toxicological basis for the subdivision*

The basic biochemical processes that are involved in the generation of adverse effects during chemical exposure have been recognised to be dependent on two main aspects: the movement and disposition of the toxicant in the body (toxicokinetics) and the expression of its toxicity after reaching the target organ(s) (toxicodynamics) (Renwick, 1991; Renwick, 1993). The toxicokinetic aspect is dependent on the processes relating the external dose and the internal dose: absorption of the chemical from the site of administration, its distribution, metabolism and excretion. The toxicodynamic aspect is dependent upon the concentration of the proximate toxicant (parent compound, metabolite or both) in the target organ (s) and the sensitivity of the target organ (s) itself (Renwick, 1991; Renwick, 1993).

Because of the considerable lack of data on the toxicokinetics and toxicodynamics of food additives and contaminants in humans, the rationale for the human uncertainty factor has been mainly investigated using the extensive database on therapeutic drugs and kinetic parameters reflecting chronic and acute exposure have been analysed (Hattis *et al.,* 1987; Renwick., 1991; Renwick., 1993; Naumann and Weidman., 1995; Hattis, 1996; Naumann *et al.,* 1997; Renwick and Lazarus., 1998; Silvermann *et al.,* 1999; Suhn *et al.,*

1999). The parameters of choice were the clearance and area under the plasma concentration time curve (AUC) for chronic exposure since these reflect the chronic blood concentration and body burden, whereas the maximum concentration in plasma (Cmax) reflects acute exposure. For these analyses, important well recognised assumptions were that the kinetic and dynamic data followed a log-normal distribution and that the interindividual variability, observed using data for single doses would reflect chronic exposure (Renwick and Lazarus., 1998; Silverman *et al.*, 1999).

***III.2.4.2 The uncertainty factors allowing for interspecies differences and human variability can be divided into toxicokinetics and toxicodynamics***

Renwick (1991) analysed the validity of the 100-fold factor by subdividing the interspecies (x10) and the human uncertainty factor (x10) into four equal factors of $10^{0.5}$ (3.16) to allow for the toxicokinetic (x 3.16) and toxicodynamic (x 3.16) differences, which constitute both aspects of uncertainty. Subsequently, the author analysed a small database describing interspecies differences, expressed as the ratio between the animal species and humans for a particular parameter, for the main physiological processes/toxicokinetics (liver weight, liver blood flow, renal blood flow, absorption, elimination) and, for sensitivity to a chemical (toxicodynamics). The analysis of the human variability was based on a number of parameters that reflected the toxicokinetic (absorption, excretion of the parent compound in the urine and area-under-the plasma-concentration-curve) and toxicodynamic (Concentration at steady state (sedation, pain relief...)) differences between healthy adults (Renwick, 1993). From analysis of the results, the 10-fold default factors were subdivided to allow for toxicokinetic $10^{0.6}$ (x 4.0) and toxicodynamic $10^{0.4}$(x 2.5)(Renwick, 1993).

The aim of this subdivision was to allow chemical-specific toxicokinetic and mechanistic data to contribute quantitatively to the selection of the uncertainty factor (Renwick, 1993). For example, when animal or human data on a particular chemical are available in any area of uncertainty (toxicokinetics and /or toxicodynamics) the default factors can be replaced by a data-derived uncertainty factor. The principle of subdivision was accepted by the International Programme on Chemical Safety (IPCS) workshop on the derivation of guidance values, and modified to allocate an even $10^{0.5}$ (3.16) factor for toxicokinetic and toxicodynamic differences in humans whereas the interspecies uncertainty factors remained as the auhor suggested (IPCS, 1994).

**III.3 Are the toxicokinetic and toxicodynamic uncertainty factors sufficient to cover the whole of human variability?**

A recent analysis of the human uncertainty factor (Renwick and Lazarus., 1998) assessed human variability using a database including 60 therapeutic drugs subject to a range of metabolic and elimination pathways. The analysis of the kinetic data revealed a coefficient of variation of 38% for the kinetic aspect (range: 9-114%) and that 860 individuals per million would not be covered by the 3.16 toxicokinetic default factor. The variability in dynamics was 51 % (range: 8-137%) and 8323 individuals per million fell oustide the 3.16 toxicodynamic default. Importantly, the authors argued that the database on toxicodynamics included patients undergoing treatment and the disease process could have contributed to the higher variability in the reviewed responses. Overall, the analysis supported the even subdivision for kinetics and dynamics ($10^{0.5}$ or 3.16) and that more than 99.9% of the population was covered by the product of both factors (7 per million not covered).

Another recent study examined the literature available for 6 different pharmaceuticals (amiloride, enalapril, famotidine, indomethacin, lisinopril and valproic acid) using AUC and Cmax values for kinetics in different human subpopulations (mainly healthy adults and elderly). The AUC comparison between the different subpopulations and the use of the ratio of the 95$^{th}$ upper confidence limit of the subpopulation to the mean of the healthy population identified 3 cases where the 3.16 and the 10 fold factors would be inappropriate (amiloride, enalapril and lisinopril with respectively 28, 7 and 3.8 % of the population not covered) (Naumann *et al.,* 1997; Silvermann *et al.,* 1999).

Finally, an evaluation of the different interspecies and interindividual defaults with 9 pharmaceuticals (antihypertensive and antianxiety agents) metabolised by different pathways concluded that the 100-fold factor was over conservative with composite factors ranging from 9.7 for oxazepam to 96.5 for buspirone. The analysis included sensitive subgroups, like the elderly and renal disease patients but a major disadavantage was that, the variability of the healthy subgroup was not directly included in the calculation of the adjustment factor with only the mean contributing to the calculation, therefore giving an underestimation of variability (Abdel-Rahman and Kadry, 1995; Suhn *et al.*, 1999).

However, these studies provided the evidence that the toxicokinetic and toxicodynamic defaults would be conservative enough to cover the whole of the healthy adult human population, several sensitive subgroups have been identified and the current 3.16 kinetic factor could not cover human variability for CYP2D6 genetic polymorphism between extensive/poor metabolizers substrates and the differences between preterm infants and adults (theophylline) (Renwick and Lazarus, 1998).

### III.4 Future refinements of uncertainty factors

This discussion on the history of uncertainty factors highlighted the fact that there is a need to move away from default assumptions to provide more scientific data in non-cancer risk assessment. Consequently, it is critical to include knowledge on recent advances in the field of toxicology and to quantify interspecies differences and human variability in both areas of uncertainty (toxicokinetic and toxicodynamic). Such analyses can then define the magnitude of the difference between experimental animals/healthy adults and healthy adults/potentially susceptible groups of the population. Ideally, databases, describing the metabolism, toxicokinetics and/or toxicodynamics of a particular chemical under assessment in animals and/or humans can be used to provide data-derived-uncertainty factors to replace the defaults. Such data-derived-uncertainty factors can be calculated directly from the real data or using constructed models such as physiologically-based pharmacokinetic-pharmacodynamic model (PB-PK models). However, such databases on the behavior of food and environmental contaminants in humans are either extremely limited or non-existent for obvious ethical reasons.

Probabilistic approaches have emerged recently with the aim of proposing a new framework to derive acceptable human limits or reference doses (Slob and Pieters., 1998; Swartout *et al.,* 1998). Slob and Pieters (1998) proposed to quantify the uncertainties present in the various extrapolation steps required to generate human limit values using uncertainty distributions and Monte Carlo simulation (uncertainty in the calculation of the NAEL (section II) and uncertainty factors mainly). Quantal data were used to derive NAELs, using CEDs as an extension of the benchmark dose approach, and various uncertainty distributions were plotted for the different uncertainty factors: interspecies, intraspecies (human varability), sub-chronic and short term, LOAEL to NOAEL extrapolation. The main advantages of this framework is that uncertainty factors are analysed as lognormal distributions and not point estimates, however the generation of uncertainty distributions still requires default assumptions on interspecies differences and

human variability. A relatively similar approach was developed by Swartout *et al* (1998) but a major limitation, acknowledged by the authors and justified as inherent to the RfD methodology, was the assumption that the 10-fold defaults were considered as conservative enough and used to generate the distributions for interspecies differences and human variability (Slob and Pieters, 1998; Swartout *et al.,* 1998).

The size of the database on particular chemicals still remains a critical aspect to generate science-based uncertainty factors and an intermediary option in between default assumptions and data-derived-uncertainty factors has been proposed recently and constitutes the focal point of the present investigation: Categorical-default uncertainty factors (Renwick and Lazarus, 1998).

### III.4.1 Rationale for categorical default uncertainty factors

The Renwick and Lazarus (1998) paper led to the proposal that a number of categorical-default uncertainty factors could be generated for both the interspecies differences and the human variability. Toxicokinetic differences could be quantified using physiological differences between species (species specific-categorical default factors) or differences in metabolic pathways, for both interspecies and human variability (pathway-related uncertainty factors). Similarly for the toxicodynamic aspects, knowledge of class-related mechanisms of toxicity would define chemical class-effect specific uncertainty factors (Figure 1).

Such categorical-default uncertainty factors could constitute an intermediary option between the current default factors and the ideal data-derived uncertainty factors (recently renamed chemical-specific-adjustment-factors: CSAFs) (IPCS, 2001). Based on the degree of knowledge and the size of the database, this flexible option has a major advantage which is, the possible combination of kinetic and/or dynamic data-derived factors (for either interspecies, human variability or both in an ideal situation) and the use of the available default factors in the absence of detailed chemical specific data. For example, a more refined uncertainty factor can be determined when one or more aspect of uncertainty is known (pathway of metabolism, mechanisms of toxicity, etc...) and the defaults could be replaced by CSAFs. The analysis of human variability and the assumption that the data follow a lognormal distribution can provide a basis to quantify the percentage of a specific subgroup of the population covered by the current $10^{0.5}$ defaults allowing for toxicokinetic and toxicodyamic differences (Renwick and Lazarus,

1998). Depending on the particular end-point and the regulatory agency, a range of categorical uncertainty factors can then be generated to cover particular default circumstances (specific metabolic pathways/subpopulations) and a particular proportion of the population (i.e to the $95^{th}$ or $99^{th}$ centiles).

### III.4.2 Aims and presention of the present work

The present work will investigate the scientific basis for the use of the $10^{0.5}$ (3.16) uncertainty factor currently in use by regulatory agencies and accounting for human variability in kinetics. Databases describing the pharmacokinetics of substances handled by single metabolic pathways in humans are constructed and because of the lack of data on the toxicokinetics of environmental contaminants and chemicals in humans, data are mostly gathered from therapeutic drugs. The variability in kinetics is estimated for parameters reflecting steady state after oral and intravenous exposure (Clearances and Area-under-the-plasma-concentration-curve) and oral acute exposure (maximum concentration) in healthy adult volunteers and subgroups of the population (Hattis *et al.,* 1996; Renwick and Lazarus, 1998; Silvermann *et al.,* 1999; Suhn *et al.,* 1999).

The major human pathways of xenobiotic metabolism are analysed:

**I. Phase I**

CYP isoforms

-Monomorphic: CYP1A2, CYP2E1, CYP2C9, CYP 3A4.

-Polymorphic: CYP2D6 and CYP2C19.

Hydrolysis

Alcohol Dehydrogenase

**II. Phase II**

Monomorphic

Glucuronidation

Sulphation

Glycine conjugation

Polymorphic

N-acetylation

**III.Renal excretion**

Differences in internal dose and variability between healthy adults and potentially susceptible subgroups of the population (ethnic minorities, elderly, children, infants, neonates, smokers, pregnant women, patients with liver and kidney diseases) are estimated as the ratios of the mean kinetic parameters and the variability.

The concept of pathway-related uncertainty factors is then be explored as an intermediate alternative between the 3.16 kinetic default and the chemical-specific approach. Three pathway-related uncertainty factors are calculated to cover three risk management scenarios ($95^{th}$, $97.5^{th}$ or $99^{th}$ centiles) for each pathway and subgroups of the population.

### III.4.3 Plan of the thesis

The method chapter (chapter II) will describe the various criteria used to select the probe substrates, kinetic studies and subgroups of the population for each metabolic pathway together with the statistical analysis of the data and the derivation of the pathway-related uncertainty factors.

The first result chapter will present the analysis of human variability for the glucuronidation pathway which constitutes the major phase II monomorphic pathway in humans and the largest database analysed in this work. The analysis of the two major cytochrome P450 pathways will follow with the polymorphic CYP2D6 and CYP3A4 metabolism. A summary of the data gathered for all the other metabolic pathways (phase I, phase II and renal excretion) will lead to a chapter describing the use of Monte Carlo simulation to predict human variability in kinetics. Finally, the major findings of this work will be discussed in relation to their application for chemical risk assessment and future improvements of this approach will lead to a conclusion.

| | *Toxicokinetics* | *Toxicodynamics* |
|---|---|---|
| ***Interspecies*** | Chemical specific<br>i.e based on compound specific kinetic data.<br>*or*<br><br>Pathway and species specific<br>i.e based on species/pathway specific-related data (eg.CYP1A2 in rats and humans).<br>*or*<br><br>General default **4.0** | Chemical specific<br>i.e based on the compound specific dynamic data.<br>*or*<br><br>process and species specific<br>i.e based on class-related mechanistic data.<br>*or*<br><br>General default **2.5** |
| ***Inter-individual*** | Data-derived<br>i.e based on the compound specific kinetic data.<br>*or*<br><br>Pathway-related<br>i.e based on pathway-specific related data (eg.CYP1A2 in humans).<br>*or*<br><br>General default **3.16** | Data-derived<br>i.e based on compound specific dynamic data.<br>*or*<br><br>process specific<br>i.e based on class-related mechanistic data.<br>*or*<br><br>General default **3.16** |

# Chapter II Methods

This chapter will describe the general method used for the analysis of each metabolic pathway presented in the result chapters (chapter III to VII). However, any specific methodological aspects for a particular pathway will be presented in each result chapter when relevant.

## I. Metabolic pathways

Compounds handled primarily by a single metabolic pathway, were selected from the literature to built a database describing the variability in pharmacokinetics for the main human metabolic pathways (phase I, phase II and renal excretion):

**Phase I metabolism**

-Alcohol Dehydrogenase

-Cytochromes P450 (CYP isoforms)

CYP1A2, CYP2C9, CYP2C19 (polymorphic), CYP2D6 (polymorphic), CYP2E1, CYP3A4.

-Hydrolysis

**Phase II metabolism**

-Glucuronidation

-Glycine Conjugation

-N-Acetyltransferases (polymorphic)

-Sulphation

**Renal excretion**

## II. Literature search

Literature searches were carried out using BIDS-EMBASE (1980- December 2000), MEDLINE (1966-December 2000) and TOXLINE (1966- December 2000) to select therapeutic drugs as probe substrates for each metabolic pathways in humans.

The compounds and kinetic studies from different human subpopulations were selected and abstracted according to the following criteria:

-Absorption

-Metabolism

- Quality of the kinetic study

## II.1 Absorption

Each selected probe substrate was well absorbed from the gastrointestinal tract after oral administration (>90%) so that the interindividual variability in the kinetics did not arise from absorption but from the enzyme involved in the metabolism of the compound.

## II.2 Metabolism

Substrates were selected on the basis that the metabolic pathway was their main primary route of elimination in healthy adult volunteers with between 60-100% of an oral dose excreted as relevant metabolites (in the urine/faeces). For compounds handled by CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) the metabolism criteria were validated for substrates which were oxidised primarily by a particular isoform (*in vitro* and *in vivo* data). Probe substrates for compounds handled by other pathways were selected on the basis that the parent compound was excreted as the relevant conjugate(s) (Glucuronidation, Glycine conjugation, Sulphation, N-acetyl-transferases) or particular metabolite(s) (hydrolysis and alcohol dehydrogenase) in the urine and/or the faeces (>60-100% of an oral dose). For the renal excretion pathway, the latter criterion was validated for substrates which were recovered in the urine as the parent compound (>60-100% of an oral dose).

For all pathways, compounds with poor absorption but relevant metabolism and kinetic data (60-100% dose recovered as metabolites/parent compound for the particular pawthay), were selected for their intravenous data.

## II.3 Quality of the kinetic study

For each compound, the literature was screened for all the studies available from BIDS, MEDLINE and TOXLINE and from the bibliography of each paper to avoid omitting studies not cited in the databases. Publications describing the kinetics of the single compound were abstracted first and data describing the interactions between the compound and another compound were also abstracted using only the control column of

data. For compounds with a very large database (>2500 hits: caffeine, theophylline: (CYP1A2 pathway) and paracetamol: (glucuronidation), publications describing the oral and intravenous kinetics of the single compound in healthy adults were abstracted and the author stopped abstracting after a minimum number of 20 publications and 200 individuals (for all parameters and routes) was reached.

For each probe substrate, the kinetic data were selected according to four main criteria:

1.The study used sensitive analytical techniques (preferably HPLC, gas chromatography, etc…).

2. The minimum number of subjects used in the study was 3 (see below for data analysis).

3. The study published a mean (X) and reliable estimates of variability (standard deviation (SD) and/or standard error of the mean (SEM) and/or coefficient of variation (CV)).

4. The study was only published once: duplicate results from different publications when discovered, even with different orders of authorship, were only reported once in the tables (as the publication published first historically) and only contributed once to the analysis.

Any studies failing to meet these four criteria were rejected.

All individual studies were abstracted and filed using hand-written forms. The meta-analysis was carried out for each publication/compound/pathway for the normally distributed data and the whole database was recalculated independently for the lognormal transformation of the data.

All individual publications were rechecked against the hand-written forms before submission of the CYP1A2 and glucuronidation papers.

In addition, random samples ($20<n<50$) of the original publications were also rechecked for all pathways. Finally, the data transcription was rechecked for all metabolic clearances and all data for phenotyped individuals for the CYP2D6/CYP2C19/NAT pathways.

## III.Data analysis

### III.1 Ranking of the data

Two different analyses were undertaken; intravenous Clearances (CL), oral Clearances (CL/F) and area-under-the-plasma-concentration-curve for both routes (AUC) were assessed as markers of the internal dose during chronic exposure, and the maximum plasma concentration (Cmax) as a marker following acute exposure.

The kinetic parameters representing chronic exposure were ranked according to the following priorities:

1. Data for oral kinetics are relevant to the usual route of human exposure to environmental contaminants and were abstracted primarily. Intravenous data were selected when data for the oral route were not available.

2. Metabolic clearance ($mlmin^{-1}kg^{-1}$or $mlmin^{-1}$) values were abstracted independently of total clearances because these would reflect the true variability in each metabolic pathway. The variability in metabolic clearances was compared with the variability in total plasma clearance for the selected probe substrates in order to validate the metabolism criteria.

3. The metabolic or total plasma clearance adjusted to body weight (CLm; CL/F; CL) were abstracted in preference of the metabolic or total plasma clearance not adjusted to body weight (CLm; CL/F; CL); abstracted in preference of the AUC. For each study, only the AUC to infinity (or the AUC corresponding to a minimum of 5 half lives) was sampled for which one can assume that over 99% of the compound has been eliminated.

4. The highest ranked (priority) estimate was used for each subject per study so that one subject contributed to only one parameter/route to each analysis.

The maximum concentration after oral dosing (Cmax) was abstracted on every occasion as a marker of acute exposure and independently of markers of chronic exposure.

## III.2 Body weight Adjustement

To allow comparisons between subgroups of the population, the mean AUC and Cmax values were normalised to the total dose (mg) and the dose adjusted to body weight ($mgkg^{-1}$) without affecting the variability of the original data. Body weight corrections were carried out using the available mean body weight, or 70 kg (males), 60 kg (females), 65 kg (mixed males and females) when body weight data were missing from the kinetic study.

## III.3 Statistical analysis of kinetic studies

### III.3.1 Statistical assumptions

For all kinetic parameters, the data were presented in each original publication as following a normal distribution with a mean (X), standard deviation (SD), standard error of the mean (SEM from which the SD can be calculated as $SEM.\sqrt{n}$) and coefficient of variation ($CV_N$). However, kinetic data are generally recognised to be lognormally

distributed (Naumann and Weidemann, 1995; Hattis and Minkowitz 1996; Naumann *et al.,* 1997; Renwick and Lazarus, 1998; Dorne *et al.,* 2001a, Slob., 1986).

***III.3.1.1.1 Why would kinetic data follow a lognormal distribution ?***

Lognormal distributions constitute a multiplicative model i.e a large set of observations are affected by multiplicative random factors whereas a large set of observations affected by additive random factors would follow a normal distribution (Saltzman, 1997). Moreover, the lognormal distribution has no negative values whereas the normal distribution can theoretically have negative values. For example, given a drug clearance of a mean of a 100 and a standard deviation of 70, one would find many negative values which is physiologically impossible. The description of the data using the lognormal distribution including the geometric standard deviation would not show negative values and would be more relevant to kinetics and physiology (Saltzman, 1997). Efforts have been made to replace the use of the additive model for the multiplicative model in ecology and biology (Slob, 1986) and many biological phenomena have been shown to follow the lognormal distribution including body weights, particle sizes, tolerance to drugs, systolic and diastolic blood pressure (Aitchison and Brown, 1966, Slob, 1986). Generally speaking, Slob (1986) argued that size, chemical and time measurements would follow the multiplicative lognormal model rather than the additive normal one. However, most statistical textbooks describe the normal distribution in detail and length and in all the examples discussed; data with a small coefficient of variation were reported (4 to 12%) and with such small CVs, both normal and lognormal distribution would be virtually identical.

From these assumptions both distributions were analysed to compare differences in estimates. For the lognormal data, a transformation of the normal data from individual kinetic studies on the logscale was required to derive the geometric mean (GM), geometric standard deviation (GSD) and a coefficient of variation ($CV_{LN}$) (rather than arithmetic mean (X), standard deviation (SD) and coefficient of variation ($CV_N$).

### III.3.2 Analysis of individual kinetic studies

#### *III.3.2.1 Normal distribution*

The analysis of variability for the normal distribution uses the coefficient of variation ($CV_N$) as the ratio between the standard deviation (SD) and the mean (X) (equation (1) (Armitage and Berry, 1994).

$$CV_N = \frac{SD}{X} \times 100 \qquad (1)$$

#### *III.3.2.2 Lognormal distribution*

The analysis of variability for the lognormal distribution required the convertion of the normal data from individual kinetic study (arithmetic mean and standard deviation) into a geometric mean (GM), geometric standard deviation (GSD) using equations 2 and 3 (Aitchison and Brown, 1966). Clearly, the individual $CV_{LN}$ can be back calculated from the GSD using equation 4.

$$GM = \frac{X}{\sqrt{(1 + CV_N^2)}} \qquad (2)$$

$$GSD = \exp\{\ln\sqrt{(1 + CV_N^2)}\} \qquad (3)$$

$$CV_{LN} = \sqrt{\exp(\sigma^2) - 1} \quad with \quad \sigma^2 = \ln(GSD) \qquad (4)$$

Importantly for the analysis of both distributions, the coefficient of variation represented inter-individual differences rather than measurement errors; clearance (CL) and AUC are derived from multiple measurements so that random analytical errors would not greatly influence the coefficients of variation of CL or AUC. Systematic errors would be minimised by the use of data from a number of different studies and data were pooled using the weighted mean/weighted standard method.

### III.3.3 Weighted analysis

The results of each selected kinetic study were combined for each compound, parameter (CL $mlmin^{-1}kg^{-1}$, Cl $mlmin^{-1}$, AUC and Cmax), and subpopulation using the weighted mean method for both distributions (Armitage and Berry, 1994). The weights were determined by the number of subjects in each study for both distributions (equation 5-8).

### *III.3.3.1 Normal distribution*

The mean and standard deviation (X and SD respectively) were combined to give a weighted mean ($X_w$) and weighted standard deviation ($SD_w$) for each compound using equations (1) and (2) (Armitage and Berry, 1994).

$$X_W = \sum \frac{X \times n}{n} \qquad (5)$$

$$SD_W = \frac{\sum (n-1) \times SD^2}{\sum n - N} \qquad (6)$$

From $X_w$ and $SD_w$, the weighted coefficient of variation ($CV_N$) was calculated using equation 1 applied to weighted data.

$$CV_N = \frac{SD_w}{X_w} \times 100 \qquad (7)$$

### *III.3.3.2 Lognormal distribution*

The weighted geometric mean ($GM_w$), weighted geometric standard deviation ($GSD_w$), and weighted CV ($CV_{LN}$) were derived from the normal data transformed on the logscale using equations 8 and 9.

$$GM_W = \sum \frac{GM \times n}{n} \qquad (8)$$

$$GSD_W = \frac{\sum (n-1) \times GSD^2}{\sum n - N} \qquad (9)$$

From the weighted geometric standard deviation ($GSD_w$), the coefficient of variation ($CV_{LN}$) was calculated using equation 4 applied to the weighted data.

$$CV_{LN} = \sqrt{\exp(\sigma_w{}^2) - 1} \quad with \quad \sigma_w{}^2 = \ln(GSD_w) \qquad (10)$$

### III.3.4 Variation between studies

The variation between studies was calculated for each compound (when data were available for more than one study per parameter) as the ratio between the individual study

(GM) and the overall weighted value ($GM_w$), for both the weighted geometric mean ($VBS_{GM}$) and weighted coefficient of variation ($VBS_{CV}$) (11 and 12).

$$VBS_{GM} = \frac{GM}{GM_w} \quad (11)$$

$$VBS_{CV} = \frac{CV_{LN}}{CV_{LN_w}} \quad (12)$$

Bubble graphs for each pathway that included all kinetic parameters for healthy adults, were plotted with the size of the bubble proportional to the study group size (n), and with the overall weighted value for each compound/ parameter normalised to 1.

**III.3.5 Analysis of potential sensitive subgroups**

Kinetic data describing the pharmacokinetics of pathway-specific probe substrates in different human subpopulations were limited, and the analysis had to be restricted to those parameters and groups given in the publications.

Four main subgroups have been investigated:

1. Healthy adults for whom a phenotype has been given (polymorphic CYP pathways : CYP2D6 and CYP2C19 (extensive and poor metabolisers) and N-acetyl-tranferases (fast and slow acetylators)).

2. Ethnic minorities (mainly Asian and African healthy adults) to quantify inter-ethnic differences for the metabolic pathways.

3. Effect of age (elderly (>70 years), neonates (< 1 month), infants (1 month to 1 year), children (1 year to 16 years)).

4. Effect of disease: Patients with liver or kidney disease were compared to healthy adults to investigate the influence of liver and renal dysfucnction on xenobiotic metabolism and kinetics since the liver and the kidney are the main organs involved in xenobiotic elimination.

Comparisons between healthy adults and each subpopulation for the lognormal data aimed

to quantify the difference in the internal dose for both chronic (AUC and CL) and acute markers (Cmax) of exposure. The ratio of the geometric mean value (Ratio H/S) for the kinetic parameters (CL, AUC and Cmax) in healthy adults and in the subpopulation, and the ratio of the variability (Ratio $CV_{LN}$) were calculated. The mean ratio (Ratio H/S) was expressed as the magnitude of any increase in the internal dose in the subpopulation compared to healthy adults (ie ratio of 2 would arise from a 2-fold lower clearance or 2-fold higher AUC or Cmax in the subgroup). Similarly, the variability ratio (Ratio $CV_{LN}$) was expressed as the magnitude of any increase in the subgroup variability compared to healthy adults (a ratio of 2 would indicate a 2-fold greater variability in the subgroup).

## III.4 Overall pooled analysis

### III.4.1 Healthy adults

The weighted analysis for normal and lognormal data provided an estimation of a parameter-specific variability for each probe substrate (Weighted $CV_N$ and $CV_{LN}$). For each metabolic pathway, the parameter-specific variability (clearance adjusted to body weight, clearance, AUC (oral and intravenous route) and Cmax (oral route)) was derived from all the drugs.
Each drug had the same weighting of 1 in the overall parameter-specific CVs to avoid the bias of the result with a compound for which a large database was available and to obtain an overall CV based on different substrates (different affinities, different binding sites on the enzyme etc...). The overall CV based on the normal data were derived as an arithmetic average whereas the CV based on the lognormal data were averaged on the log-scale (the $CV_{LN}$ as ratios are lognormally distributed).

### III.4.2 Subgroups of the population

The overall $CV_{LN}$, geometric mean ratios and variability ratios were derived for each subgroup using the same method than that for healthy adults based on the fact that these ratios were all lognormally distributed (average calculated on the logscale).

## III.5 Derivation of pathway-related default uncertainty factors

Pathway-related default uncertainty factors necessary to cover the $95^{th}$, $97.5^{th}$ and $99^{th}$ centiles of the healthy adult population were calculated for each kinetic parameter assuming a lognormal distribution.

### III.5.1 Healthy adult data

The pathway-related default uncertainty factors were calculated using the parameter-specific (clearances ($mlmin^{-1}$, $mlmin^{-1}kg^{-1}$), AUC and Cmax) geometric standard deviation for the healthy adults associated with an arbitray geometric mean of 1 (since the uncertainty factors for the healthy adults were calculated on the basis of the overall variability for a pathway and not the mean values od each drug). Any uncertainty factor corresponding to a particular $n^{th}$ centile can then be calculated using the corresonding Zscores for each percentile and three sets of uncertainty factors were calculated with Z=1.64, 1.95 and 2.33 for the $95^{th}$, $97.5^{th}$ and $99^{th}$ percentile respectively.

$$n^{th}{}_{percentile} = \left(\ln(GSD) x Zscore\right) \qquad (13)$$

The uncertainty factors (UFs) for each kinetic parameter were simply the antilog of the percentile (in this case ln, the exponential). This method has also been described previously (Slob, 1994).

$$UF = e^{\left(n^{th}\,percentile\right)} \qquad (14)$$

For each percentile, the parameter-specific UFs for parameters reflecting chronic exposure (Clearances and AUC) were pooled using the weighted mean method to derive the overall pathway-related default uncertainty factors (II.3.3). For Cmax reflecting acute exposure, the uncertainty factor was derived directly from equation 13 and 14.

### II.5.2 Subgroup data

The uncertainty factors for each subgroup were calculated using the same method than previously described for healthy adults. However the magnitude of the difference in internal dose between each subgroup and the healthy adults (ratio of geometric means (ratio GM)) was also included in the calculation to include both the difference in internal dose and the subgroup specific variability.

$$n^{th}{}_{percentile} = \left(\ln(GSD) x Zscore + \ln(ratioGM)\right) \qquad (15)$$

The uncertainty factor (UF) for the subgroup was simply the exponential of the percentile as described in equation 14. For subgroups that included more than one parameter for one route, the UFs were also pooled using the weighted mean method.

# Chapter III Human Variability in Glucuronidation in relation to uncertainty factors for risk assessment

## I. Introduction

The mammalian uridine 5'-diphosphate (UDP) glucuronosyltransferases (UGT) enzyme superfamily consists of two main gene families (UGT1A and UGT2B) with up to 50 isoforms. Both families play a crucial role in the metabolism, activation and detoxification of drugs, xenobiotics and endogenous substrates such as bile acids and oestrogens. The enzymes catalyse the transfer of glucuronic acid from UDP-glucuronic acid to the substrate functional group (hydroxyl, carboxyl, amino or sulfhydryl) which increases the polarity and water solubility of potentially toxic lipophilic compounds resulting in their excretion via the kidneys (Burchell *et al.*, 1995; de Wildt *et al.*, 1999; Pritchard *et al.*, 1993).

The UGT1 family has been shown to conjugate phenols and bilirubin, with 5 main isoforms expressed in the liver (1A1, 1A3, 1A4, 1A6 and 1A9), and 3 extrahepatic isoforms (1A7, 1A8 and 1A10) expressed in the intestine, stomach and gall bladder (Burchell *et al.*, 1995; Radominska-Pandya *et al.*, 1999). In terms of xenobiotic metabolism, the 1A1 isoform catalyses the glucuronidation of octyl and propyl gallate via their hydroxy group and after hydrolysis. The 1A4 covers a wide range of substrates such as 2-aminofluorene, benzidine and imipramine via glucuronidation of an amino group, the 1A9 conjugates paracetamol and phenols such as 4-t-butylphenol, 4-methylumbelliferone. The 1A10 isoform expressed in the stomach is responsible for the glucuronidation of benzopyrene metabolites after activation via the Cytochrome P 450 system.

The UGT2 family is divided into three subfamilies 2A, 2B and 2C with the most abundant 2B subfamily responsible for conjugation of steroids and carboxylic acids (Burchell *et al.*, 1995; de Wildt *et al.*, 1999; Pritchard *et al.*, 1993; Radominska-Pandya *et al.*, 1999).

Relevant examples of xenobiotics handled by the major hepatic UGT2B7 isoform are morphine, naloxone, codeine and other opioids and carboxylic acids (planar phenolic NSAIDs) (Burchell *et al.*,1995; de Wildt *et al.*,1999; Pritchard *et al.*,1993; Radominska-Pandya *et al.*,1999).

From this body of evidence, glucuronidation is a major pathway for the metabolism of food additives, plant xenobiotics and environmental contaminants, especially compounds containing a phenolic/carboxylic functional group. Therefore, understanding inter-individual differences in glucuronidation will provide a basis to develop pathway–related uncertainty factors for xenobiotics handled by this pathway. This chapter will therefore focus on the analysis of the human kinetic variability in the glucuronidation pathway using probe substrates to quantify interindividual variability in the healthy adult population and the magnitude of any differences between healthy adults and potentially sensitive subgroups. From these analyses, pathway-related default uncertainty factors to cover centiles of each available subgroup of the population ($95^{th}$, $97.5^{th}$ and $99^{th}$ centile) will be calculated.

## II. Methods

The literature was searched with online databases: BIDS-EMBASE (1980 to December 2001), MEDLINE (1966 to December 2000) and TOXLINE (1966 to December 2000) to select substrates. The methods employed in this chapter are described in chapter II.

## III. Results

### III.1 Probe substrates

Probe substrates were selected on the basis that glucuronidation is the major pathway of primary metabolism, i.e. >60% is excreted as the glucuronide. The probe substrates were AZT, carprofen, chloramphenicol, clofibric acid, diflunisal, lamotrigine, lorazepam, lormetazepam, ketoprofen and its R- and S- enantiomers, morphine, oxazepam, paracetamol, zileuton and zomepirac. The different substrates covered a wide range of structures and three distinct functional sites for glucuronidation; hydroxy-, carboxy- and secondary amino- groups. Metabolism data after oral or intravenous administration to healthy adult volunteers are summarised in Table 1. Most compounds were totally absorbed from the intestine with the exception of morphine, and only intravenous data were considered for this substrate.

**Table 1. Metabolism data for the glucuronidation probe substrates in healthy adult volunteers [a]**

| Drug | References for % | n | Dose (mg) | Route | % glucuronide in urine* | UGT isoform | References for isoform of enzyme |
|---|---|---|---|---|---|---|---|
| ***Hydroxy glucuronide (R-OH)*** | | | | | | | |
| AZT | Stagg et al., 1992 | 3 | 100 | PO | 75±6.5 | UGT2B7 | Barbier *et al.*, 2000 |
| Chloramphenicol | Uesugi et al., 1974 | 4 | 500 | PO | 68 (64-77) | UGT2B7 (minor) | Jin *et al.*, 1993 |
| Diflunisal | Verbeeck et al., 1990 | 6 | 250-500 | PO | 30 | UGT2B7, (UGT1A8)[I], UGT1A6, multiple | Cheng *et al.*, 1999; Jin et al., 1993, Sabolovic *et al.*, 2000 |
| Morphine | Hasslestrom and Sawe, 1993 | 7 | 5 | IV | 57 (**M3G**) | UGT2B7, (UGT1A8)[I] | Coffman *et al.*, 1997 |
| Morphine | Hasslestrom and Sawe, 1993 | 7 | 5 | IV | 10 (**M6G**) | UGT2B7, (UGT1A8)[I] | Coffman *et al.*, 1997 |
| Oxazepam | Sonne et al., 1988 | 6 | 15 | IV | 79 ± 4 | UGT2B7 | Patel *et al.*, 1995 |
| Paracetamol | Coldwell et al., 1976 | 5 | 650 | PO | 65[Δ] | UGT1A6, UGT1A9 | Bock *et al.*, 1993 |
| Zileuton | Wong et al., 1995 | 14 | 200 | PO | 73-76 | Not known | |
| Lorazepam | Herman et al., 1989 | 7 | 2 | PO | 72±12 | UGT2B7 | Miners *et al.*, 1997, de Wildt *et al.*, 1999 |
| Lormetazepam | Huempel et al., 1980 | 6 | 1 | IV | 73±9 | Not known (UGT2B7 like lorazepam?) | |
| ***Carboxy glucuronide (R-COOH)*** | | | | | | | |
| Carprofen | Ray and Wade, 1982 | 3 | 100 | PO/IV | 63±2 | UGT2B7, UGT1A6, UGT1A3, multiple | Terrier *et al.*, 1999, Sabolovic *et al.*,2000 |
| Clofibric acid | Emudianughe et al., 1983 | 5 | 500 | PO | 77 | UGT2B7 | Terrier *et al.*, 1999; Jin *et al.*, 1993; Sabolovic *et al.*, 2000 |
| Diflunisal | Verbeeck et al., 1990 | 6 | 250-500 | PO/IV | 47-48 | UGT2B7, (UGT1A8)[I], multiple | Jin *et al.*, 1993, Cheng *et al.*, 1999; Sabolovic *et al.*, 2000 |
| Ketoprofen | Houghton et al., 1984a | 9 | 200 | PO | 84[Δ] | UGT2B7, UGT1A6, UGT1A3, multiple | Terrier *et al.*, 1999; Jin *et al.*, 1993; Sabolovic *et al.*, 2000 |
| R-Ketoprofen | Rudy et al., 1998 | 25 | 25-100 | PO | 62-66 | UGT2B7, UGT1A6, UGT1A3, multiple | Terrier *et al.*, 1999; Jin *et al.*, 1993 Sabolovic *et al.*, 2000 |
| Zomepirac | O'Neill et al., 1982 | 5 | 200 | PO | 72-83 | UGT2B7, multiple | Jin *et al.*, 1993, Sabolovic *et al.*, 2000 |
| ***Secondary amino glucuronide ($R_2$-NH)*** | | | | | | | |
| Lamotrigine | Cohen et al., 1987 | 10 | 120 | PO | 63 | UGT1A4 | Magdalou *et al.*, 1992; Green and Tephly, 1998; Hiller *et al.*, 1999 |

[a] **n** number of subjects; **PO** oral administration; **IV** intravenous administration; * Expressed as the percentage of the dose recovered as the glucuronide in the urine; [Δ] Expressed as the percentage of the total amount recovered in the urine; **M3G** Morphine 3 glucuronide; **M6G** Morphine 6 glucuronide; [I] intestinal UGT isoform probably playing a minor role in the glucuronidation.

Morphine and AZT have a high clearance and therefore in vivo variability will reflect differences in liver blood flow, as well as enzyme activity. A more extensive review of the metabolism of each compound in humans and animals (mouse, rat, rabbit and dog) has been published (Walton *et al.*, 2001).

## III.2 Kinetic data for glucuronidation probe substrates in healthy adults

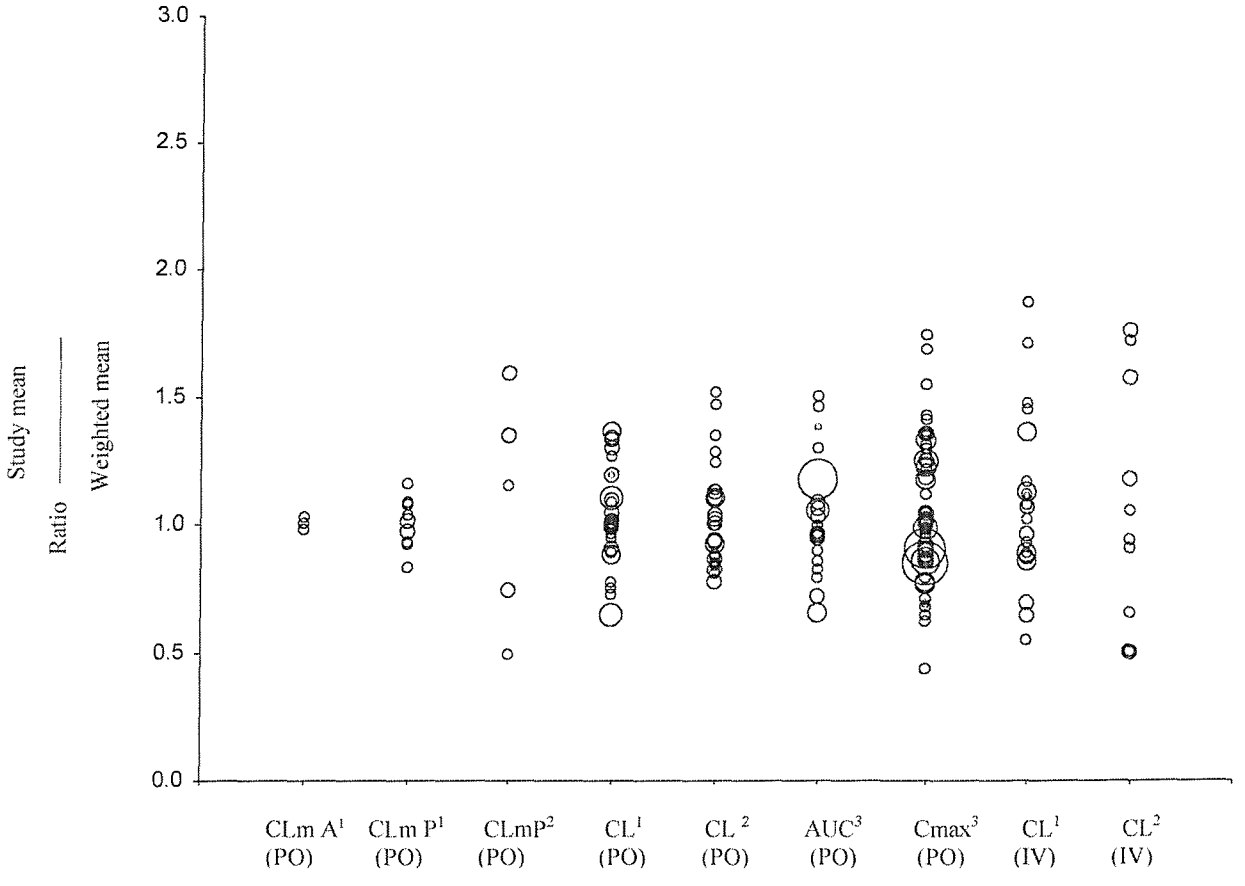
The available parameters for each probe substrate after oral and intravenous administration to healthy adult volunteers were analysed and tabulated as clearance adjusted to body weight, clearance, AUC and Cmax adjusted to body weight.

### III.2.1 Variability between studies

All compound-specific kinetic parameters were pooled using the reported means and standard deviations in individual studies to derive a weighted mean, a weighted standard deviation and a weighted coefficient of variation (CV). The variation between studies was calculated for each compound with data from more than one study per parameter, as the ratio between the individual study and the overall weighted value, for both the mean parameter estimate and the CV. Figures 1 and 2 give the data for all the kinetic parameters (clearances, AUC and Cmax) as bubble graphs with the size of the bubble proportional to the study group size (n), and with the overall weighted value for each compound normalised to 1.

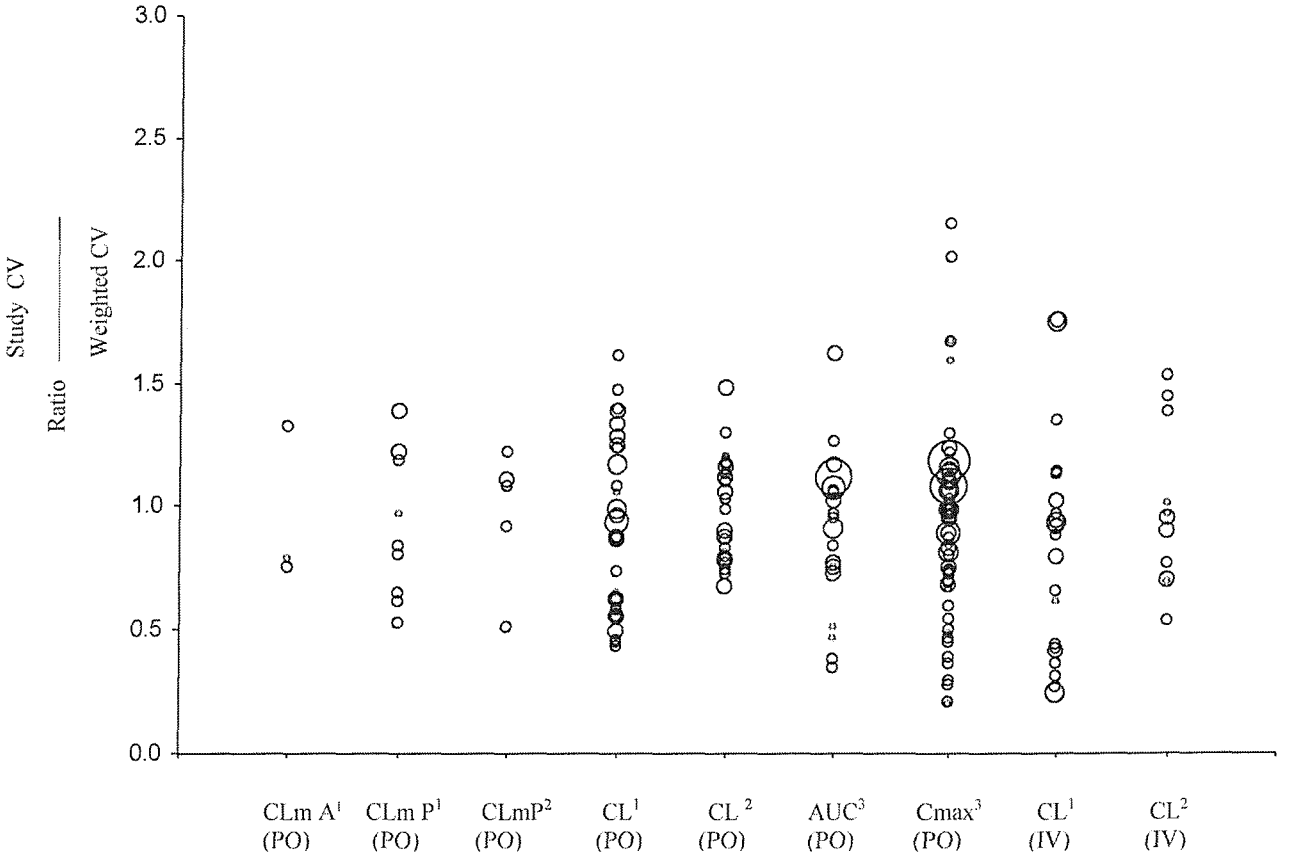
Figure 1 shows that the mean results from individual studies were mostly within 20-30% of the overall weighted mean, and that the maximum differences were about 50%. Figure 2 shows that the inter-study differences in the CV were mostly within 30-40% of the overall weighted CV, and that greater differences were found for smaller studies (Cmax and intravenous clearance adjusted to body weight). These analyses support the need to use weighted means for analysis of the database, rather than simply taking the unweighted mean of the different studies.

**Figure 1. Inter-study variation in kinetic parameters for glucuronidation probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**




The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; ; CLmA[1] Metabolic Clearance for the acyl glucuronide ($ml.min^{-1}kg^{-1}$); CLmP[1] Metabolic Clearance for the phenolic glucuronide ($ml.min^{-1}kg^{-1}$); CLm P[2] Metabolic Clearance for the phenolic glucuronide ($ml.min^{-1}$); CL[1] Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); CLmA[1] (PO)-data for diflunisal (3 studies); CLm P[1] (PO)- data for diflunisal (2 studies), paracetamol (7 studies); CLmP[2] (PO)-data for paracetamol (3 studies), propranolol (2 studies); CL[1] (PO)-data for AZT (8 studies), ketoprofen (2 studies), Lamotrigine (2 studies), Lorazepam (2 studies), Oxazepam (6 studies), Paracetamol (9 studies) and Zomepirac (2 studies); CL[2](PO) -data for AZT (4 studies), diflunisal (2 studies), Lamotrigine (2 studies), Lorazepam (2 studies), Lormetazepam (2 studies), Paracetamol (2 studies), Zileuton (9 studies); AUC[3]-data for carprofen (3 studies), Ketoprofen (2 studies), Lamotrigine (2 studies), Lorazepam (4 studies), Oxazepam (4 studies), Paracetamol (6 studies), Zomepirac (2 studies); Cmax[4]-data for AZT (9 studies), Carprofen (3 studies), Diflunisal (2 studies), Ketoprofen (3 studies), Lamotrigine (4 studies), Lorazepam (7 studies), Oxazepam (5 studies), Paracetamol (5 studies),R-Ketoprofen (studies), Zileuton (9 studies), Zomepirac (4 studies); CL[1] (IV) -data for morphine(13 studies), Lorazepam (8 studies); CL[2](IV) -data for Ketoprofen (4 studies), Morphine (7 studies).

**Figure 2. Inter-study variation in kinetic parameters for glucuronidation probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**




The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; ; CLmA[1] Metabolic Clearance for the acyl glucuronide ($ml.min^{-1}kg^{-1}$); CLmP[1] Metabolic Clearance for the phenolic glucuronide ($ml.min^{-1}kg^{-1}$); CLm P[2] Metabolic Clearance for the phenolic glucuronide ($ml.min^{-1}$); CL[1] Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); CLmA[1] (PO)-data for diflunisal (3 studies); CLm P[1] (PO)- data for diflunisal (2 studies), paracetamol (7 studies); CLmP[2] (PO)-data for paracetamol (3 studies), propranolol (2 studies); CL[1] (PO)-data for AZT (8 studies), ketoprofen (2 studies), Lamotrigine (2 studies), Lorazepam (2 studies), Oxazepam (6 studies), Paracetamol (9 studies) and Zomepirac (2 studies); CL[2](PO) -data for AZT (4 studies), diflunisal (2 studies), Lamotrigine (2 studies), Lorazepam (2 studies), Lormetazepam (2 studies), Paracetamol (2 studies), Zileuton (9 studies); AUC[3]-data for carprofen (3 studies), Ketoprofen (2 studies), Lamotrigine (2 studies), Lorazepam (4 studies), Oxazepam (4 studies), Paracetamol (6 studies), Zomepirac (2 studies); Cmax[4]-data for AZT (9 studies), Carprofen (3 studies), Diflunisal (2 studies), Ketoprofen (3 studies), Lamotrigine (4 studies), Lorazepam (7 studies), Oxazepam (5 studies), Paracetamol (5 studies),R-Ketoprofen (studies), Zileuton (9 studies), Zomepirac (4 studies); CL[1] (IV) -data for morphine(13 studies), Lorazepam (8 studies); CL[2](IV) -data for Ketoprofen (4 studies), Morphine (7 studies).

### III.2.2 Interindividual variability

All tables (Tables 2-13) give the weighted mean analysis for normal and lognormal data. Interindividual differences are described as the coefficient of variation for both distribution ($CV_N$ for normal and $CV_{LN}$ for lognormal). In the text, the coefficients of variation are described by a single value if this was identical for the two distributions but if differences are observed both values are given. The majority of studies did not define the ethnic origin of the subjects, but based on the origins of the data and location of the studies they can be assumed to be Caucasian. Studies reporting data for non-Caucasians were considered separately (see later).

#### *III.2.2.1 Metabolic clearances*

All the tables give the weighted mean analysis for normal and lognormal data. Interindividual differences are described as the coefficient of variation for both distributions ($CV_N$ for normal and $CV_{LN}$ for lognormal). In the text, the coefficients of variation are described by a single value representing both distributions, unless differences are observed in which case both values are described. The majority of studies did not define the ethnic origin of the subjects, but based on the origins of the data and location of the studies they can be assumed to be Caucasian. Studies reporting data for non-Caucasians were considered separately (see later).

Data on metabolic clearance specifically *via* glucuronidation were available for several major glucuronidation substrates: diflunisal, paracetamol, morphine and zomepirac, and also for nalmefene and propranolol, which undergo glucuronidation to an extent that does fulfil the metabolism selection criteria. After intravenous dosing of nalmefene, 33-47% of the dose was recovered as the phenolic glucuronide (Dixon *et al.,* 1986), whereas 17% of an oral dose of propranolol (80mg) was recovered in the urine as the glucuronide (Walle *et al.,* 1996).

After oral administration to healthy adults, the variability in metabolic clearance by glucuronidation of organic acids (carboxyl- group: acyl glucuronide) was 39% (2 compounds, 4 publications and 27 subjects) and was 29% for alcohols and phenols (4 compounds, 14 publications and 141 subjects) (Table 2). The overall variability irrespective of the chemical group undergoing glucuronidation and distribution was 32% (5 compounds, 18 publications and 168 subjects) (Table 2). Intravenous data were limited to compounds with a hydroxyl- group, and the variability (24%) (3 compounds, 3 publications and 38

subjects) was similar to that for oral data. Metabolic clearance data were not available for the glucuronidation of secondary amines.

**Table 2. Metabolic clearances for the glucuronidation pathway of elimination in healthy adult volunteers [a].**

| Drug (Clearance unit) | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| ***Acyl glucuronide*** | | | | | ***Oral Administration*** | | | | |
| Diflunisal ($ml min^{-1}$) | 3 | 3[1] | 17 | 5.1 | 1.2 | 22 | 5.0 | 1.2 | 22 |
| Zomepirac ($ml min^{-1} kg^{-1}$) | 1 | 1[2] | 10 | 2.2 | 1.2 | 55 | 1.9 | 1.7 | 55 |
| ***Hydroxy glucuronide*** | | | | | | | | | |
| Paracetamol ($ml min^{-1} kg^{-1}$) | 7 | 4[3] | 60 | 3.3 | 0.83 | 25 | 3.1 | 1.3 | 25 |
| Propranolol ($ml min^{-1} kg^{-1}$) | 1 | 1[4] | 7 | 8.2 | 1.2 | 15 | 8.1 | 1.2 | 15 |
| Diflunisal ($ml min^{-1}$) | 3 | 3[5] | 17 | 3.5 | 0.71 | 20 | 3.4 | 1.2 | 19 |
| Paracetamol ($ml min^{-1}$) | 3 | 3[6] | 26 | 170 | 62 | 37 | 140 | 1.4 | 34 |
| Propranolol ($ml min^{-1}$) | 2 | 2[7] | 18 | 280 | 140 | 51 | 240 | 1.6 | 47 |
| R-Propranolol ($ml min^{-1}$) | 1 | 1[8] | 13 | 390 | 79 | 27 | 380 | 1.2 | 20 |
| ***Hydroxy glucuronide*** | | | | | ***Intravenous Administration*** | | | | |
| Morphine (as 3-G) ($ml min^{-1} kg^{-1}$) | 1 | 1[9] | 7 | 12 | 3.3 | 27 | 11.6 | 1.3 | 28 |
| Nalmefene ($ml min^{-1} kg^{-1}$) | 1 | 1[10] | 12 | 4.4 | 1.2 | 27 | 4.2 | 1.3 | 27 |
| Paracetamol ($ml min^{-1} kg^{-1}$) | 1 | 1[11] | 19 | 2.5 | 0.44 | 18 | 2.5 | 1.2 | 18 |

[a]**Ns** number of studies; **Np** number of publications; **n** number of subjects; $\mathbf{X_w}$ weighted mean; $\mathbf{SD_w}$ weighted standard deviation; $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Loewen et al., 1988, Verbeeck et al., 1990, McDonald et al., 1992; [2]Witassek et al., 1983; [3]Miners et al., 1983 (2), Miners et al., 1984 (2), Miners et al., 1988, Osborne et al., 1991(2);[4]Walle et al., 1986;[5]Loewen et al., 1988, Verbeeck et al., 1990, McDonald et al., 1992; [6]Miners et al., 1986, Baraka et al., 1990, Rumble et al., 1991;[7]Walle et al., 1996, Zhou et al., 1989); [8]Sowinski et al., 1996; [9] Hasselstrom and Sawe, 1993; [10]Frye et al., 1997; [11]Wynne et al., 1990.

### *III.2.2.1 Markers of chronic and acute exposure*

#### *III.2.2.1.1 Markers of chronic exposure*

The coefficient of variation for the most relevant oral parameter (oral clearance adjusted to body weight) ranged from 15 to 51% and 15-47% (normal distribution/lognormal distribution) with an overall mean of 27/25% (11 compounds, 28 publications and 328 subjects). The variability in clearance after intravenous dosage was 32/31% with a range from 19 to 40% for both asssumptions (5 compounds, 24 publications and 227 subjects) (Table 3). The coefficient of variation for the oral clearance uncorrected for body weight was 30-31% and ranged from 17 to 44% (10 compounds, 23 publications and 241 subjects) (Table 4). The intravenous data showed a similar variability of 26/25% with a range from 19-38% (4 compounds, 10 publications and 93 subjects) (Table 4).

**Table 3. Interindividual variation in the clearance in ($ml min^{-1} kg^{-1}$) of glucuronidation probe substrates after oral and intravenous administration to healthy adult volunteers [a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | |
| AZT | 6 | 5[1] | 40 | 35 | 13 | 36 | 33 | 1.4 | 36 |
| Carprofen | 1 | 1[2] | 8 | 0.47 | 0.13 | 29 | 0.45 | 1.3 | 29 |
| Clofibric acid | 1 | 1[3] | 8 | 0.12 | 0.03 | 29 | 0.12 | 1.3 | 25 |
| Ketoprofen | 2 | 2[4] | 17 | 1.2 | 0.17 | 15 | 1.2 | 1.2 | 15 |
| Lamotrigine | 2 | 2[5] | 23 | 0.55 | 0.090 | 16 | 0.54 | 1.2 | 17 |
| Lorazepam | 2 | 2[6] | 31 | 1.3 | 0.38 | 30 | 1.2 | 1.3 | 30 |
| Lormetazepam | 1 | 1[7] | 10 | 3.5 | 0.60 | 17 | 3.4 | 1.2 | 17 |
| Oxazepam | 6 | 4[8] | 77 | 1.3 | 0.68 | 51 | 1.1 | 1.6 | 47 |
| Paracetamol | 9 | 6[9] | 84 | 6.1 | 1.3 | 21 | 5.9 | 1.2 | 20 |
| R-Ketoprofen | 2 | 2[10] | 14 | 1.3 | 0.27 | 22 | 1.2 | 1.2 | 21 |
| Zomepirac | 2 | 2[11] | 16 | 4.0 | 1.4 | 35 | 3.8 | 1.4 | 34 |
| Overall | 34 | 28 | 328 | | | 27 | | | 25 |
| ***Intravenous Administration*** | | | | | | | | | |
| AZT | 1 | 1[12] | 6 | 18 | 5.0 | 27 | 18 | 1.3 | 27 |
| Chloramphenicol | 1 | 1[13] | 8 | 3.2 | 1.3 | 40 | 3.0 | 1.5 | 40 |
| Lorazepam | 8 | 8[14] | 84 | 1.2 | 0.49 | 39 | 1.1 | 1.4 | 34 |
| Morphine | 13 | 12[15] | 104 | 20.5 | 6.4 | 31 | 19 | 1.3 | 30 |
| Oxazepam | 1 | 1[16] | 8 | 1.05 | 0.36 | 34 | 0.99 | 1.4 | 34 |
| Paracetamol | 1 | 1[17] | 19 | 4.7 | 0.87 | 19 | 4.6 | 1.2 | 19 |
| Overall | 25 | 24 | 227 | | | 32 | | | 31 |

[a]**Ns** number of studies; **Np** number of publications; **n** number of subjects; $X_w$ weighted mean; $SD_w$ weighted standard deviation: $CV_N$ coefficient of variation (normal distribution); $GM_W$ Geometric weighted mean (lognormal distribution); $GSD_w$ Weighted geometric standard deviation (lognormal distribution); $CV_{LN}$ coefficent of variation; (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Morse *et al.*, 1989, Taburet *et al.*, 1990, Fletcher *et al.*, 1992 (2), Gallicano *et al.*, 1993, Zhou and Sommadossi, 1996; [2]Crevoisier *et al.*, 1982; [3]Millard *et al.*, 1980; [4]Ishizaki *et al.*, 1980, Advenier *et al.*, 1983; [5]Posner *et al.*, 1989,Wootton *et al.*, 1997; [6]Mineshita *et al.*, 1988, Friedman *et al.*, 1991; [7]Doenicke *et al.*, 1991;[8] Alvan *et al.*, 1977 (2), Greenblatt *et al.*, 1980 (2), Abernethy *et al.*, 1983, Scott *et al.*, 1983; [9]Andreasen and Hutters, 1979, Miners *et al.*, 1983 (3), Bedjaoui *et al.*, 1984, Miners *et al.*, 1984 (2), Miners *et al.*, 1988, Osborne *et al.*, 1991(2); [10]Foster *et al.*, 1988b, Foster *et al.*, 1989; [11]Wu *et al.*, 1980, Witassek *et al.*, 1983; [12]Stagg *et al.*, 1992; [13]Burke *et al.*, 1982; [14]Greenblatt *et al.*, 1978, Kraus *et al.*, 1978, Greenblatt *et al.*, 1979, Aaltonen *et al.*, 1982, Abernethy *et al.*, 1983, Niels-Kudsk *et al.*, 1983, Greenblatt *et al.*, 1989, Crom *et al.*, 1991: [15]Dahlstrom *et al.*, 1982, Woolner *et al.*, 1986, Chauvin *et al.*, 1987, Mazoit *et al.*, 1987, Sawe and Odar, 1987, Baillie *et al.*, 1989, Watson *et al.*, 1988, Crotty *et al.*, 1989, Hoskin *et al.*, 1989, Hasselstrom *et al.*, 1990, Mazoit *et al.*, 1990, Hasselstrom and Sawe, 1993, Westerling *et al.*, 1993; [16]Sonne *et al.*,1988; [17]Wynne *et al.*,1990.

**Table 4. Interindividual variation in the clearance in ($mlmin^{-1}$) of glucuronidation probe substrates after oral and intravenous administration to healthy adult volunteers [a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | |
| AZT | 1 | 1[1] | 12 | 2200 | 850 | 39 | 2040 | 1.5 | 39 |
| Diflunisal | 4 | 4[2] | 24 | 9.1 | 1.6 | 17 | 8.9 | 1.2 | 16 |
| Ketoprofen | 1 | 1[3] | 8 | 52 | 14 | 17 | 50 | 1.3 | 27 |
| Lamotrigine | 2 | 2[4] | 16 | 29 | 8.3 | 29 | 27 | 1.3 | 28 |
| Lorazepam | 2 | 2[5] | 17 | 110 | 48 | 43 | 104 | 1.5 | 44 |
| Lormetazepam | 1 | 1[6] | 6 | 290 | 110 | 38 | 270 | 1.4 | 38 |
| Oxazepam | 1 | 1[7] | 5 | 107 | 43 | 40 | 99 | 1.5 | 40 |
| Paracetamol | 5 | 5[8] | 48 | 350 | 81 | 23 | 340 | 1.2 | 21 |
| R-Ketoprofen | 1 | 1[9] | 25 | 95 | 25 | 26 | 92 | 1.3 | 26 |
| Zileuton | 8 | 5[10] | 80 | 590 | 140 | 24 | 570 | 1.3 | 24 |
| Overall | 26 | 23 | 241 | | | 31 | | | 29 |
| ***Intravenous Administration*** | | | | | | | | | |
| Carprofen | 1 | 1[11] | 6 | 36 | 7.0 | 19 | 36 | 1.2 | 19 |
| Ketoprofen | 4 | 1[12] | 29 | 93 | 21 | 23 | 90 | 1.2 | 21 |
| Lorazepam | 1 | 1[13] | 6 | 71 | 27 | 38 | 66 | 1.4 | 38 |
| Morphine | 7 | 7[14] | 52 | 1300 | 302 | 23 | 1100 | 1.3 | 24 |
| Overall | 13 | 10 | 93 | | | 26 | | | 25 |

[a]**Ns** number of studies; **Np** number of publications; **n** number of subjects; **$X_w$** weighted mean; **$SD_w$** weighted standard deviation; **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation. [1]Drew *et al.*, 1989; [2] Verbeeck et al., 1979, Loewen *et al.*, 1988, Eriksson *et al.*,1989, McDonald *et al.*,1992; [3]Queneau *et al.*, 1985; [4]Yuen and Peck, 1988, Depot *et al.*, 1990; [5]Camu *et al.*,1988, Greenblatt *et al.*,1988; [6] Huempel *et al.*, 1980; [7]Klotz and Reimann, 1980; [8]Andreansen and Hutters, 1979, Villeneuve *et al.*, 1983, Miners *et al.*, 1986, Baraka *et al.*, 1990, Rumble *et al.*, 1991; [9]Rudy *et al.*, 1998; [10]Awni *et al.*, 1995a, Awni *et al.*,1995b, Awni *et al.*, 1995c (3), Braeckman *et al.*,1995 (2), Wong *et al.*, 1995; [11]Crevoisier, 1982; [12] Debruyne *et al.*, 1987 (4); [13]Morrison *et al.*, 1984; [14] Patwardhan *et al.*, 1981, Mojaverian *et al.*, 1982, Moore *et al.*, 1984, Sear *et al.*, 1989a and b, Osborne *et al.*, 1993, Fromm *et al.*, 1997.

**Table 5. Interindividual variation in the area under the plasma concentration curve ((AUC/dose ($ngml^{-1}h$) per (mg/kg) of glucuronidation probe substrates after oral and intravenous administration to healthy adult volunteers [a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | |
| AZT | 2 | 2[1] | 68 | 7800 | 4300 | 56 | 6800 | 1.7 | 56 |
| Carprofen | 3 | 3[2] | 17 | 43000 | 7000 | 16 | 42000 | 1.2 | 17 |
| Chloramphenicol | 1 | 1[3] | 5 | 8200 | 3600 | 44 | 7500 | 1.5 | 44 |
| Diflunisal | 1 | 1[4] | 6 | 1500000 | 410000 | 28 | 1400000 | 1.3 | 28 |
| Ketoprofen | 2 | 2[5] | 21 | 14000 | 4400 | 32 | 13000 | 1.4 | 32 |
| Lamotrigine | 2 | 2[6] | 16 | 30000 | 9600 | 32 | 29000 | 1.3 | 30 |
| Lorazepam | 4 | 4[7] | 89 | 9600 | 7000 | 70 | 7800 | 1.8 | 65 |
| Oxazepam | 2 | 2[8] | 14 | 10000 | 3600 | 36 | 9400 | 1.4 | 34 |
| Paracetamol | 6 | 6[9] | 46 | 3010 | 1040 | 35 | 2800 | 1.4 | 34 |
| R-Ketoprofen | 1 | 1[10] | 8 | 9800 | 2200 | 23 | 9500 | 1.3 | 23 |
| Zileuton | 1 | 1[11] | 18 | 2900 | 820 | 29 | 2800 | 1.3 | 28 |
| Zomepirac | 2 | 2[12] | 29 | 5800 | 200 | 34 | 5500 | 1.4 | 32 |
| Overall | 27 | 27 | 337 | | | 36 | | | 33 |
| ***Intravenous Administration*** | | | | | | | | | |
| Chloramphenicol | 1 | 1[13] | 8 | 5800 | 980 | 17 | 5700 | 1.2 | 17 |

[a]**Ns** number of studies; **Np** number of publications; **n** number of subjects; **$X_w$** weighted mean; **$SD_w$** weighted standard deviation; **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Singlas *et al.*,1989, Child *et al.*, 1991; [2]Ray *et al.*, 1979, Ray and Wade, 1982, Holazo *et al.*,1985; [3]Stein *et al.*, 1989; [4]Verbeeck *et al.*,1990; [5]Houghton *et al.*, 1984b, Bannwarth *et al.*, 1988; [6]Cohen *et al.*, 1987, Fillastre *et al.*, 1993; [7]Greenblatt *et al.*, 1984, Bruguerolle *et al.*, 1985, Saano *et al.*, 1992, Greenblatt *et al.*, 1993; [8]Mellander *et al.*, 1977, Van Hecken *et al.*, 1985; [9]Rawlins *et al.*, 1977, Fulton *et al.*, 1979, Clements *et al.*, 1984, Adjepon *et al.*, 1986, Prescott *et al.*, 1989, Rashid and Bateman,1990; [10]Foster *et al.*, 1988a; [11]Awni *et al.*, 1995d; [12]Nayak *et al.*, 1980, O' Neill *et al.*, 1982; [13]Narang *et al.*, 1981.

The oral AUC after body weight correction (Table 5) (12 compounds, 27 publications and 337 subjects) was slightly more variable than the other parameters with an average of 36% for both assumptions. The intravenous database was limited to one study on one compound with only 8 subjects and showed a coefficient of variation of 17%.

*III.2.2.1.2 Markers of acute exposure*

The Cmax analysis (adjusted to body weight) (Table 6) reflecting acute exposure, was based on an extensive database which contained 14 compounds, 55 publications, 648 individuals which showed an average variability of 31/26%.

**Table 6. Interindividual variation in the maximum plasma concentration ((Cmax/dose ($ngml^{-1}$) per (mg/kg)) of glucuronidation probe substrates after oral administration to healthy adult volunteers [a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| AZT | 9 | 8[1] | 120 | 390 | 200 | 52 | 340 | 1.7 | 54 |
| Carprofen | 3 | 3[2] | 22 | 10000 | 5400 | 54 | 9040 | 1.4 | 36 |
| Chloramphenicol | 1 | 1[3] | 5 | 2400 | 660 | 28 | 2300 | 1.3 | 28 |
| Clofibric acid | 1 | 1[4] | 8 | 4700 | 840 | 18 | 4600 | 1.2 | 17 |
| Diflunisal | 2 | 2[5] | 13 | 15000 | 2500 | 17 | 14000 | 1.1 | 10 |
| Ketoprofen | 4 | 4[6] | 37 | 7200 | 2050 | 28 | 6900 | 1.3 | 29 |
| Lamotrigine | 4 | 4[7] | 36 | 920 | 160 | 18 | 910 | 1.2 | 17 |
| Lorazepam | 7 | 7[8] | 107 | 620 | 230 | 36 | 570 | 1.4 | 33 |
| Lormetazepam | 2 | 2[9] | 16 | 410 | 52 | 13 | 405 | 1.1 | 11 |
| Oxazepam | 5 | 4[10] | 61 | 1400 | 390 | 28 | 1300 | 1.3 | 24 |
| Paracetamol | 5 | 5[11] | 42 | 980 | 300 | 31 | 920 | 1.4 | 31 |
| R-Ketoprofen | 4 | 4[12] | 47 | 3100 | 1200 | 37 | 2900 | 1.4 | 36 |
| Zileuton | 9 | 6[13] | 89 | 630 | 210 | 33 | 570 | 1.3 | 30 |
| Zomepirac | 4 | 4[14] | 45 | 3200 | 1400 | 46 | 2900 | 1.5 | 43 |
| Overall | 60 | 55 | 648 | | | 31 | | | 26 |

[a]**Ns** number of studies; **Np** number of publications; **n** number of subjects; $\mathbf{X_w}$ weighted mean; $\mathbf{SD_w}$ weighted standard deviation; $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Drew *et al.*, 1989, Morse *et al.*, 1989, Singlas *et al.*, 1989, Taburet *et al.*, 1990, Child *et al.*, 1991, Fletcher *et al.*, 1992 (2), Gallicano *et al.*, 1993, Zhou and Sommadossi, 1996; [2]Ray *et al.*, 1979, Ray and Wade, 1982, Holazo *et al.*, 1985; [3]Stein *et al.*, 1989; [4]Millart *et al.*, 1980; [5]Verbeeck *et al.*, 1979, Eriksson *et al.*, 1989; [6]Ishizaki *et al.*, 1980, Advenier *et al.*, 1983, Bannwarth *et al.*, 1988, Rudy *et al.*, 1998; [7]Cohen *et al.*, 1987, Posner *et al.*, 1989, Fillastre *et al.*, 1993, Wootton *et al.*, 1997; [8]Greenblatt *et al.*, 1984, Morrison *et al.*, 1984, Bruguerolle *et al.*, 1985, Camu *et al.*, 1988, Greenblatt *et al.*, 1988, Mineshita *et al.*, 1988, Greenblatt *et al.*, 1993; [9]Huempel *et al.*, 1980, Doenicke *et al.*, 1991; [10] Greenblatt *et al.*, 1980(2), Scott *et al.*, 1983, Greenblatt *et al.*, 1984, Van Hecken *et al.*, 1985,; [11]Bedjaoui *et al.*, 1984, Adjepon *et al.*, 1986, Baraka *et al.*, 1990, Rashid and Bateman,1990, Rumble *et al.*, 1991; [12]Foster *et al.*, 1988a, Foster *et al.*, 1988b, Foster *et al.*, 1989, Rudy *et al.*, 1998; [13]Awni *et al.*, 1995a, Awni *et al.*, 1995b, Awni *et al.*, 1995c (3), Awni *et al.*, 1995d, Braeckman *et al.*, 1995(2), Wong *et al.*, 1995; [14]Nayak *et al.*, 1980, O' Neill *et al.*, 1982.

## III.3 Overall kinetic variability in the healthy adult population

The variability in the different markers of oral exposure for healthy adults was similar for both distributions with an overall mean of about 30% (15 compounds and 906 subjects) (Table 7) comparable to the metabolic clearance values. The latter confirmed the validity of

the criteria for the selection of probe substrates as representative of the variability in the glucuronidation pathway.

**Table 7. Overall inter-individual variability for the pharmacokinetic parameters of the glucuronidation probe substrates in healthy adult volunteers.**

| PK parameter | Nc | Ns | Np | n | $CV_N$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|
| ***Oral administration*** | | | | | | |
| $CL_m$ Acyl ($mlmin^{-1}kg^{-1}$) | 1 | 1 | 1 | 10 | 55 | 55 |
| $CL_m$ Hydroxy ($mlmin^{-1}kg^{-1}$) | 2 | 8 | 5 | 67 | 20 | 20 |
| $CL_m$ Acyl ($mlmin^{-1}$) | 1 | 3 | 3 | 17 | 22 | 22 |
| $CL_m$ Hydroxy ($mlmin^{-1}$) | 4 | 9 | 9 | 74 | 34 | 28 |
| CL ($mlmin^{-1}kg^{-1}$) | 10 | 34 | 28 | 328 | 27 | 25 |
| CL ($mlmin^{-1}$) | 10 | 26 | 23 | 241 | 31 | 29 |
| AUC/dose ($ngml^{-1}h$)* | 12 | 27 | 27 | 337 | 36 | 33 |
| Cmax/dose ($ngml^{-1}$)* | 14 | 60 | 55 | 648 | 33 | 26 |
| ***Intravenous administration*** | | | | | | |
| $CL_m$ Hydroxy ($mlmin^{-1}kg^{-1}$) | 3 | 3 | 3 | 38 | 24 | 24 |
| CL ($mlmin^{-1}kg^{-1}$) | 6 | 25 | 24 | 227 | 32 | 31 |
| CL ($mlmin^{-1}$) | 4 | 13 | 10 | 93 | 26 | 25 |
| AUC/dose ($ngml^{-1}h$)* | 1 | 1 | 1 | 8 | 17 | 17 |

[a] **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $CV_N$ coefficient of variation (normal distribution); $CV_{LN}$ coefficient of variation (lognormal distribution); *Mean data corrected for dose expressed per mean body weight (mg/kg).

## III.4 Comparison between healthy adults and subgroups of the population

Published pharmacokinetic studies on the same probe substrates for the glucuronidation pathway, in potentially sensitive subpopulations were abstracted. Data were available for neonates (<1 month), infants (>1 month, <1year), children (>1 year,<16 years), the elderly (>70 years), and patients with liver and kidney diseases. Limited data were also available for different ethnic groups; these specific healthy adult data have been analysed separately, and compared with the general healthy adult groups, which were either Caucasian or not defined.

### III.4.1 Metabolic Clearances in ethnic minorities

The metabolic clearance of propranolol by glucuronide conjugation has been reported in healthy adult Caucasian and Chinese subjects and for each enantiomeric form in Caucasians and black African-Americans (Table 8). The Caucasian data showed 51/47% variability for the formation of propanolol glucuronide, 20-25% variability for the formation of the enantiomer glucuronides and revealed greater glucuronidation of the S-

enantiomer compared to the R-enantiomer. The interethnic differences were characterised by slightly higher total metabolic clearance as the glucuronide in Chinese and in Blacks, associated with higher variability (60% in Chinese and 47-48% for R and S enantiomers in Blacks), compared to Caucasians. In consequence the ethnic groups would not represent "at risk" subgroups for glucuronidation, although the number of subjects studied were too low for definite conclusions (10 and 13 respectively) .

**Table 8. Metabolic clearances ($ml min^{-1}$) for the total R- and S-hydroxy-glucuronide of propranolol in healthy adult volunteers from different ethnic origins [a].**

| Drug | Group | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Propranolol | Caucasian | 2 | 2[1] | 18 | 280 | 140 | 51 | 240 | 1.6 | 47 | | |
| | Chinese | 1 | 1[2] | 10 | 340 | 200 | 60 | 290 | 1.7 | 60 | 0.83 | 1.3 |
| R-Propranolol | Caucasian | 1 | 1[3] | 13 | 390 | 140 | 20 | 380 | 1.2 | 20 | | |
| S-Propranolol | Caucasian | 1 | 1[3] | 13 | 610 | 150 | 25 | 590 | 1.3 | 25 | | |
| R-Propranolol | Black | 1 | 1[3] | 13 | 509 | 240 | 47 | 460 | 1.6 | 47 | 0.83 | 2.4 |
| S-Propranolol | Black | 1 | 1[3] | 13 | 690 | 330 | 48 | 620 | 1.6 | 48 | 0.95 | 2.4 |

[a] **Ns** number of studies; **Np** number of publications; **n** number of subjects; **$X_w$** weighted mean; **$SD_w$** weighted standard deviation; **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $H/S_{LN}$** Ratio of geometric means between healthy adults and subgroup (lognormal distribution); **Ratio $CV_{LN}$** Variability ratio between healthy adults and subgroup (lognormal distribution).

[1]Zhou *et al.*. 1989, Walle *et al.*, 1996;[2] Zhou *et al.*, 1989,[3]Sowinski *et al.*. 1996.

### III.4.2 Neonates, infants and children

The data for these subgroups are summarised in Table 9. Neonates showed significantly lower clearance than healthy adults. Oral clearance was two-fold lower with greater variability (1.7- fold) in neonates (clofibric acid and 16 subjects). Comparable 2- to 5-fold differences and higher variability were found for clearance in neonates after intravenous administration (4 compounds, 94 subjects). Only a very limited database was available for infants, and the data were comparable to healthy adults. Compared to adults, children showed a 1.3-fold higher clearance after oral dosage (4 compounds, 126 subjects) and after intravenous administration (4 compounds; 161 subjects), and a 1.3-fold lower oral AUC (1 compound; 5 subjects). The variability in clearance after both routes of administration differed markedly between the compounds studied, and overall was slightly greater in children than in adults (1.2- and 1.6-fold) whereas the variability in oral AUC was slightly lower (only 5 individuals).

Higher Cmax values were found in neonates (1.8-fold) and lower in children (1.3-fold) compared to healthy adults. Variability in Cmax was also greater in both neonates and

children (1.5- and 1.7-fold). No Cmax data were available for the infant subgroup.

**Table 9. Pharmacokinetics of glucuronidation probe substrates: comparison between healthy adults, neonates, infants and children after oral and intravenous administration [a].**

| Route | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | | | | |
| CL($ml\,min^{-1}kg^{-1}$) | | | | | | | | | | | | |
| Neonates | Clofibric acid | 2 | 1[1] | 16 | 0.050 | 0.025 | 50 | 0.044 | 1.6 | 52 | 2.6 | 2.1 |
| Infants | Paracetamol | 1 | 1[2] | 4 | 6.3 | 0.52 | 8.3 | 6.3 | 1.1 | 8 | 0.94 | 0.41 |
| Children | AZT | 1 | 1[3] | 8 | 37 | 6.4 | 17 | 36 | 1.2 | 17 | 0.90 | 0.48 |
| | Ketoprofen | 2 | 1[4] | 19 | 1.2 | 0.080 | 6.6 | 1.2 | 1.1 | 6.0 | 0.98 | 0.42 |
| | Lamotrigine | 3 | 2[5] | 22 | 1.0 | 0.42 | 42 | 0.86 | 1.5 | 39 | 0.63 | 2.34 |
| | Paracetamol | 5 | 4[6] | 77 | 6.6 | 1.8 | 28 | 6.2 | 1.3 | 28 | 0.71 | 0.94 |
| AUC/dose ($ngml^{-1}h$) [b] | | | | | | | | | | | | |
| Children | Paracetamol | 1 | 1[7] | 5 | 2500 | 670 | 27 | 2400 | 1.3 | 27 | 0.86 | 0.79 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | | |
| Neonates | Clofibrate | 2 | 1[8] | 16 | 2600 | 680 | 27 | 2400 | 1.3 | 27 | 1.9 | 1.6 |
| Children | Ketoprofen | 2 | 1[4] | 19 | 4600 | 3200 | 69 | 3800 | 1.9 | 69 | 0.55 | 2.3 |
| | Lamotrigine | 3 | 2[5] | 22 | 660 | 190 | 29 | 630 | 1.3 | 28 | 0.69 | 1.7 |
| | Paracetamol | 3 | 2[8] | 61 | 860 | 380 | 45 | 780 | 1.5 | 44 | 0.84 | 1.4 |
| *Intravenous administration* | | | | | | | | | | | | |
| CL($ml\,min^{-1}kg^{-1}$) | | | | | | | | | | | | |
| Neonates | Chloramphenicol | 1 | 1[9] | 9 | 1.1 | 0.6 | 55 | 0.97 | 1.7 | 55 | 3.1 | 1.4 |
| | Lorazepam | 1 | 1[10] | 10 | 0.23 | 0.11 | 47 | 0.21 | 1.6 | 47 | 5.3 | 1.4 |
| | Morphine | 11 | 6[11] | 70 | 4.4 | 2.4 | 56 | 3.5 | 1.7 | 54 | 5.4 | 1.8 |
| | Paracetamol | 1 | 1[12] | 5 | 2.5 | 1.1 | 45 | 2.3 | 1.5 | 45 | 2.0 | 2.4 |
| Infants | Chloramphenicol | 1 | 1[13] | 4 | 2.8 | 0.97 | 35 | 2.6 | 1.4 | 35 | 1.1 | 0.88 |
| | Morphine | 3 | 2[14] | 21 | 18 | 7.6 | 43 | 15 | 1.5 | 41 | 1.2 | 1.3 |
| Children | Chloramphenicol | 6 | 4[15] | 68 | 5.1 | 1.7 | 36 | 4.5 | 1.4 | 35 | 0.63 | 0.87 |
| | Lorazepam | 3 | 2[16] | 66 | 1.2 | 0.51 | 41 | 1.1 | 1.5 | 41 | 0.98 | 1.2 |
| | Morphine | 3 | 3[17] | 20 | 26 | 11 | 43 | 24 | 1.5 | 39 | 0.80 | 1.3 |
| | Paracetamol | 1 | 1[18] | 7 | 6.1 | 3.7 | 60 | 5.2 | 1.7 | 60 | 0.89 | 3.2 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); ); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Bourget *et al.*, 1995; [2]Nahata *et al.*, 1984; [3]Gibb *et al.*, 1995; [4]Lempiainen and Makela, 1987(2); [5]Vauzelle-kervroedan *et al.*, 1996 (2); Chen *et al.*, 1999; [6]Nahata and Powell., 1982, Wilson *et al.*, 1982 (2), Brown *et al.*, 1992, Anderson *et al.*, 1998. [7]Mehta *et al.*, 1982. [8] Wilson *et al.*, 1982 (2), Brown *et al.*, 1992; [9]Rajchgot *et al.*, 1983; [10]Mc Dermott et al. ., 1992; [11]Lynn and Slattery.,1987, Choonara *et al.*, 1989, Chay *et al.*, 1992 (2), Pokela *et al.*, 1993, Mikkelsen *et al.*, 1994 (2), Scott *et al.*, 1994 (4); [12]Autret *et al.*, 1993; [13]Burckart *et al.*, 1983; [14]Lynn and Slattery., 1987, Pokela *et al.*, 1993 (2); [15]Sack *et al.*, 1980, Nahata and Powell, 1983, Burckart *et al.*, 1983 (2), Kearns *et al.*, 1985 (2); [16]Relling *et al.*, 1989, Crom *et al.*, 1991(2); [17]Vandenberghe *et al.*, 1983, Nahata *et al.*, 1985, Dampier *et al.*, 1995; [18]Autret *et al.*, 1993 (2).

### III.4.3 The elderly

The comprehensive database on the elderly (Table 10) revealed consistently lower clearance and higher AUC and Cmax values as compared with the same parameters in healthy adults. The difference was approximately 1.4-fold after oral or intravenous dosing for each of the parameters investigated with the exception of the oral AUC for paracetamol which indicated a higher 2.5-fold difference (Table 10). The variability was also about 1.4-

fold higher in the elderly compared to that in healthy adults. The paracetamol data are difficult to interpret because the oral and intravenous clearance data showed only minor age-related differences, but the data for AUC /dose (from different subjects and studies) indicated a greater difference; this may have arisen from differences in the extent of infirmity in the elderly study groups in the different studies (the clearance values were based on 6 studies (n = 82) and the AUC values on 2 studies (n =19).

**Table 10. Pharmacokinetics of glucuronidation probe substrates: comparison between healthy adults and elderly after oral and intravenous administration [a].**

| Parameter | Drug | Ns | Np | n | $X_W$ | $SD_W$ | $CV_N$ | $GM_W$ | $GSD_W$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | | | | |
| CLm[a] | Paracetamol | 1 | 1[1] | 8 | 3.5 | 0.53 | 15 | 3.5 | 1.2 | 15 | 0.88 | 0.60 |
| CL[a] | Carprofen | 1 | 1[2] | 8 | 0.45 | 0.18 | 41 | 0.42 | 1.5 | 40 | 1.1 | 1.4 |
| | Ketoprofen | 1 | 1[3] | 7 | 0.62 | 0.09 | 15 | 0.61 | 1.2 | 15 | 1.9 | 0.97 |
| | R-ketoprofen | 1 | 1[4] | 9 | 1.1 | 0.28 | 25 | 1.1 | 1.3 | 25 | 1.1 | 1.1 |
| | Lorazepam | 1 | 1[5] | 10 | 0.59 | 0.18 | 30 | 0.57 | 1.3 | 30 | 2.2 | 1.0 |
| | Paracetamol | 3 | 3[6] | 50 | 4.7 | 1.4 | 30 | 4.5 | 1.3 | 30 | 1.3 | 1.5 |
| CL[b] | Diflunisal | 2 | 1[7] | 13 | 7.5 | 3.0 | 41 | 6.9 | 1.5 | 39 | 1.3 | 2.4 |
| | Lormetazepam | 1 | 1[8] | 6 | 220 | 59 | 27 | 210 | 1.3 | 27 | 1.3 | 0.7 |
| | Zileuton | 2 | 1[9] | 18 | 430 | 59 | 14 | 430 | 1.2 | 14 | 1.3 | 0.60 |
| AUC[c] | Paracetamol | 2 | 2[10] | 19 | 7400 | 2300 | 31 | 4800 | 1.4 | 34 | 1.6 | 0.99 |
| Cmax[d] | Carprofen | 1 | 1[2] | 8 | 7700 | 3400 | 44 | 7050 | 1.5 | 44 | 0.78 | 1.2 |
| | Diflunisal | 2 | 1[7] | 13 | 16000 | 5200 | 26 | 15000 | 1.3 | 24 | 1.0 | 0.86 |
| | Ketoprofen | 1 | 1[3] | 7 | 8200 | 1600 | 19 | 8020 | 1.2 | 19 | 1.2 | 0.65 |
| | Lormetazepam | 1 | 1[8] | 6 | 450 | 85 | 19 | 440 | 1.2 | 17 | 1.1 | 1.6 |
| | R-ketoprofen | 1 | 1[4] | 9 | 3900 | 1400 | 36 | 3600 | 1.4 | 36 | 1.3 | 0.99 |
| | Lorazepam | 1 | 1[5] | 16 | 990 | 150 | 15 | 980 | 1.2 | 15 | 1.7 | 0.47 |
| | Paracetamol | 2 | 2[11] | 21 | 1200 | 410 | 34 | 1100 | 1.4 | 36 | 1.2 | 1.1 |
| | Zileuton | 2 | 1[9] | 18 | 450 | 130 | 28 | 435 | 1.3 | 27 | 0.76 | 0.91 |
| *Intravenous administration* | | | | | | | | | | | | |
| CLm[a] | Paracetamol | 3 | 2[12] | 24 | 1.65 | 0.28 | 17 | 1.6 | 1.2 | 19 | 1.6 | 1.05 |
| CL[a] | Lorazepam | 1 | 1[13] | 16 | 0.77 | 0.24 | 31 | 0.77 | 1.08 | 8 | 1.4 | 0.23 |
| | Morphine | 1 | 1[14] | 9 | 14 | 3.5 | 26 | 13 | 1.29 | 26 | 1.5 | 0.85 |
| | Paracetamol | 3 | 2[12] | 29 | 3.3 | 0.42 | 13 | 3.2 | 1.13 | 12 | 1.4 | 0.65 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects: **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_W$** Weighted standard deviation (normal distribution); **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_W$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$** Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.: **Clm[a]** Metabolic clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL[a]** Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) **CL[b]** Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC[c]** AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax[d]** Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Miners *et al.*, 1988; [2]Crevoisier, 1982; [3]Advenier *et al.*,1983; [4]Foster *et al.*,1988b; [5]Mineshita *et al.*,1988; [6]Briant *et al.*,1976, Bedjaoui *et al.*,1984, Miners *et al.*,1988; [7]Eriksson *et al.*,1989 (2); [8]Huempel *et al.*,1980; [9]Braeckman *et al.*,1995 (2); [10]Fulton *et al.*,1979, Rashid and Bateman, 1990; [11]Bedjaoui *et al.*,1984, Rashid and Bateman, 1990; [12]Wynne *et al.*,1990 (2); Kamali *et al.*,1993; [13]Greenblatt *et al.*,1979; [14]Baillie *et al.*,1989.

### III.4.4 Patients with Liver disease

Patients with liver disease (Table 11) demonstrated a lower clearance through the

glucuronidation pathway with a 2-fold difference in oral clearance adjusted to body weight and a 1.3-fold difference in unadjusted oral clearance. In contrast, the oral AUC, adjusted to body weight, did not show any difference, but this was based on only one compound. The mean intravenous clearance and AUC data showed an increase in internal dose (1.3-fold and 2-fold respectively) associated with greater variability (1.3 and 1.7-fold) in patients with liver disease. The Cmax analysis did not show a clear difference between patients with liver disease and healthy adults with a mean ratio of 1.2 and a variability ratio of 0.9.

**Table 11. Pharmacokinetics of glucuronidation probe substrates: comparison between healthy adults and patients with liver disease after oral and intravenous administration [a].**

| Parameter | Drug | Ns | Np | n | $X_W$ | $SD_W$ | $CV_N$ | $GM_W$ | $GSD_W$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral administration*** | | | | | | | | | | | | |
| CL [a] | AZT | 3 | 3[1] | 24 | 15 | 2.8 | 18 | 13 | 1.4 | 31 | 2.5 | 0.85 |
| | Paracetamol | 1 | 1[2] | 11 | 2.7 | 0.94 | 34 | 2.5 | 1.4 | 35 | 2.3 | 1.7 |
| | Zomepirac | 2 | 1[3] | 18 | 2.2 | 0.67 | 30 | 2.1 | 1.3 | 30 | 1.8 | 0.87 |
| CL [b] | Diflunisal | 1 | 1[4] | 5 | 11 | 3.0 | 28 | 11 | 1.3 | 28 | 0.84 | 1.7 |
| | Zileuton | 2 | 1[5] | 8 | 380 | 120 | 31 | 360 | 1.3 | 26 | 1.6 | 1.1 |
| AUC[c] | Carprofen | 1 | 1[6] | 12 | 43000 | 8600 | 20 | 41000 | 1.2 | 20 | 0.99 | 1.2 |
| Cmax[d] | AZT | 3 | 3[1] | 24 | 830 | 410 | 49 | 750 | 1.5 | 40 | 2.2 | 0.74 |
| | Zileuton | 2 | 1[5] | 8 | 750 | 230 | 31 | 7200 | 1.4 | 34 | 0.80 | 0.95 |
| | Carprofen | 1 | 1[6] | 12 | 7600 | 2300 | 34 | 714 | 1.4 | 31 | 1.3 | 1.0 |
| | Zomepirac | 2 | 1[3] | 18 | 4700 | 2400 | 51 | 4200 | 1.6 | 52 | 0.70 | 1.2 |
| ***Intravenous administration*** | | | | | | | | | | | | |
| CL [a] | AZT | 1 | 1[7] | 14 | 20 | 6.3 | 32 | 19 | 1.4 | 32 | 0.94 | 1.2 |
| | Lorazepam | 2 | 1[8] | 22 | 0.78 | 0.43 | 55 | 0.69 | 1.7 | 54 | 1.6 | 1.6 |
| | Morphine | 5 | 5[9] | 39 | 14 | 5.5 | 41 | 12 | 1.5 | 40 | 1.6 | 1.3 |
| AUC[c] | Chloramphenicol | 6 | 1[10] | 42 | 12000 | 3500 | 29 | 11000 | 1.3 | 29 | 2.0 | 1.7 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_W}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_W}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; **Clm**[a] Metabolic clearance adjusted to body weight ($ml min^{-1} kg^{-1}$); **CL**[a] Total clearance adjusted to body weight ($ml min^{-1} kg^{-1}$) **CL**[b] Total clearance not adjusted to body weight ($ml min^{-1}$); **AUC**[c] AUC/dose ($ng ml^{-1} h$) with mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$); **Cmax**[d] Cmax/dose ($ng ml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$).

[1]Taburet et al., 1990, Fletcher et al., 1992, Moore et al., 1995; [2]Andreasen and Hutters, 1979; [3]Witassek et al., 1983 (2); [4]McDonald et al., 1992; [5]Awni et al., 1995c (2); [6]Holazo et al., 1985; [7]Moore et al., 1995; [8]Kraus et al., 1978 (2); [9]Patwardhan et al., 1981, Mazoit et al., 1987, Watson et al., 1988, Crotty et al., 1989, Hasselstrom et al., 1990; [10]Narang et al., 1981 (6).

The major disease-related difference for AZT in oral clearance (which depends on hepatic enzyme activity and liver blood flow) was not found for intravenous clearance (which depends largely on liver blood flow), and this may be related to intestinal conjugation; the disease-related difference observed for oral Cmax supports a role for first pass metabolism.

### III.4.5 Patients with renal disease

Comparative pharmacokinetic data for patients with renal disease and healthy adults are presented in Table 12. The data indicate an approximately 2-fold lower clearance, which was consistent between the different parameters and routes of exposure. There was greater variability in oral and intravenous measurements of clearance, but lower variability for the oral AUC. Cmax values did not demonstrate any consistent difference between patients with renal disease and healthy adults.

**Table 12. Pharmacokinetics of glucuronidation probe substrates: comparison between healthy adults and patients with renal disease after oral and intravenous administration [a].**

| Parameter | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral administration*** | | | | | | | | | | | | |
| CL[a] | Clofibric acid | 1 | 1[1] | 8 | 0.04 | 0.02 | 43 | 0.04 | 1.5 | 0.43 | 3.3 | 1.7 |
| | Lamotrigine | 1 | 1[2] | 10 | 0.51 | 0.30 | 60 | 0.44 | 1.7 | 0.59 | 1.2 | 3.5 |
| CL[b] | AZT | 1 | 1[3] | 14 | 1200 | 520 | 43 | 1100 | 1.5 | 0.43 | 1.8 | 1.1 |
| | Diflunisal | 5 | 3[4] | 33 | 4.5 | 1.20 | 27 | 3.9 | 1.3 | 0.29 | 2.3 | 1.8 |
| | Lamotrigine | 1 | 1[5] | 14 | 28 | 22 | 79 | 22 | 2.0 | 0.76 | 1.2 | 2.7 |
| AUC[c] | Paracetamol | 2 | 1[6] | 13 | 4500 | 990 | 22 | 4300 | 1.3 | 0.23 | 1.5 | 0.67 |
| Cmax[d] | AZT | 1 | 1[3] | 14 | 590 | 210 | 36 | 550 | 1.4 | 0.36 | 1.6 | 0.67 |
| | Clofibric acid | 1 | 1[6] | 12 | 3200 | 780 | 25 | 3070 | 1.3 | 0.25 | 1.5 | 1.5 |
| | Diflunisal | 4 | 2[7] | 27 | 7300 | 2800 | 37 | 6600 | 1.4 | 0.38 | 0.46 | 3.8 |
| | Lamotrigine | 2 | 2[8] | 24 | 870 | 230 | 26 | 860 | 1.3 | 0.27 | 0.95 | 1.6 |
| | Lorazepam | 2 | 1[9] | 17 | 330 | 55 | 16 | 305 | 1.2 | 0.15 | 0.53 | 0.47 |
| | Paracetamol | 2 | 1[6] | 13 | 1300 | 520 | 39 | 1200 | 1.4 | 0.38 | 1.3 | 1.2 |
| ***Intravenous administration*** | | | | | | | | | | | | |
| CL[a] | Morphine | 6 | 5[10] | 50 | 12 | 6.1 | 52 | 12 | 1.6 | 0.52 | 1.5 | 1.7 |
| CL[b] | Lorazepam | 2 | 1[11] | 17 | 83 | 39 | 46 | 76 | 1.5 | 0.45 | 2.0 | 1.6 |
| | Morphine | 1 | 1[12] | 9 | 530 | 300 | 56 | 470 | 1.7 | 0.56 | 2.4 | 2.4 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_w$** Weighted standard deviation (normal distribution); **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$** Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; **Clm[a]** Metabolic clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL[a]** Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) **CL[b]** Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC[c]** AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax[d]** Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Millart et al., 1980; [2]Wootton et al., 1997; [3]Pioger et al., 1989; [4]Verbeeck et al., 1979 (3). Eriksson et al., 1989, Dickinson et al., 1991; [5]Fillastre et al., 1993; [6]Prescott et al., 1989 (2); [7]Verbeeck et al., 1979 (3), Eriksson et al., 1989; [8]Fillastre et al., 1993, Wootton et al., 1997; [9]Morrison et al., 1984 (2); [10]Woolner et al., 1986, Chauvin et al., 1987, Sawe and Odar, 1987, Wolff et al., 1988; [11]Osborne et al., 1993 (2); [12]Sear et al., 1989b)

## III.5 Identification of potentially susceptible subgroups

A pooled analysis that combined individual drugs for each parameter, route of exposure and subgroup was performed (Table 13). Differences in the clearance of glucuronidated substrates identified neonates as the most potentially susceptible subgroup and patients

with liver or kidney disease were also potentially susceptible subgroups (although there was a wide variability in the estimates).

## III.6 Derivation of pathway-related uncertainty factors for glucuronidation

Pathway-related uncertainty factors were derived for all groups of the population to cover 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ centiles of each subpopulation using parameters reflecting oral exposure and assuming log-normally distributed data (Table 14). Uncertainty factors for glucuronidation in the healthy adult population were calculated using the variability on the kinetic parameters reflecting chronic oral exposure (clearances and AUC) and values of 1.6, 1.8 and 2.0 would cover the 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ centiles respectively. Uncertainty factors were below the 3.16 for all subgroups except neontes for whom values of 8.6, 10 and 12 would cover the former percentiles respectively.

Finally, the possibility of generating pathway-related uncertainty factors for specific UGT isoforms (UGT1A4 , UGT1A6 and UGT2B7) has been investigated using clearance and AUC data for healthy adults for specific compounds (UGT1A4 - lamotrigine; UGT1A6 - paracetamol; UGT2B7 – AZT (oral data only), lorazepam, clofibric acid and oxazepam). The overall CVs for UGT1A4 and UGT1A6 were 24% (n=55) and 25% (178 subjects) respectively, leading to default factors for both isoforms of 1.5, 1.6 and 1.8 to cover the 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ percentiles respectively of the healthy adult population. The UGT2B7 isoform appeared to be more variable than UGT1A4 or UGT1A6 with 45% variability (n=361) leading to default values of 2.0, 2.3 and 2.7 to cover the 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ percentiles respectively of the healthy adult population.

**Table 13. Relevance of the 3.16 kinetic default factor towards human subpopulations: parameters reflecting chronic and acute exposure after oral and intravenous administration [a].**

| Group | PK parameter | Route | Nc | Ns | Np | n | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| ***Chronic exposure*** | | | | | | | | |
| Chinese | $CLm^2$ | PO | 1 | 1 | 1 | 10 | 0.83 | 1.3 |
| Blacks | $CLm^2$ | PO | 1 | 1 | 1 | 13 | 0.83 | 2.4 |
| Neonates | $CL^1$ | PO | 1 | 2 | 1 | 16 | 2.6 | 2.1 |
| | $CL^1$ | IV | 4 | 14 | 9 | 94 | 3.7 | 1.7 |
| Infants | $CL^1$ | PO | 1 | 1 | 1 | 4 | 0.94 | 0.41 |
| | $CL^1$ | IV | 2 | 4 | 3 | 25 | 1.2 | 1.1 |
| Children | $CL^1$ | PO | 4 | 11 | 8 | 126 | 0.79 | 0.82 |
| | $AUC^3$ | PO | 1 | 1 | 1 | 5 | 0.86 | 0.79 |
| | $CL^1$ | IV | 4 | 13 | 10 | 161 | 0.81 | 1.4 |
| Elderly | $CLm^1$ | PO | 1 | 1 | 1 | 8 | 0.92 | 0.59 |
| | $CL^1$ | PO | 5 | 7 | 7 | 84 | 1.4 | 1.2 |
| | $CL^2$ | PO | 3 | 5 | 3 | 37 | 1.3 | 1.0 |
| | $AUC^3$ | PO | 1 | 2 | 2 | 19 | 1.7 | 0.99 |
| | $CLm^1$ | IV | 1 | 2 | 1 | 24 | 1.5 | 0.95 |
| | $CL^1$ | IV | 3 | 5 | 4 | 49 | 1.4 | 0.51 |
| Liver disease | $CL^1$ | PO | 3 | 6 | 5 | 53 | 2.2 | 1.1 |
| | $CL^2$ | PO | 2 | 3 | 2 | 13 | 1.2 | 1.4 |
| | $AUC^3$ | PO | 1 | 1 | 15 | 12 | 1.0 | 1.2 |
| | $CL^1$ | IV | 3 | 8 | 7 | 68 | 1.4 | 1.4 |
| | $AUC^3$ | IV | 1 | 6 | 1 | 42 | 2.0 | 1.7 |
| Renal disease | $CL^1$ | PO | 2 | 2 | 2 | 18 | 2.1 | 2.5 |
| | $CL^2$ | PO | 3 | 7 | 6 | 61 | 1.7 | 1.7 |
| | $AUC^3$ | PO | 1 | 2 | 1 | 13 | 1.5 | 0.67 |
| | $CL^1$ | IV | 1 | 6 | 5 | 48 | 1.4 | 1.5 |
| | $CL^2$ | IV | 2 | 3 | 2 | 19 | 2.1 | 2.0 |
| ***Acute exposure*** | | | | | | | | |
| Neonates | $Cmax^3$ | PO | 1 | 2 | 1 | 16 | 1.8 | 1.5 |
| Children | | PO | 3 | 8 | 5 | 102 | 0.69 | 1.8 |
| Elderly | | PO | 8 | 11 | 9 | 92 | 1.1 | 0.91 |
| Liver Disease | | PO | 4 | 8 | 6 | 62 | 1.1 | 0.97 |
| Renal Disease | | PO | 6 | 12 | 8 | 98 | 0.96 | 1.2 |

[a] **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$** variability ratio between subgroups and healthy adults; [1]Data corrected to body weight ($mlmin^{-1}kg^{-1}$); [2]Data not corrected to body weight ($mlmin^{-1}$); [3]Mean data corrected for dose expressed per mean body weight (mg/kg).

**Table 14. Overall pathway-related uncertainty factors derived for glucuronidation (multiple isoforms) in subgroups of the population basedon pooling of the data for related parameters [a].**

| Subgroup | PK parameter/Route | Nc | Ns | Np | n | Mean $CV_{LN}$ | Ratio $S/H_{LN}$ | Ratio $CV_{LN}$ | Glucuronidation-related Uncertainty factors (Lognormal distribution) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 95th | 97.5th | 99th |
| ***Chronic exposure[1]*** | | | | | | | | | | | |
| Healthy | $CL^1$, $CL^2$, $AUC^3$ (PO) | 15 | 87 | 78 | 906 | 29 | | | 1.6 | 1.8 | 2.0 |
| Neonates | $CL^1$ (PO) | 1 | 2 | 1 | 16 | 52 | 2.3 | 1.7 | 5.2 | 6.0 | 7.2 |
| Neonates | $CL^1$ (IV) | 4 | 14 | 9 | 94 | 50 | 3.9 | 1.7 | 8.6 | 10 | 12 |
| Infants | $CL^1$ (PO) | 1 | 1 | 1 | 4 | 8 | 0.97 | 0.39 | 1.1 | 1.1 | 1.2 |
| Infants | $CL^1$ (IV) | 2 | 4 | 3 | 25 | 38 | 1.2 | 1.1 | 2.2 | 2.5 | 2.8 |
| Children | $CL^1$, $AUC^3$ (PO) | 5 | 13 | 9 | 131 | 23 | 0.86 | 1.2 | 1.3 | 1.4 | 1.5 |
| Elderly | $CL^1$, $CL^2$, $AUC^3$ (PO) | 10 | 14 | 12 | 140 | 28 | 1.4 | 1.2 | 2.3 | 2.5 | 2.7 |
| ***Acute exposure[2]*** | | | | | | | | | | | |
| Healthy | Cmax[3] | 14 | 60 | 55 | 648 | 26 | | | 1.5 | 1.6 | 1.8 |
| Neonates | | 1 | 2 | 1 | 16 | 27 | 1.8 | 1.5 | 2.8 | 3.1 | 3.4 |
| Children | | 3 | 8 | 5 | 102 | 47 | 0.74 | 1.7 | 1.6 | 1.8 | 2.1 |
| Elderly | | 8 | 11 | 9 | 98 | 28 | 1.1 | 0.91 | 1.7 | 1.9 | 2.1 |

[a] **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **Mean $CV_N$** Mean coefficient of variation (normal distribution);. **Mean $CVL_N$** Mean coefficient of variation (lognormal distribution) **Ratio $S/H_{LN}$** Mean ratio between healthy adults and subgroup (for the AUC the 1/Ratio mean was calculated); **Ratio CV** variability ratio between subgroup and healthy adults; [1]Individual data corrected for dose expressed per mean body weight ($mgkg^{-1}$); [2]Data not corrected to body weight ($ml\ min^{-1}$); [3]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

## IV. Discussion

This chapter aimed to estimate the human variability in the glucuronidation pathway using *in vivo* metabolic and kinetic data for fifteen substrates. The analysis provided a basis to derive uncertainty factors for compounds primarily handled by this route of metabolism. Two large databases reflecting chronic exposure in healthy adults (oral and intravenous clearance/AUC data for 906 and 328 subjects respectively) and oral acute exposure (Cmax data for 648 subjects) were built and data for each compound and parameter were pooled using the assumption that they were normally or lognormally distributed. More limited data were also available for subgroups (ethnic minorities, neonates, infants, children, elderly, liver and renal disease patients).

Human variability in kinetics for the glucuronidation pathway (lognormal assumption) was overall about 30% for the chronic exposure estimates (metabolic clearances, clearances and AUC) and 26% for the acute exposure estimate (Cmax). Glucuronidation -related uncertainty factors for the healthy adults were found to be below the 3.16 kinetic default with values between 1.6 and 2.0 to cover 95 and 99% of healthy adults.

Genetic polymorphism in the glucuronidation pathway has been described (Patel *et al.,* 1995, a and b; Lévesque *et al.,* 1999) and 10% of adult subjects were phenotyped to be poor metabolisers of S-oxazepam using urinary excretion of S-oxazepam glucuronide. The influence of these polymorphisms on the *in vivo* plasma kinetics of glucuronidation probe substrates has not been investigated. Quantification of the extent of any phenotypic differences in Caucasians and ethnic minorities might require a re-evaluation of the *in vivo* variability for the glucuronidation pathway.

No major quantitative inter-ethnic differences for the metabolic clearance of propranolol by glucuronidation were shown between Caucasians and black African-Americans but a slightly higher clearance was found in Chinese compared to Caucasians. The metabolism of codeine via glucuronidation, measured as the urinary recovery of the glucuronide, has been reported to be twice as efficient in Swedish as in Chinese subjects (Yue *et al.,* 1989), but no differences in paracetamol metabolism were shown between Chinese and Caucasians (Osborne *et al.,* 1991; Miners and Mackenzie, 1991). It has been suggested that inter-ethnic differences in glucuronidation could be isozyme specific, with different

UDPGTs involved (Osborne *et al.,* 1991; Miners and Mackenzie, 1991).

The differences between subgroups and healthy adults identified neonates and patients with liver or kidney disease as showing the greatest difference compared to healthy adults, with averages of 30% for the former and 20% for both latter subgroups exceeding a factor of 3.16 away from the mean for healthy adults. Because glucuronidation is nearly always a detoxication reaction, the lower clearance and higher AUC in these subgroups can be considered to result in greater susceptibility. Neonates have also been identified as a potentially susceptible group using a database on CYP1A2 kinetic variability (Dorne *et al.,* 2001). Quantitative age-related differences in glucuronidation *in vitro* have been reported previously, which are consistent with the neonate *in vivo* data analysis in this paper (Miners and Mackenzie, 1991; de Wildt *et al.,* 1999).

Decreased clearance for high hepatic clearance drugs metabolised via glucuronidation has been shown previously in the elderly and considered to be due to a lower liver blood flow (Miners and Mackenzie, 1991). In contrast, the clearances of capacity limited drugs like paracetamol are generally unaffected by old age (Miners and Mackenzie, 1991). Minor differences were seen in the drugs in our database because most of them had a relatively low clearance. There are large *in vitro* differences in the glucuronidation capacity of liver from patients with liver disease compared to healthy adults (Little *et al.,* 1999); the present *in vivo* database showed a greater difference after oral than after intravenous dosage, consistent with liver disease affecting both first-pass metabolism and clearance.

From our database, pathway-related uncertainty factors for variability in toxicokinetics in humans of 1.6, 1.8 or 2.0 applied to contaminants that are eliminated largely by glucuronidation (isoform not specified) would cover 95, 97.5 or 99% of healthy adults. In contrast neonates were identified as the most sensitive subgroup and would require an uncertainty factor of 12 (to cover them up to the $99^{th}$ centile).

Although the overall pathway of metabolism of a compound under evaluation may be known, the isoform of an enzyme responsible for its metabolism will only rarely have been defined. The increasing availability of *in vitro* enzyme expression systems means that future risk assessments may have isoform-related information available in the absence of chemical-specific toxicokinetic data. Pathway-derived uncertainty factors have been calculated for three UGT isoforms (UGT1A4, UGT1A6 and UGT2B7); the UGT1

isoforms showed less variability (25% versus 45%), and would require lower pathway-related factors than for substrates of the UGT2. Recently, UGT2B7 has been shown to be polymorphic with 2 forms (UGT2B7 *1 and *2) (Bhasker *et al.,* 2000), however differences in enzyme activity *in vitro* have not been clearly established, and *in vivo* kinetic data for probe substrates are not available.

This chapter demonstrates that a series of pathway-related uncertainty factors can be generated for the healthy adult population and potentially sensitive subgroups from analyses of pathway-related kinetic variability. These pathway-related uncertainty factors give an intermediate option to move away from standard default factors.

# Chapter IV Human variability in polymorphic CYP2D6 metabolism: is the 3.16 kinetic default still relevant ?

## I.Introduction

Amongst the CYP isoforms, the well characterised CYP2D6 polymorphism has been shown to be clinically important in the oxidation (mainly via hydroxylation/ N-dealkylation) of more than 25 drugs including anti-arrhythmic drugs, neuroleptics, antidepressants (tricyclic and SSRIs), β-blockers and opiates (Gaedigk *et al.,* 1991; Marzo and Balant,1996). The discovery of this polymorphism was originally linked with the impaired hydroxylation of debrisoquine and bufuralol, associated with marked hypotension in some individuals, and a decrease in the oxidative metabolism of sparteine associated with an increase in side effects (Balant *et al.,* 1976; Maghoub *et al.,* 1977; Tucker *et al.,* 1977; Eichelbaum *et al.,* 1979,1986). The hydroxylation capacity was at that time defined as the metabolic urinary ratio between the parent drug and its hydroxylated derivative and was shown to follow a bimodal distribution corresponding to two main phenotypes: extensive metabolisers (EMs) and poor metabolisers (PMs).

Three substrates (debrisoquine, sparteine and dextromethorphan) have been traditionally used in drug metabolism studies to differentiate PMs from EMs and to determine the prevalence of poor metabolism (Alvan *et al.,* 1990). The PM phenotype was shown to have a prevalence of 7.4% in the Caucasian population and was associated with a considerable homogeneity amongst the different European populations (overall range 5-10%) (data based on the three probe drugs and 8700 samples) (Alvan *et al.,* 1990). The frequency of PMs in Oriental populations was found to be much lower than in Caucasians ranging from 0-1% (Johansson *et al.,* 1991,1994), while prevalence of PMs in Africans averaged 2% and was more variable (range: 0.50-19%) (Masimirembwa *et al.,* 1997).

The molecular genetic background for the different CYP2D6 phenotypes has been investigated and allelic variants have been classified in four main classes: i) defect alleles, ii) alleles causing impaired rate of metabolism, iii) duplicated or amplified alleles causing increased rate of metabolism, iv) alleles with structural differences but having no influence on the rate of metabolism (Ingelman-Sundberg *et al.,* 1995). Examination of genomic DNA from Caucasian PMs revealed that the major defective allele was CYP2D6B with a frequency of 21% whereas CYP2D6D allele was more evenly distributed between black, Oriental and Caucasian PM populations (4.0-6.0%) (Dahl *et al.,* 1995). In contrast, CYP2D6L alleles were amplified or duplicated in ultra rapid metabolisers with up to 13 copies in some subjects (Dahl *et al.,* 1995).

At the population level, the relevance of genetic polymorphisms towards the handling of xenobiotics is indisputable. Quantification of interindividual differences between EMs and PMs would allow such susceptible individuals to be taken into account in non-cancer risk assessment and replacement of traditional uncertainty factors. Data for some substrates handled by CYP2D6 suggested that the 3.16 kinetic default factor applied to EMs would not provide sufficient protection for PMs (Renwick and Lazarus, 1998), however the compounds studied were handled by multiple pathways. Therefore, this chapter aims to evaluate the human variability in kinetics for the polymorphic CYP2D6 pathway using probe substrates metabolised primarily via this route. Inter-individual differences will be determined between EMs, PMs and other available subgroups of the population. Moreover, the differences between EMs and PMs will also be considered for compounds handled by CYP2D6 and other pathways to investigate the nature of the relationship between the extent of CYP2D6 metabolism and the magnitude of the difference between EMs and PMs. Finally, this analysis will be applied to chemicals handled by CYP2D6 metabolism to develop CYP2D6-related default uncertainty factors.

## II. Methods

The method used in this chapter follows that described in chapter II for the literature search, criteria, data analysis and all calculation methods (weighted mean analysis for both normal and lognormal distibution assumptions). However, the nature of the data describing a polymorphic pathway required adjustement of the methods to select major and minor probe substrates handled by CYP2D6 and to quantify differences between phenotypes.

## II.1 Selection of probe substrates

- Major CYP2D6 probe substrates were selected on the basis that their oral absorption was >90%, and that CYP2D6 metabolism represented between 60-100% of an oral dose excreted as metabolites in EMs. In the case of compounds with enantiomers, the biological active form was selected.

- Minor CYP2D6 probe substrates were also readily absorbed after oral administration (>90%) and CYP2D6 metabolism represented between 10-60% of an oral dose in EMs.

## II.2 Data analysis

### II.2.1 Healthy adults

The kinetic data for healthy adults were available for three distinct groups (non-phenotyped individuals, EMs, SEMs and PMs). Data describing human variability in kinetics in non-phenotyped individuals were analysed separately from the data for phenotyped individuals (for both major and minor CYP2D6 probe substrates) for which both poor metaboliser phenotypes (PMs and SEMs) were treated as a subgroup and compared to the extensive metabolisers (ratio of the geometric mean and coefficient of variation).

### II.2.2 Subgroups

Data describing kinetics of CYP2D6 probe substrates for subgroups of the population (effect of ethnicity, age and disease) were compared (geometric mean and variability ratios) to non-phenotyped healthy adults if the data described kinetics in non-phenotyped subjects and were compared to healthy adult EMs if the data described kinetics in either EMs, SEMs or PMs. However, the data in Asian healthy adults were complex and in some cases the absence of EM data in healthy adults required a comparison to non-phenotyped healthy adults.

## II.3 Quantitative Relationship between CYP2D6-metabolism and differences in internal dose between EMs and PMs

Differences in geometric means for the internal dose between EMs and PMs were calculated for major and minor substrates and plotted against the percentage of the dose handled by CYP2D6 in EMs to investigate the relationship between these two variables.

### II.4 Derivation of CYP2D6-related uncertainty factors

CYP2D6-related uncertainty factors necessary to cover the 95$^{th}$, 97.5$^{th}$ and 99$^{th}$ percentile of the healthy adult (lognormal) population were calculated for each kinetic parameter and combined using the weighted mean analysis described in Chapter II. For subpopulations, the default factors were calculated using the mean ratios for the subgroup compared to that for healthy adults, and the variability within the subgroup.

CYP2D6-related uncertainty factors for major and minor substrates were also calculated using differences in geometric means for the internal dose between EMs and PMs to investigate the nature of the relationship between the uncertainty factor and the extent of CYP2D6 metabolism.

## III. Results

### III.1. Metabolism Data

Several drugs (despiramine, encainide, metoprolol, propafenone, tolterodine and venlafaxine) were selected on the basis that at least 60% of their metabolism was mediated by CYP2D6 in EMs. Metabolism data are presented for the two main phenotypes and for the intermediate phenotype (SEM: Slow Extensive Metabolisers) when data were available (Table1).

Substrates for which the metabolism is not largely mediated via the CYP2D6 isoform have also been selected to investigate the effect of percentage involvement of CYP2D6 on EM/PM differences and the percentage of CYP2D6 metabolism has been estimated from available metabolism data (*in vitro* and *in vivo*) (Table1).

#### III.1.1 Major substrates for the CYP2D6 isoform

##### *III.1.1.1 Desipramine*

Desipramine is metabolised via CYP2D6-dependent 2-hydroxylation. Over 66% of an oral dose is recovered as the 2-hydroxy derivative in EMs with approximately 2% excreted as unchanged drug. PMs excreted only 12% of the 2-hydroxy derivative and 8.5% of unchanged desipramine (Steiner and Spina., 1987).

##### *III.1.1.2 Encainide*

Encainide metabolism consists largely of an O-demethylation leading to O-desmethylencainide and its 3-methoxy derivative and a minor N-demethylation reaction

leading to the N-desmethyl and to the N,O-didesmethyl metabolites has also been described. Both demethylation reactions have been shown to be CYP2D6-dependent, and more than 80-90% of the elimination of intravenous encainide was mediated by this isoform in EMs, with only 10-20% recovered as the parent drug; in contrast most of the drug (>80%) is excreted unchanged in the urine of PMs (Funck-Brentano *et al.,* 1989). The metabolism of oral encainide has also been investigated in healthy men and 47% and 39% of the dose was recovered as metabolites in the urine and faeces respectively, more than 85% of which were CYP2D6 mediated in EMs; encainide is largely eliminated unchanged in PMs (Wang *et al.,* 1984; Jajoo *et al.,* 1990).

### *III.1.1.3 Metoprolol*

Oral metoprolol is metabolised extensively via three major routes of oxidation which are regioselective and stereoselective: α-hydroxylation (10% of the dose), O-demethylation (65%), N-dealkylation (10%) with 85% of these metabolites excreted in the urine (Borg *et al.,* 1975; Mautz *et al.,* 1995). The polymorphic nature of metoprolol metabolism via the CYP2D6 isoform has been recognised for a number of years and studies in human liver microsomes demonstrated that the α-hydroxylation is totally impaired in PMs, the O-demethylation is partially impaired but the correlation between CYP2D6 and metoprolol N-dealkylation was not presented (Lennard *et al.,* 1982; Otton *et al.,* 1988). A major fraction of metoprolol is excreted unchanged in PMs (36% in PMs versus 6% in EMs) and authors have concluded than most of an oral dose of metoprolol is metabolised by the CYP2D6 isoform in EMs (>75% of the dose) (Borg *et al.,* 1975; Lennard *et al.,* 1982; Otton *et al.,* 1988; Mautz *et al.,* 1995).

### *III.1.1.4 Propafenone*

Propafenone, given as an oral racemate, is extensively metabolised (>95%) in EMs with 53% excreted in the faeces (55 hours) and between 19-38% excreted in the urine (48 hours) (Hege *et al.,* 1984). The major routes of metabolism are 5-hydroxylation (with further conjugation) and N-dealkylation; the formation of the 5-hydroxy-derivative correlates with CYP2D6 while N-dealkylation is associated with CYP3A4 and CYP1A2 in human liver microsomes (Kroemer *et al.,* 1989; Botsch *et al.,* 1993). The 5-hydroxy and its derivatives represent more than 83% of the urinary metabolites in non-phenotyped individuals with an overall value of around 70% of the dose in the urine and faeces of EMs. PMs excrete as little as 1.5% of 5-hydroxypropafenone in the urine and as much as 52% of propafenone glucuronide (Vozeh *et al.,* 1990; Latini *et al.,* 1992; Botsch *et al.,* 1994; Dilger *et al.,* 1999).

### *III.1.1.5 Tolterodine*

Tolterodine metabolism by human liver microsomes involves two main reactions: 5-hydroxylation with oxidation to the acid, and further dealkylation mediated by the polymorphic CYP2D6 isoform, and N-dealkylation via the CYP3A4 isoform with further 5-hydroxylation and oxidation leading to the N-dealkylated acid (Postlind *et al.,* 1998). The *in vivo* metabolism exhibits high first-pass extraction and metabolism in EMs. More that 85% of the systemic clearance corresponds to CYP2D6 metabolites, with the acid and its N-dealkylated form accounting for 56-77% of an oral dose in EMs, 18-52% in SEMs and non identified metabolites (>10% in EMs). Both metabolites are undetectable in the urine of PMs. The proportion of unchanged tolterodine excreted in the urine is low in EMs (<1.5%), and higher in SEMs (1.3-15%) and PMs (23-29%). The CYP3A4 dependent metabolite is higher in PMs (33-38%) than EMs (13-17%) and SEMs (13-19%) (Brynne *et al.,* 1999a).

### *III.1.1.6 Venlafaxine*

Venlafaxine is extensively metabolised via O-demethylation with further metabolism and conjugation: 74% of an oral dose was recovered in the urine as the O-demethyl metabolite and its derivatives, 4.7% as unchanged drug and 14% as unidentified metabolites in non-phenotyped adults (Howell *et al.,* 1993). The CYP2D6 isoform has been shown to mediate the O-demethylation reaction while the minor N-demethylation is mediated by CYP3A4 (Otton *et al.,* 1996). Urinary metabolites were quantified in humans after 12 hours and PMs excreted less O-Desmethylvenlafaxine than EMs (11% against 36%) and much more N-desmethyl derivative (23% versus 6%) and parent drug (16% versus 2%) (Lessard *et al.,* 1999).

## III.1.2 Minor substrates for the CYP2D6 isoform

### *III.1.2.1 Imipramine*

Imipramine is metabolised via two main pathways, demethylation mediated by mixed CYP isoforms: the polymorphic CYP2C19, CYP3A4 and CYP1A2 and hydroxylation (with further conjugation) mediated by CYP2D6. A variable fraction of the 2-hydroxy derivative is recovered in the urine in non-phenotyped healthy adults (18% with very high variability) with 8% of excreted unchanged. Metabolic clearances for the 2-hydroxylation in phenotyped individuals were also available in the literature with the 2-hydroxy (and its derivatives)

representing about 44%, 30% and 20% of the dose in EMs, SEMs and PMs (Brosen *et al.*, 1986; Bergstrom *et al.*, 1992; Brosen *et al.*, 1991; Lemoine *et al.*, 1993; Chiba *et al.*, 1994).

### *III.1.2.2 Sparteine*

Sparteine has been used as a CYP2D6 probe substrate for a number of years with two main metabolites: 2 and 5-dehydrosparteine excreted in the urine of EMs (>50%) while PMs excrete the unchanged drug (>95%) (Eichelbaum *et al.*, 1986).

### *III.1.2.3 Amitriptyline and Nortryptiline*

Amitriptyline and nortryptiline are both metabolised to a considerable extent and in a stereoselective dependent manner (E and Z enantiomers). The enantiomeric derivatives (hydroxy-amitriptyline and 10-hydroxy-nortriptyline for amitriptyline and 10-hydroxy-nortriptyline for nortryptiline) are formed by CYP2D6 metabolism. No correlations between CYP2D6 metabolism and the Z enantiomer have been found for either drug. For each compound, the CYP2D6 metabolites represent approximately 50 and 48% of the dose excreted in the urine of EMs, 15 and 18% in the urine of PMs, whereas the Z enantiomer metabolites represents between 10 and 20% in both phenotypes (Mellstrom *et al.*, 1981; Balant-Gorgia *et al.*, 1982; Breyer–Pfaff et al.,1992; Dalen *et al.*, 1998).

### *III.1.2.4 Codeine*

Codeine is metabolised mainly via glucuronidation (>50%) and to a minor extent via O-demethylation which has been shown to be CYP2D6-dependent in EMs (<6% in EM, <0.4% in PM) (Dayer *et al.*, 1988; Yue *et al.*, 1991).

### *III.1.2.5 Hydrocodone and Dihydrocodeine*

Hydrocodone and dihydrocodeine are structurally related to codeine and are also oxidised to a minor extent via a CYP2D6-dependent O-demethylation. Data from liver microsome studies, combined with human *in vivo* studies in EMs and PMs showed that less than 6% of oral hydrocodone and 9% of oral dihydrocodeine underwent O-demethylation in EMs and only 1 and 1.3% in PMs respectively (Otton *et al.*, 1993; Fromm *et al.*, 1995).

### *III.1.2.6 Mexiletine*

Mexiletine has been shown to be hydroxylated in a stereoselective manner and formation of the hydroxymethyl derivatives of the p-enantiomer is mediated by the CYP2D6 isoform in liver microsomes. More than 40% of an oral dose corresponds to CYP2D6 metabolites in

EMs with a 2-fold reduction in PMs (Broly *et al.,* 1990; Vandamme *et al.,* 1993; Abolfathi *et al.,* 1993).

### *III.1.2.7 Propranolol*

Propranonol metabolism involves several metabolic pathways: glucuronidation of the parent drug, 4-hydroxylation (with further sulphate and glucuronide conjugation) and N-deisopropylation. Propranolol 4-hydroxylation of both R and S enantiomers is mediated via CYP2D6. In EMs over 40% of an oral dose of racemate or R-enantiomer and 20% of the S-enantiomer is excreted as the 4-hydroxy derivative. This reaction is considerably impaired in PMs for the racemate (<3%), the R-enantiomer (25%) and the S-enantiomer (8 %), with an increase in excretion of the parent drug and its glucuronide (Shaheen *et al.,* 1989; Ward *et al.,* 1989; Masubuchi *et al.,* 1994; Yoshimoto *et al.,* 1995).

**Table 1. Metabolism data for the CYP2D6 probe substrates in healthy adult volunteers: estimation of the quantitative differences between extensive, slow extensive and poor metabolisers[a].**

| Drug | EM | | SEM | | PM | |
|---|---|---|---|---|---|---|
| | n | % CYP2D6 | n | % CYP2D6 | n | % CYP2D6 |
| *Major CYP2D6 substrates* | | | | | | |
| Desipramine | 5 | 68[1] | | | 4 | 12 |
| Encainide | 7 | 85[2] | | | 4 | 10-20 |
| Metoprolol | 6 | 75[3] | | | 2 | 10 |
| Propafenone | 22 | >70[4] | | | 6 | <1.5 |
| Tolterodine | 3 | 85[5] | 4 | >40 | 4 | 8.4 |
| Venlafaxine | 9[NP] | >72[6] | | | | |
| *Minor CYP2D6 substrates* | | | | | | |
| Amitryptiline | 4 | 50[7] | | | 3 | 48 |
| Codeine | 8 | 5.7[8] | | | 6 | 0.37 |
| Dihydrocodeine | 6 | 5.9[9] | | | 5 | 1.00 |
| Hydrocodone | 8 | 8.9[10] | | | 6 | 1.30 |
| Imipramine | 6 | 44[11] | 6 | 30.3 | 6 | 19 |
| Mexiletine | 7 | 44[12] | | | 2 | 12 |
| Nortryptiline | 4 | 48[13] | | | 4 | 18 |
| Propranonol | 6 | 42[14] | | | | 10-20 |
| R-Propranonol | 6 | 43[15] | | | 4 | 17 |
| S-Propranonol | 6 | 25[15] | | | 4 | 12 |
| Sparteine | 10 | 53[16] | | | 1 | 8.7 |

[a]**N** Number of subjects; **NP** Data in non-phenotyped healthy individuals; **EM** Extensive metabolisers; **PM** Poor metabolisers; **SEM** Slow extensive metabolisers; **% CYP2D6** percentage of the dose metabolised by the CYP2D6 isoform.

[1]Steiner and Spina., 1987; [2]Funck-Brentano *et al.*, 1989; [3]Borg et al ., 1975, Lennard *et al.*, 1982;. Mautz *et al.*, 1995; [4]Hege *et al.*, 1984, Siddoway *et al.*, 1987, Botsch *et al.*, 1994, Dilger *et al.*, 1999; [5]Brynne *et al.*, 1999a; [6]Howell *et al.*, 1993, Lessard *et al.*, 1999; [7]Balant-Gorgia *et al.*, 1982; [8]Yue *et al.*, 1991; [9]Fromm *et al.*, 1995; [10]Otton *et al.*, 1993; [11] Brosen *et al.*, 1986; [12]Broly et al ., 1990; [13]Mellstrom *et al.*, 1981; [14]Walle *et al.*, 1985; [15]Ward *et al.*, 1989; [16]Eichelbaum *et al.*, 1986.

This analysis of CYP2D6 metabolism demonstrates that PMs possess alternative routes of metabolism which are impaired compared to EMs and involve mainly renal excretion of the parent drug, and to a minor extent other CYP isoforms and conjugation reactions (mainly CYP3A4, CYP1A2, glucuronidation and sulphation).

## III.2. Kinetic data

Tables 2-10 present the weighted mean analysis for normal and lognormal data. Interindividual differences described as the coefficient of variation for both distributions ($CV_N$ for normal and $CV_{LN}$ for lognormal), are presented in the text as a single value, unless differences are observed in which case both values are described.

## III.2.1 Kinetic parameters reflecting chronic and acute exposure in general healthy adults

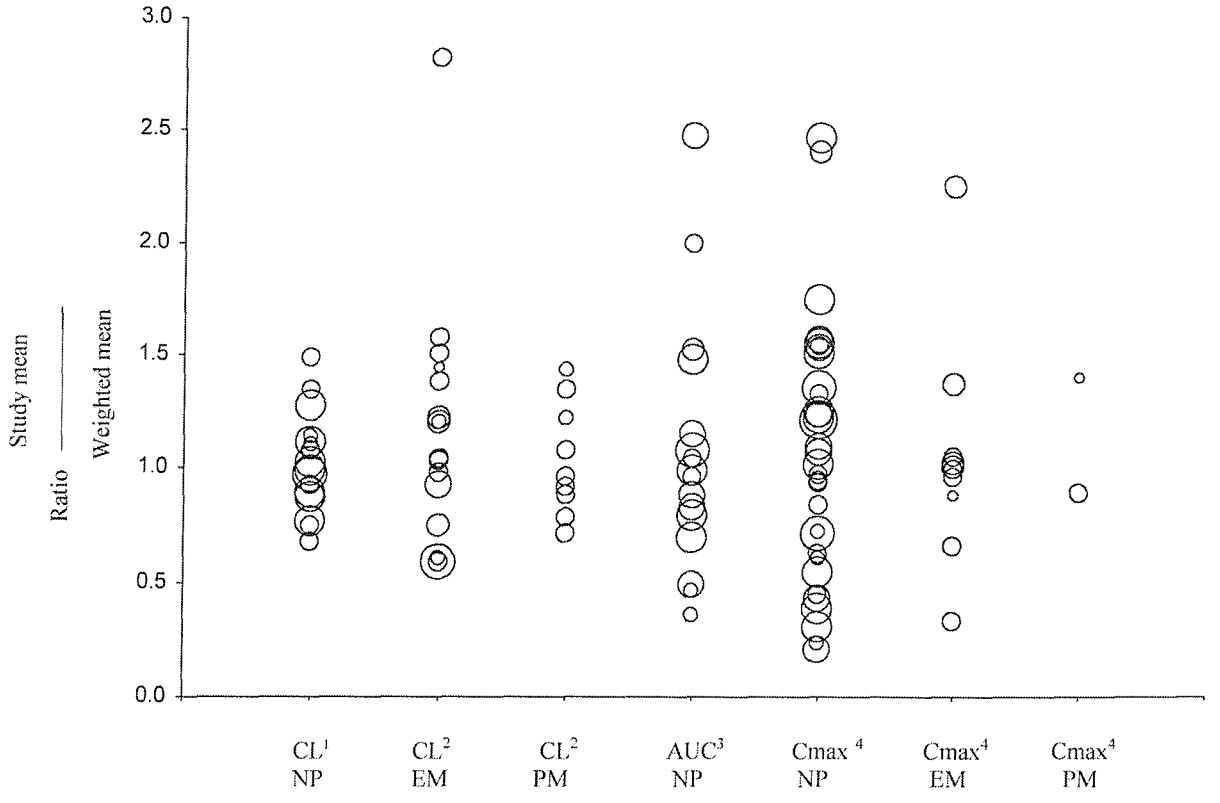
### *III.2.1.1 Variability between studies*

The variation in $GM_w$ and $CV_{LN}$ between studies for each compound with data from more than one study per parameter, was calculated as the ratio between the individual study and the overall weighted value. Figures 1 and 2 give the inter-study variability data for each kinetic parameter (clearance adjusted to body weight, clearance, AUC and Cmax) as bubble graphs with the size of the bubble proportional to the study group size (n), and with the overall weighted value for each parameter for each compound normalised to 1.

Figure 1 shows the interstudy variability in the geometric mean parameter estimate for non-phenotyped healthy adults, extensive and poor metabolisers. Inter-study differences for non-phenotyped healthy adults were mostly within a 30% range of the overall weighted mean. However larger differences were observed for some studies with metoprolol (AUC and Cmax) and with venlafaxine (Cmax). The data for EMs showed similar inter-study variability to that from non-phenotyped healthy adults with an outlier for propafenone (CL) and metoprolol (Cmax). The inter-study variability for PMs (20-30%) was slightly less than that NP and EM individuals.

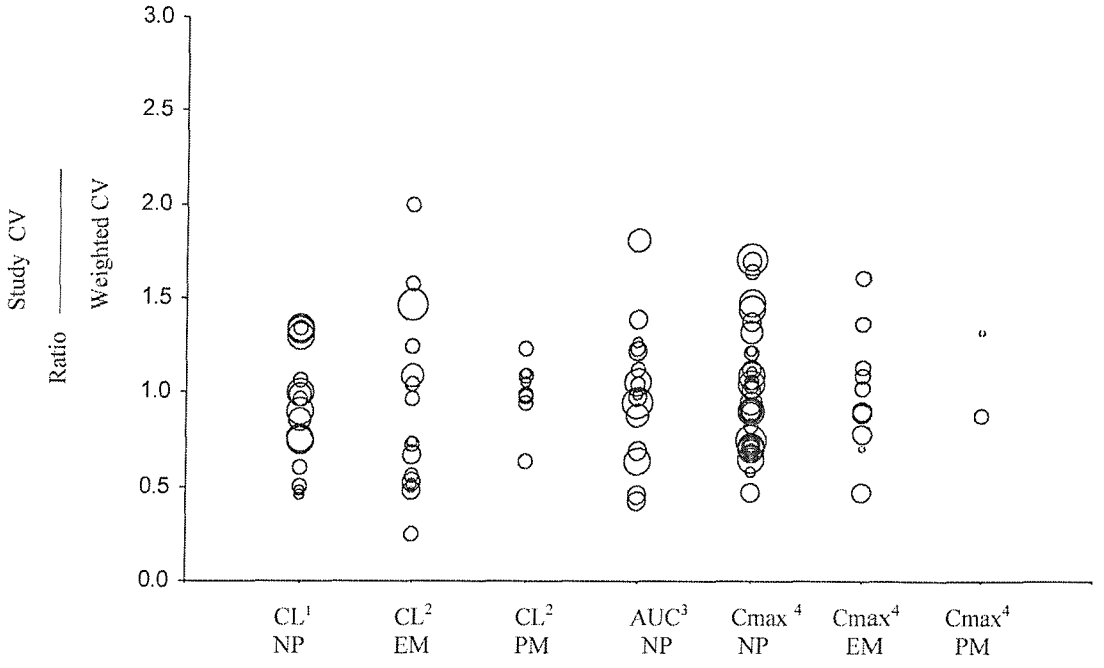
Figure 2 shows that the inter-study differences in the $CV_{LN}$ were mostly within 30-50% of the overall weighted CV for both NP and EM with less variability for PMs (20-30%). A large difference was observed for some studies; examples of outliers are venlafaxine (AUC in NP subjects), (Cmax in NP subjects) and metoprolol (CL in EMs), desipramine (CL in EMs) and S-metoprolol (Cmax in EMs).

**Figure 1. Inter-study variation in kinetic parameters for CYP2D6 probe substrates after oral administration in healthy adult volunteers (non-phenotyped, extensive and poor metabolisers). Comparisons of individual study means versus weighted geometric means.**




The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$NP-data for despramine (6 studies), metoprolol (2 studies), propafenone (2 studies), venlafaxine (7 studies) in non phenotyped subjects; $CL^2$EM-data for desipramine (3 studies), encainide (2 studies), metoprolol (3 studies), propafenone (4 studies), tolterodine (2 studies), venlafaxine (2 studies) in extensive metabolisers; $CL^2$PM data for desipramine (2 studies), metoprolol (3 studies), propafenone (2 studies), venlafaxine (2 studies) in poor metabolisers; $AUC^3$NP-data for metoprolol (11 studies), venlafaxine (5 studies) in non phenotyped subjects; $Cmax^4$NP-data for desipramine (8 studies), metoprolol (9 studies), propafenone (3 studies), venlafaxine (13 studies) in non-phenotyped subjects; $Cmax^4$EM-data for metoprolol (6 studies), propafenone (2 studies), tolterodine (2 studies) in extensive metabolisers; $Cmax^4$PM-data for tolterodine (2 studies) in poor metabolisers.

**Figure 2. Inter-study variation in kinetic parameters for CYP2D6 probe substrates after oral administration in healthy adult volunteers (non-phenotyped, extensive and poor metabolisers). Comparisons of individual study coefficient of variations ($CV_{LN}$) versus weighted coefficient of variations ($CV_{LN}$).**




The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$NP-data for despramine (6 studies), metoprolol (2 studies), propafenone (2 studies), venlafaxine (7 studies) in non phenotyped subjects; $CL^2$EM-data for desipramine (3 studies), encainide (2 studies), metoprolol (3 studies), propafenone (4 studies), tolterodine (2 studies), venlafaxine (2 studies) in extensive metabolisers; $CL^2$PM data for desipramine (2 studies), metoprolol (3 studies), propafenone (2 studies), venlafaxine (2 studies) in poor metabolisers; $AUC^3$NP-data for metoprolol (11 studies), venlafaxine (5 studies) in non phenotyped subjects; $Cmax^4$NP-data for desipramine (8 studies), metoprolol (9 studies), propafenone (3 studies), venlafaxine (13 studies) in non-phenotyped subjects; $Cmax^4$EM-data for metoprolol (6 studies), propafenone (2 studies), tolterodine (2 studies) in extensive metabolisers; $Cmax^4$PM-data for tolterodine (2 studies) in poor metabolisers.

### *III.2.1.2 Variability in non phenotyped individuals*

Kinetic data for the main probe substrates in non-phenotyped healthy individuals are presented for both the oral and intravenous route of administration (Table 4). The parameters reflecting chronic exposure for the oral route (clearances and AUCs) were highly variable with CVs of 66/64% (normal/lognormal, $mlmin^{-1}kg^{-1}$, 243 subjects), 85% ($mlmin^{-1}$, 47 subjects) and 73/76% (normal/lognormal, AUC/dose and 244 subjects); overall the variability for 7 compounds ranged from 35% to 130%. The variability after intravenous dosage was lower for both clearance estimates with values of 37/38% ($mlmin^{-1}kg^{-1}$, 4 compounds, 64 subjects) and 16% ($mlmin^{-1}$, 1 compound, 8 subjects).

Most of the major CYP2D6 substrates were high clearance compounds and interindividual differences for the intravenous route would largely reflect liver blood flow, whereas the variability for the oral route reflects both the hepatic blood flow and the CYP2D6 enzyme

activity. Therefore, the oral data provide a better indication of the impact of differences in CYP2D6 activity on toxicokinetics.

The variability in Cmax was 66/63%, (normal/lognormal, 6 compounds, 445 subjects).

### *III.2.1.3 Variability in phenotyped healthy individuals*

#### *III.2.1.3.1 Extensive metabolisers (EMs)*

The oral clearance and AUC data for EMs (Table 5) supported the pattern demonstrated with the metabolic clearances and the overall kinetic data in NP subjects. The calculated interindividual variability depended on the assumption about the population distribution, with a range between 49-130% for a normal distribution and 37-89% for a lognormal distribution (9 compounds, 192 subjects). The mean coefficients of variation for the clearances were 59/56% (normal/lognormal, $mlmin^{-1}kg^{-1}$, 2 compounds, 25 subjects) and 85/70% (normal/lognormal, $mlmin^{-1}$, 7 compounds and 138 subjects) and 62% for the AUC (2 compounds, 29 subjects). As found for NP subjects, intravenous clearance ($mlmin^{-1}$) in EMs showed a lower variability than the equivalent for the oral route (34% for both distributions, 3 compounds, 35 subjects) (Table 6).

The variability in Cmax for EMs was 58/59% (5 compounds (plus 2 enantiomers),102 subjects) (Table 5).

#### *III.2.1.3.2 Poor metabolisers (PMs)*

The oral clearance data ($mlmin^{-1}$) for the PMs demonstrated a 12-fold higher internal dose (6 compounds and 61 subjects) compared to EMs (only limited data were available for clearance adjusted to body weight and AUC) (Table 5). This was much lower than the 73-fold difference in internal dose demonstrated with the metabolic clearance ($mlmin^{-1}$). The variability in clearances in PMs was 32%. The intravenous data (Table 6) showed a 5-fold difference in the total clearance between EMs and PMs ($mlmin^{-1}$, 2 compounds, 14 subjects) with a mean coefficient of variation of 18%.

The Cmax data showed a 3.5-fold difference between EMs and PMs; the PM data had a variability of 21/20% (normal/lognormal, 5 compounds, 41 subjects) (Table 5).

**Table 4. Interindividual variation in pharmacokinetic parameters of CYP2D6 probe substrates after oral and intravenous administration to non-phenotyped healthy adult volunteers[a].**

| DRUG | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| ***Oral administration*** | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | |
| Desipramine | 6 | 5[1] | 58 | 31 | 17 | 57 | 26 | 1.7 | 55 |
| Metoprolol | 2 | 2[2] | 11 | 24 | 14 | 57 | 21 | 1.7 | 55 |
| Propafenone | 2 | 2[3] | 16 | 170 | 130 | 80 | 130 | 2.01 | 79 |
| Tolterodine | 1 | 1[4] | 8 | 34 | 27 | 80 | 27 | 2.01 | 80 |
| Venlafaxine | 8 | 8[5] | 136 | 26 | 15 | 57 | 23 | 1.6 | 52 |
| CL ($mlmin^{-1}$) | | | | | | | | | |
| Desipramine | 1 | 1[6] | 6 | 2000 | 890 | 45 | 2000 | 1.5 | 45 |
| Encainide | 1 | 1[7] | 8 | 12000 | 12000 | 98 | 8900 | 2.3 | 98 |
| Propafenone | 1 | 1[8] | 23 | 9700 | 12000 | 130 | 6100 | 2.6 | 130 |
| S-Metoprolol* | 1 | 1[9] | 10 | 1100 | 730 | 66 | 920 | 1.8 | 66 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | |
| Desipramine | 1 | 1[10] | 8 | 780 | 280 | 35 | 775 | 1.4 | 35 |
| Metoprolol | 11 | 9[11] | 151 | 2900 | 2900 | 99 | 1900 | 2.1 | 84 |
| Venlafaxine | 5 | 3[12] | 85 | 820 | 694 | 85 | 630 | 2.0 | 79 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | |
| Desipramine | 8 | 7[13] | 79 | 34 | 19 | 54 | 26 | 1.5 | 45 |
| Encainide | 1 | 1[14] | 9 | 230 | 180 | 79 | 180 | 2.0 | 79 |
| Metoprolol | 9 | 7[15] | 89 | 310 | 170 | 53 | 220 | 1.7 | 55 |
| Propafenone | 3 | 3[16] | 39 | 67 | 66 | 99 | 48 | 2.2 | 92 |
| Tolterodine | 1 | 1[4] | 8 | 130 | 77 | 59 | 110 | 1.7 | 59 |
| Venlafaxine | 13 | 11[17] | 221 | 130 | 68 | 53 | 93 | 1.6 | 48 |
| ***Intravenous administration*** | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | |
| Desipramine | 2 | 1[18] | 13 | 14 | 1.9 | 14 | 13 | 1.2 | 16 |
| Encainide | 1 | 1[19] | 9 | 13 | 5.6 | 43 | 12 | 1.5 | 43 |
| Metoprolol | 1 | 1[20] | 18 | 15 | 8.7 | 57 | 13 | 1.7 | 57 |
| Propafenone | 3 | 3[21] | 24 | 12 | 4.0 | 34 | 11 | 1.4 | 35 |
| CL ($mlmin^{-1}$) | | | | | | | | | |
| Metoprolol | 1 | 1[22] | 8 | 900 | 140 | 16 | 890 | 1.2 | 16 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_W}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_W}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)**, in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); *Given as the racemate.

[1]De Vane *et al.*, 1981, Rudorfer *et al.*, 1984, Pi *et al.*, 1986, Ciraulo *et al.*, 1988 (2), Spina *et al.*, 1993; [2]Hogstedt *et al.*, 1985, Braat *et al.*, 1992; [3]Hollmann *et al.*, 1983, Vozeh *et al.*, 1990; [4]Brynne *et al.*, 1997; [5]Klamerus *et al.*, 1992, Troy *et al.*, 1994a, Troy *et al.*, 1995a, Klamerus *et al.*, 1996, Troy *et al.*, 1996, Troy *et al.*, 1997a, Troy *et al.*, 1997b, Troy *et al.*, 1998; [6]Kurtz *et al.*, 1997; [7]Bergstrand *et al.*, 1986; [8]Axelson *et al.*, 1987; [9]Jonhson and Burlew *et al.*, 1996; [10]Spina *et al.*, 1996; [11]Jack *et al.*, 1982a (3), Jack *et al.*, 1982b, Briant *et al.*, 1983, Godbillon *et al.*, 1983, Laarson *et al.*, 1984, Darmansjah *et al.*, 1990, Deroubaix *et al.*, 1996, Lloyd *et al.*, 1990, Lundborg *et al.*, 1993; [12]Troy *et al.*, 1995b, Troy *et al.*, 1997c, Troy *et al.*, 1997d(3); [13]De Vane *et al.*, 1981, Abernethy *et al.*, 1985 (2), Pi *et al.*, 1986, Bergstrom *et al.*, 1992, Spina *et al.*, 1993, Spina *et al.*, 1996, Kurtz *et al.*, 1997; [14]Winkle *et al.*, 1981; [15]Jack *et al.*, 1982a (3), Jack *et al.*, 1982b, Briant *et al.*, 1983, Darmansjah *et al.*, 1990, Lloyd *et al.*, 1990, Lundborg *et al.*, 1993, Deroubaix *et al.*, 1996; [16]Hollmann *et al.*, 1983, Axelson *et al.*, 1987,Vozeh *et al.*, 1990; [17]Klamerus *et al.*, 1992, Troy *et al.*, 1994, Troy *et al.*, 1995a, Troy *et al.*, 1995b, Klamerus *et al.*, 1996, Troy *et al.*, 1996, Troy *et al.*, 1997a,Troy *et al.*, 1997b, Troy *et al.*, 1997c, Troy *et al.*, 1997d (3), Troy *et al.*, 1998; [18]Ciraulo *et al.*, 1988 (2); [19]Winkle *et al.*, 1981; [20]Richard *et al.*, 1994; [21]Connolly *et al.*, 1984, Lee *et al.*, 1987, Burgess *et al.*, 1989; [22]Larsson *et al.*, 1984.

**Table 5. Interindividual variation in pharmacokinetic parameters of CYP2D6 probe substrates in phenotyped healthy adult volunteers (EMs, SEMs and PMs) after oral administration [a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $EM/PM_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *CL (mlmin$^{-1}$kg$^{-1}$)* | | | | | | | | | | | |
| Desipramine (EM) | 1 | 1[1] | 5 | 29 | 16 | 57 | 25 | 1.7 | 57 | | |
| Desipramine (PM) | 1 | 1[1] | 4 | 3.0 | 0.9 | 32 | 2.9 | 1.4 | 32 | 8.8 | 0.56 |
| S-Metoprolol (EM)* | 2 | 1[2] | 20 | 28 | 17 | 60 | 23 | 1.7 | 54 | | |
| *CL (mlmin$^{-1}$)* | | | | | | | | | | | |
| Desipramine (EM) | 3 | 3[3] | 16 | 3300 | 180 | 55 | 2800 | 1.4 | 37 | | |
| Desipramine (SEM) | 2 | 1[4] | 10 | 1100 | 270 | 24 | 1100 | 1.3 | 23 | 2.5 | 0.61 |
| Desipramine (PM) | 1 | 1[5] | 4 | 245 | 66 | 27 | 210 | 1.3 | 27 | 13 | 0.68 |
| Encainide (EM) | 2 | 2[6] | 13 | 9300 | 970 | 105 | 6500 | 1.9 | 71 | | |
| Encainide (PM) | 1 | 1[7] | 4 | 245 | 66 | 27 | 240 | 1.3 | 27 | 27 | 0.38 |
| Metoprolol (EM) | 3 | 3[8] | 23 | 3600 | 460 | 130 | 2600 | 1.8 | 67 | | |
| Metoprolol (PM) | 3 | 3[8] | 18 | 590 | 210 | 36 | 550 | 1.4 | 31 | 4.8 | 0.46 |
| Propafenone (EM) | 4 | 4[9] | 49 | 1800 | 130 | 71 | 1300 | 2.0 | 77 | | |
| Propafenone (PM) | 2 | 2[10] | 13 | 400 | 140 | 35 | 360 | 1.3 | 29 | 3.5 | 0.37 |
| S-Propafenone (EM) | 1 | 1[11] | 6 | 3300 | 290 | 88 | 2500 | 2.1 | 88 | | |
| Tolterodine (EM) | 2 | 2[12] | 17 | 5600 | 501 | 89 | 4200 | 2.2 | 89 | | |
| Tolterodine (SEM) | 1 | 1[13] | 4 | 1300 | 660 | 51 | 1200 | 1.6 | 51 | 3.6 | 0.56 |
| Tolterodine (PM) | 1 | 1[14] | 8 | 200 | 72 | 36 | 190 | 1.4 | 36 | 22 | 0.40 |
| Venlafaxine (EM) | 2 | 2[15] | 14 | 1700 | 102 | 60 | 1500 | 1.7 | 60 | | |
| Venlafaxine (PM) | 2 | 2[15] | 14 | 360 | 130 | 37 | 340 | 1.4 | 37 | 4.3 | 0.61 |
| *AUC/dose (ngml$^{-1}$ h)[a]* | | | | | | | | | | | |
| Metoprolol (EM) | 1 | 1[16] | 6 | 1100 | 570 | 51 | 1000 | 1.6 | 51 | | |
| S-Metoprolol (EM)* | 1 | 1[17] | 8 | 510 | 440 | 85 | 390 | 2.1 | 85 | | |
| S-Metoprolol (EM) | 1 | 1[18] | 9 | 350 | 170 | 49 | 310 | 1.6 | 49 | | |
| S-Metoprolol (PM) | 1 | 1[18] | 3 | 2600 | 200 | 7.7 | 2600 | 1.1 | 7.7 | 8.2 | 0.16 |
| Propafenone (EM) | 1 | 1[19] | 6 | 605 | 390 | 64 | 510 | 1.8 | 64 | | |
| Propafenone (PM) | 1 | 1[19] | 6 | 4500 | 120 | 25 | 4700 | 1.3 | 25 | 9.1 | 0.38 |
| *Cmax/dose (ngml$^{-1}$)[a]* | | | | | | | | | | | |
| Desipramine (EM) | 1 | 1[20] | 4 | 17 | 5.1 | 30 | 17 | 1.3 | 30 | | |
| Desipramine (SEM) | 1 | 1[20] | 6 | 34 | 8.9 | 26 | 33 | 1.3 | 26 | 2.0 | 0.88 |
| Desipramine (PM) | 1 | 1[20] | 8 | 61 | 12 | 20 | 60 | 1.2 | 20 | 3.6 | 0.68 |
| Encainide (EM) | 1 | 1[21] | 5 | 160 | 86 | 55 | 140 | 1.7 | 55 | | |
| Metoprolol (EM) | 3 | 3[22] | 23 | 250 | 120 | 45 | 180 | 1.5 | 42 | | |
| Metoprolol (PM) | 2 | 2[23] | 13 | 550 | 150 | 27 | 370 | 1.3 | 24 | 2.1 | 0.57 |
| S-Metoprolol (EM)* | 3 | 2[24] | 28 | 190 | 79 | 41 | 170 | 1.56 | 47 | | |
| S-Metoprolol (EM) | 1 | 1[25] | 9 | 94 | 45 | 48 | 85 | 1.6 | 48 | | |
| S-Metoprolol (PM) | 1 | 1[25] | 3 | 190 | 4.6 | 2.5 | 190 | 1.02 | 2.5 | 2.2 | 0.05 |
| Propafenone (EM) | 2 | 2[26] | 16 | 190 | 83 | 43 | 180 | 1.5 | 40 | | |
| Propafenone (PM) | 1 | 1[27] | 6 | 370 | 76 | 21 | 360 | 1.2 | 21 | 2.0 | 0.52 |
| S-Propafenone (EM) | 1 | 1[11] | 6 | 28 | 30 | 105 | 20 | 2.4 | 105 | | |
| Tolterodine (EM) | 2 | 2[28] | 11 | 130 | 140 | 108 | 92 | 2.3 | 100 | | |
| Tolterodine (SEM) | 1 | 1[29] | 4 | 390 | 140 | 36 | 370 | 1.4 | 36 | 4.0 | 0.36 |
| Tolterodine (PM) | 2 | 2[30] | 11 | 750 | 240 | 33 | 700 | 1.3 | 30 | 7.6 | 0.29 |

[a]**EM** Extensive metabolisers; **PM** Poor metabolisers.; **SEM** Slow extensive metabolisers; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_w$**Weighted standard deviation (normal distribution); **$CV_N$** Coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficent of variation; (lognormal distribution); **Ratio $EM/PM_{LN}$** Ratio of geometric means between EMs and PMs (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio $CV_{LN}$** Ratio between the variability of PMs and EMs (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight (mgkg$^{-1}$); *Given as the racemate.

[1]Steiner *et al.*, 1987; [2]Luzier et al., 1999 (2 ); [3]Brosen *et al.*, 1986, Bergstrom *et al.*, 1992, Brosen *et al.*, 1993; [4]Brosen *et al.*, 1986, Brosen *et al.*, 1993; [5]Brosen *et al.*, 1986; [6]Wang *et al.*, 1984, Wensing *et al.*, 1991; [7]Wang *et al.*, 1984; [8]Jonkers *et al.*, 1991, Laurent-Kenesi *et al.*, 1993, Hamelin *et al.*, 2000; [9]Siddoway *et al.*, 1987, Boriani *et al.*, 1990, Ujhelyi *et al.*, 1993, Labbe *et al.*, 2000; [10]Siddoway *et al.*, 1987, Labbe *et al.*, 2000; [11]Brode *et al.*, 1988; [12]Brynne *et al*, 1999a, Brynne *et al*, 2000; [13]Brynne et al, 1999a; [14]Brynne et al, 1999b; [15]Lessard *et al.*, 1999, Turgeon *et al.*, 1999; [16]Somer *et al.*, 2000; [17]Hemeryck *et al.*, 2000; [18]Sandberg *et al.*, 1993; [19]Dilger *et al.*, 1999; [20]Brosen *et al.*, 1993; [21]Wensing *et al.*, 1991; [22]Laurent-Kenesi *et al.*, 1993, Hamelin *et al.*, 2000, Somer *et al.*, 2000; [23]Laurent-Kenesi *et al.*, 1993, Hamelin *et al.*, 2000; [24]Luzier et al., 1999 (2), Hemeryck *et al.*, 2000; [25]Sandberg *et al.*, 1993; [26]Boriani *et al.*, 1990, Dilger *et al.*, 1999; [27]Dilger *et al.*, 1999; [28]Brynne *et al.*, 1998, Brynne *et al.*, 1999a, [29]Brynne *et al.*, 1999a, [30]Brynne *et al.*, 1998, Brynne *et al.*, 1999b.

*III.2.1.3.3 Slow extensive metabolisers (SEMs)*

Only limited data were available for the kinetics of the probe substrates in SEM subjects. There was a 3-fold difference in internal dose between SEMs and EMs for the oral route ($mlmin^{-1}$, 2 compounds, 14 subjects) associated with 38% variability for both distributions (Table 5). The limited intravenous data were similar to those for EMs.

There was a 3-fold difference in Cmax between EMs and SEMs associated with a variability of 31% (2 compounds and 10 subjects) (Table 5).

**Table 6. Clearance ($mlmin^{-1}$) of CYP2D6 probe substrates between phenotyped healthy adult volunteers (EMs, SEMs and PMs) after intravenous administration[a].**

| Drug/ Phenotype | Ns | Np | n | $X_W$ | $SD_W$ | $CV_N$ | $GM_W$ | $GSD_W$ | $CV_{LN}$ | Ratio $EM/PM_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Desipramine (EM) | 1 | 1[1] | 4 | 850 | 110 | 13 | 840 | 1.1 | 13 | | |
| Desipramine (SEM) | 1 | 1[1] | 4 | 760 | 130 | 17 | 750 | 1.2 | 17 | 1.1 | 1.3 |
| Desipramine (PM) | 1 | 1[1] | 6 | 160 | 20 | 13 | 160 | 1.1 | 13 | 5.3 | 1.0 |
| Encainide (EM) | 3 | 3[2] | 2 | 940 | 740 | 58 | 810 | 1.7 | 58 | | |
| Tolterodine (EM) | 1 | 1[3] | 8 | 730 | 220 | 30 | 703 | 1.3 | 30 | | |
| Tolterodine (PM) | 1 | 1[3] | 8 | 150 | 35 | 23 | 150 | 1.2 | 23 | 4.8 | 0.74 |

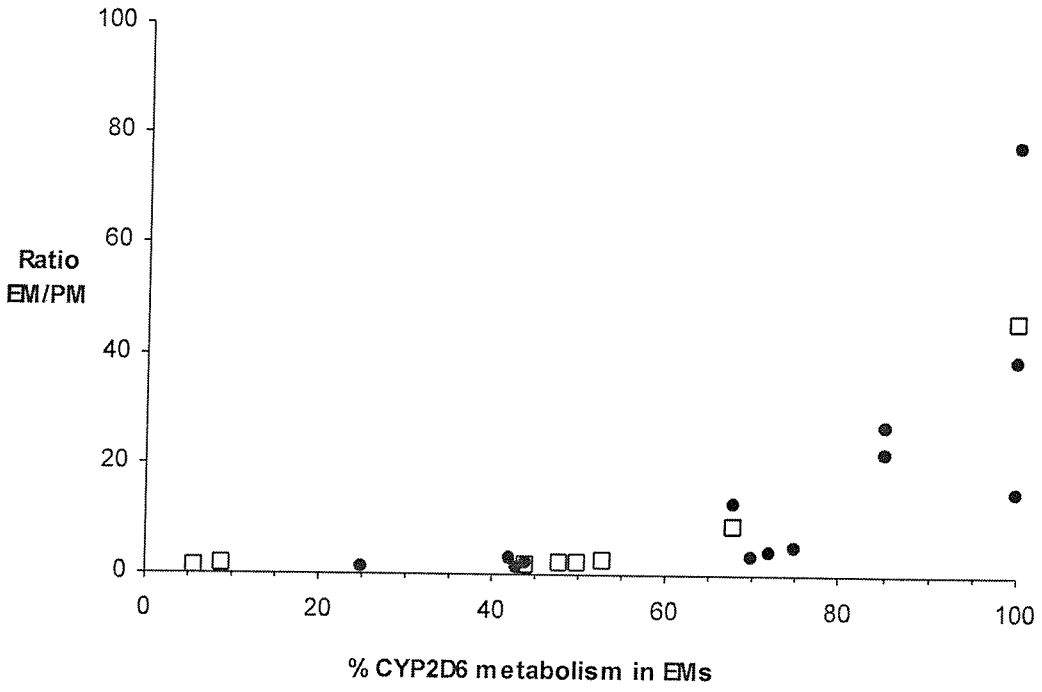
[a]**EM** Extensive metabolisers; **PM** Poor metabolisers.; **SEM** Slow extensive metabolisers; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); $SD_W$Weighted standard deviation (normal distribution); $CV_N$ Coefficient of variation (normal distribution); $GM_W$ Geometric weighted mean (lognormal distribution); $GSD_W$ Weighted geometric standard deviation (lognormal distribution); $CV_{LN}$ Coefficent of variation; (lognormal distribution); **Ratio** $EM/PM_{LN}$ Ratio of geometric means between EMs and PMs (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $CV_{LN}$ Ratio between the variability of PMs and EMs (Lognormal distribution);

[1]Brosen *et al.*, 1988; [2]Funck-Brentano *et al.*, 1989; [3]Brynne *et al.*, 1998.

## III.2.2 Relationship between quantitiative CYP2D6 metabolism and the ratio between EMs and PMs

Clearance rates ($mlmin^{-1}kg^{-1}$ and $mlmin^{-1}$) for the minor CYP2D6 substrates provided datasets to investigate the relationship between the percentage of an oral dose metabolised by CYP2D6 in EMs and the ratio between EMs and PMs (Table 1 and 7). These data were combined together with the ratios for the probe substrates (>60% metabolism by CYP2D6, Table 5) and metabolic clearances (100% of CYP2D6 metabolism; Table 3). Figure 3 shows that there is an exponential relationship between the ratio of the estimated internal dose between EMs and PMs and the extent of CYP2D6 metabolism in EMs ($R^2$= 0.80 for both clearance estimates). The $CV_{LN}$ values for the minor substrates were lower than for the main probes (Table 5) and the variability in PMs was generally less than in EMs.

**Figure 3. Relationship between the percentage of CYP2D6 metabolism after oral administration in extensive metabolisers and the ratio of clearances between poor and extensive metabolisers.**




□ CL $((ml\ min)^{-1})\ Kg^{-1}$ $y = 0.70e^{0.035x}$ $R^2 = 0.81$
● CL $((ml\ min)^{-1})$ $y = 0.20e^{0.054x}$ $R^2 = 0.78$

(see Table 1, 5 and 7 for sources of data)

**Table 7. Comparative pharmacokinetics for CYP2D6 minor substrates in phenotyped healthy adult volunteers (EMs and PMs) after oral administration[a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $EM/PM_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *CL ($ml min^{-1} kg^{-1}$)* | | | | | | | | | | | |
| Amitryptiline (EM) | 1 | 1[1] | 4 | 43 | 24 | 56 | 38 | 1.7 | 56 | | |
| Amitryptiline (PM) | 1 | 1[1] | 3 | 18 | 1.5 | 8.4 | 18 | 1.1 | 8 | 2.1 | 0.15 |
| Codeine (EM) | 1 | 1[2] | 8 | 35 | 14 | 40 | 33 | 1.5 | 40 | | |
| Codeine (PM) | 1 | 1[2] | 6 | 32 | 10.5 | 33 | 30 | 1.4 | 33 | 1.1 | 0.82 |
| Dihydrocodeine | 1 | 1[3] | 8 | 8.9 | 2.7 | 30 | 8.5 | 1.3 | 30 | | |
| Dihydrocodeine | 1 | 1[3] | 6 | 7.6 | 1.8 | 24 | 7.4 | 1.3 | 24 | 1.2 | 0.78 |
| Hydrocodone (EM) | 1 | 1[4] | 6 | 11 | 3.6 | 32 | 10 | 1.4 | 33 | | |
| Hydrocodone (PM) | 1 | 1[4] | 5 | 6.5 | 1.3 | 18 | 6.4 | 1.2 | 20 | 1.6 | 0.61 |
| Imipramine (EM) | 1 | 1[5] | 6 | 2600 | 730 | 29 | 2500 | 1.3 | 28 | | |
| Imipramine (PM) | 1 | 1[5] | 6 | 1400 | 240 | 18 | 1400 | 1.2 | 17 | 1.8 | 0.61 |
| Nortryptiline (EM) | 1 | 1[6] | 4 | 13 | 2.8 | 22 | 38 | 1.7 | 56 | | |
| Nortryptiline (PM) | 1 | 1[6] | 4 | 6.2 | 1.08 | 18 | 18 | 1.1 | 8 | 2.1 | 0.15 |
| Sparteine (EM) | 2 | 2[7] | 1 | 7.3 | 2.98 | 41 | 6.8 | 1.5 | 41 | | |
| Sparteine (PM) | 2 | 2[7] | 1 | 2.6 | 0.40 | 16 | 2.6 | 1.4 | 16 | 2.6 | 0.82 |
| *CL ($ml min^{-1}$)* | | | | | | | | | | | |
| Mexiletine (EM) | 1 | 1[8] | 1 | 620 | 300 | 48 | 560 | 1.6 | 48 | | |
| Mexiletine (PM) | 1 | 1[8] | 4 | 340 | 180 | 50 | 300 | 1.6 | 53 | 1.9 | 1.1 |
| Propranolol (EM) | 1 | 1[9] | 6 | 3700 | 2200 | 59 | 13 | 1.2 | 22 | | |
| Propranolol (PM) | 1 | 1[9] | 6 | 1300 | 520 | 41 | 6.1 | 1.2 | 17 | 2.1 | 0.81 |
| R-Propranolol (EM) | 1 | 1[10] | 1 | 2400 | 800 | 34 | 3200 | 1.7 | 59 | | |
| R-Propranolol (PM) | 1 | 1[10] | 4 | 1900 | 1100 | 60 | 1200 | 1.5 | 40 | 2.6 | 0.67 |
| S-Propranolol (EM) | 1 | 1[10] | 1 | 1700 | 620 | 37 | 2300 | 1.4 | 33 | | |
| S-Propranolol (PM) | 1 | 1[10] | 4 | 1400 | 790 | 55 | 1600 | 1.7 | 58 | 1.4 | 1.7 |

[a]**EM** Extensive metabolisers; **PM** Poor metabolisers; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_W$**Weighted standard deviation (normal distribution); **$CV_N$** Coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_W$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficent of variation; (lognormal distribution); **Ratio $EM/PM_{LN}$** Ratio of geometric means between EMs and PMs (lognormal distribution); **Ratio $CV_{LN}$** Ratio between the variability of PMs and EMs (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Balant-Gorgia *et al.*, 1982; [2]Yue *et al.*, 1991; [3]Fromm *et al.*, 1995; [4]Otton *et al.*, 1993; [5]Brosen *et al.*, 1986; [6]Mellstrom *et al.*, 1981; [7]Zekorn *et al.*, 1985, Eichelbaum *et al.*, 1986.; [8]Turgeon *et al.*, 1991; [9]Shaheen et al., 1989; [10]Ward *et al.*, 1989.

### III.2.3 Interethnic differences in the pharmacokinetics of CYP2D6 probe substrates

The influence of ethnicity on the kinetics of CYP2D6 probe substrates has been analysed for the available data in African and Asian subjects. The analysis was complex because different kinetic parameters were reported for different ethnic groups, only some of which had been phenotyped. A summary table (Table 8) describes the kinetic data and the inter-ethnic differences (general healthy adults (see Table 4 and 5) compared with Africans /Asians (Table 8)) for non-phenotyped individuals and phenotyped individuals (EMs, SEMs and PMs).

### *III.2.3.1 African adults*

The kinetics of oral S-metoprolol in black Africans were reported for both total and metabolic clearance. The mean estimates did not differ significantly from the genarl healthy adult data and the variability for both parameters was 1.3-fold lower in Africans. Data for tolterodine clearance in African American EMs showed a two-fold increase in the internal dose associated with greater variability compared to the adult EMs (Table 5).

### *III.2.3.2 Asian adults*

Data on the pharmacokinetics of several probe CYP2D6 substrates were available for non-phenotyped and phenotyped adult Asian volunteers (Table 8).

#### *III.2.3.2.1 Non phenotyped Asian healthy adults*

There were no consistent differences in the oral kinetics of desipramine, metoprolol and propafenone between non-phenotyped Asian and general healthy adults.

#### *III.2.3.2.2 Phenotyped Asian healthy adults*

The comparison between the different CYP2D6 phenotypes in the Asian population (Table 8) and the general healthy adult data was complex because in some cases it was possible to compare Asian EMs, PMs and SEMs with healthy adult EMs (Table 5); in other cases it was necessary to compare Asian subgroups with NP healthy adults (Table 4).

The data for clearance and AUC indicated that, compared to general healthy adult EMs, the internal dose during chronic exposure were overall 4-fold lower in Asian EMs (3 compounds, 52 subjects), 2-fold lower in Asian SEMs (3 compounds, 25 subjects) and similar in Asian PMs (2 compounds, 16 subjects) (Table 5). Variability was also lower in these three Asian subgroups than the corresponding data for healthy adults (1.4-fold for EMs and PMs and 1.8-fold in SEMs).

The Cmax data were similar in general healthy adults and Asian EMs (3 compounds and 52 subjects), higher in Asian SEMs (1.2 fold, 3 compounds, 25 subjects) and in Asian PMs (1.7-fold, 2 compounds, 16 subjects), whereas the variability in Asians was two-fold lower in EMs and PMs and three-fold lower in SEMs.

Analysis of the effect of the polymorphism within the Asian population (ratios not shown in Table 8) showed an average 1.6-fold (3 compounds, 25 subjects) and 3.4-fold (2 compounds,

16 subjects) higher internal dose in Asian SEMs and PMs compared to Asian EMs. The Cmax data showed a 1.5-fold (3 compounds, 25 subjects) and a 2.5-fold (2 compounds, 16 subjects) higher values in SEMs and PMs compared to Asian EMs (ratios not shown in Table 8).

Interestingly, the differences between SEMs, PMs and EMs within the Asian population were not as great as the differences observed within the general healthy adult population.

### III.2.4 Effect of age on the pharmacokinetics of CYP2D6 probe substrates

The effects of age (infancy and old age) and disease (liver and renal disease) on the pharmacokinetics of major CYP2D6 substrates have been analysed to incorporate these potentially sensitive individuals in the assessment of the CYP2D6 pathway (Table 9 and 10). Only limited data were available on phenotyped individuals in these subgroups.

#### *III.2.4.1 The Elderly*

Slightly higher internal doses (1.2-fold) would be predicted in the elderly based on data for metabolic clearance (venlafaxine; 18 subjects), oral and intravenous clearances (3 substrates, 54 subjects) and AUCs (2 substrates; 23 subjects). The intersubject variability was generally higher for these parameters compared with general healthy adults. The mean and variability in Cmax in the elderly (3 compounds; 62 subjects) were similar to NP healthy adults.

#### *III.2.4.2 Children,Infants and Neonates*

Desipramine kinetic data were available for a large number of children (n= 173) and showed a 4-fold greater internal dose associated with very wide interindividual differences (140%) (Table 9) compared with NP general healthy adults.

**Table 8. Effect of ethnicity on the pharmacokinetics of CYP2D6 probe substrates after oral administration. All data presented on Asian subpopulation except Af on black African and Af Am on African american[a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CLm ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Desipramine (NP) | 1 | 1[1] | 4 | 8.5 | 3.8 | 45 | 7.8 | 1.5 | 45 | 1.2[a] | 0.95[a] |
| CLm ($mlmin^{-1}$) | | | | | | | | | | | |
| S-Metoprolol* (NP) **Af** | 1 | 1[2] | 10 | 650 | 420 | 64 | 550 | 1.8 | 64 | 1.1[a] | 0.75[a] |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Desipramine (NP) | 2 | 2[3] | 34 | 24 | 13 | 52 | 22 | 1.6 | 52 | 1.2[a] | 0.94[a] |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| S-Metoprolol* (NP)**Af** | 1 | 1[3] | 18 | 3500 | 4050 | 120 | 2306 | 2.5 | 1.2 | 1.8[a] | 1.3[a] |
| Tolterodine (EM) **Af** | 1 | 1[5] | 16 | 3080 | 1200 | 39 | 2900 | 1.5 | 39 | 0.32[b] | 0.59[b] |
| S-Metoprolol* (EM) | 1 | 1[5] | 12 | 2020 | 640 | 32 | 1900 | 1.3 | 30 | 0.38[a] | 0.69[a] |
| S-Metoprolol* (SEM) | 1 | 1[5] | 12 | 1020 | 440 | 43 | 940 | 1.5 | 43 | 0.77[a] | 0.98[a] |
| S-Metoprolol* (PM) | 1 | 1[6] | 8 | 2600 | 1000 | 39 | 2400 | 1.5 | 39 | 0.53[b] | 0.50[b] |
| Propafenone (NP) | 3 | 3[7] | 32 | 1600 | 540 | 33 | 1500 | 1.4 | 33 | 0.10[b] | 1.2[b] |
| S-Propafenone* (EM) | 1 | 1[8] | 9 | 1500 | 400 | 27 | 1080 | 1.3 | 25 | 0.14[b] | 0.96[b] |
| S-Propafenone* (SEM) | 1 | 1[3] | 18 | 3500 | 4050 | 120 | 2306 | 2.5 | 1.2 | 1.8[a] | 1.3[a] |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Metoprolol (NP) | 2 | 2[9] | 36 | 1300 | 1030 | 78 | 940 | 2.1 | 85 | 0.49[a] | 1.0[a] |
| Venlafaxine (EM) | 1 | 1[10] | 4 | 220 | 59 | 27 | 251 | 1.3 | 27 | 0.40[a] | 0.34[a] |
| Venlafaxine (SEM) | 1 | 1[10] | 4 | 420 | 48 | 11 | 498 | 1.1 | 11 | 0.79[a] | 0.14[a] |
| Venlafaxine (PM) | 1 | 1[10] | 4 | 1300 | 430 | 33 | 1400 | 1.4 | 33 | 2.3[a] | 0.42[a] |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Desipramine (NP) | 1 | 1[11] | 20 | 52 | 27 | 52 | 51 | 1.1 | 13 | 2.0[a] | 0.28[a] |
| Metoprolol (NP) | 2 | 2[9] | 36 | 200 | 96 | 48 | 170 | 1.3 | 31 | 0.78[a] | 0.56[a] |
| Propafenone (NP) | 1 | 1[6] | 8 | 103 | 83 | 80 | 81 | 2.0 | 80 | 0.45[b] | 2.0[b] |
| S-Metoprolol* (EM) | 1 | 1[5] | 16 | 89 | 37 | 42 | 82 | 1.5 | 42 | 0.48[b] | 0.89[b] |
| S-Metoprolol* (SEM) | 1 | 1[5] | 12 | 101 | 37 | 37 | 95 | 1.4 | 35 | 0.56[b] | 0.75[b] |
| S-Metoprolol* (PM) | 1 | 1[5] | 12 | 180 | 58 | 33 | 170 | 1.4 | 33 | 0.98[b] | 0.71[b] |
| S-Propafenone* (EM) | 4 | 4[12] | 42 | 64 | 63 | 98 | 49 | 19 | 68 | 2.5[b] | 0.64[a] |
| S-Propafenone* (SEM) | 1 | 1[8] | 9 | 84 | 12 | 15 | 84 | 12 | 15 | 4.2[b] | 0.14[a] |
| Venlafaxine (EM) | 1 | 1[10] | 4 | 63 | 18 | 28 | 60 | 1.3 | 28 | 0.65[a] | 0.58[a] |
| Venlafaxine (SEM) | 1 | 1[10] | 4 | 89 | 13 | 19 | 88 | 1.2 | 15 | 0.94[a] | 0.30[a] |
| Venlafaxine (PM) | 1 | 1[10] | 4 | 180 | 34 | 15 | 170 | 1.3 | 23 | 1.9[a] | 0.49[a] |

[a]**EM** Extensive metabolisers; **PM** Poor metabolisers; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_W}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_W}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric means between healthy adults and subgroup (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); [a]Ratios between non-phenotyped healthy adults and healthy asian (non-phenotyped, extensive or por metabolisers); [b]Ratios between healthy adult extensive metbolisers and healthy asian (non-phenotyped, extensive or por metabolisers); [a] Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); *Given as the racemate.

[1]Rudorfer *et al.*, 1984; [2]Johnson and Burlew,1996; [3]Brynne *et al.*, 2000; [4]Pi *et al.*, 1986, Rudorfer *et al.*, 1984; [5]Huang *et al.*, 1999; [6]Tang-Yong *et al.*, 1994; [7]Cai *et al.*, 1999a, b, c; [8]Cai *et al.*, 1999b; [9]Shimizu *et al.*, 1992, Yuen *et al.*, 1996; [10]Fukuda *et al.*, 1999; [11]Pi *et al.*, 1986; [12]Cai *et al.*, 1999(a), (b), (c), Chen *et al.*, 2000.

**Table 9. Effect of age on the pharmacokinetics of CYP2D6 probe substrates after oral and intravenous administration[a].**

| Drug/ Phenotype/ Route | Ns | Np | n | $X_W$ | $SD_W$ | $CV_N$ | $GM_W$ | $GSD_W$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Elderly* | | | | | | | | | | | |
| CLm ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Venlafaxine (NP) (PO) | 1 | 1[1] | 18 | 4.8 | 1.7 | 35 | 4.6 | 1.4 | 35 | 1.2 | 0.73 |
| CLm ($mlmin^{-1}$) | | | | | | | | | | | |
| Propafenone (EM) (PO) | 1 | 1[2] | 6 | 35 | 18 | 51 | 31 | 1.6 | 51 | 1.1 | 1.1 |
| Propafenone (PM) (PO) | 1 | 1[2] | 1 | 0.20 | | | 0.20 | | | 180 | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Desipramine (NP) (PO) | 1 | 1[3] | 12 | 30 | 36 | 120 | 19 | 2.6 | 120 | 1.4 | 2.2 |
| Venlafaxine (NP) (PO) | 1 | 1[1] | 18 | 25 | 21 | 82 | 20 | 2.0 | 82 | 1.2 | 1.6 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| Desipramine (NP) (PO) | 2 | 1[4] | 16 | 1400 | 920 | 68 | 1100 | 1.8 | 70 | 1.8 | 5.4 |
| Metoprolol (NP) (IV) | 1 | 1[5] | 8 | 780 | 260 | 33 | 740 | 1.4 | 33 | 1.2 | 2.1 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Desipramine (NP) (PO) | 1 | 1[6] | 7 | 1020 | 1050 | 102 | 715 | 2.3 | 102 | 1.0 | 2.9 |
| Propafenone (EM) (PO) | 1 | 1[2] | 6 | 335 | 247 | 74 | 269 | 1.9 | 74 | 0.5 | 1.2 |
| Propafenone (PM) (PO) | 1 | 1[4] | 1 | 3060 | | | 3060 | 11.4 | | 6.0 | |
| Metoprolol (NP) (PO) | 2 | 2[7] | 16 | 4800 | 3700 | 78 | 3600 | 2.0 | 79 | 1.9 | 0.94 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Desipramine (NP) (PO) | 3 | 2[8] | 28 | 35 | 17 | 49 | 32 | 1.5 | 46 | 1.2 | 1.0 |
| Metoprolol (NP) (PO) | 2 | 2[9] | 16 | 240 | 150 | 63 | 170 | 1.8 | 65 | 0.78 | 1.2 |
| Propafenone (EM) (PO) | 1 | 1[2] | 6 | 104 | 80 | 0.77 | 82 | 2.0 | 77 | 0.46 | 1.9 |
| Propafenone (PM) (PO) | 1 | 1[4] | 1 | 110 | | | 110 | 1.4 | | 0.62 | |
| Venlafaxine (NP) (PO) | 1 | 1[1] | 18 | 130 | 51 | 40 | 130 | 1.5 | 40 | 1.4 | 0.83 |
| *Children* | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Desipramine (NP) (PO) | 2 | 1[10] | 17 | 11 | 16 | 140 | 6.6 | 2.8 | 140 | 4.0 | 2.6 |
| Propafenone (NP) (PO) | 2 | 1[11] | 2 | 21-8.7 | | | 21-8.7 | | | 6.0-15 | |
| Propafenone (NP) (IV) | 1 | 1[11] | 1 | 27 | | | 27 | | | | |
| *Infants* | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Propafenone (NP) (PO) | 1 | 1[11] | 2 | 50-28 | 15 | 40 | 50-28 | | | 2.5-4.5 | |
| Propafenone (NP) (IV) | 1 | 1[11] | 2 | 13-33 | 14 | 61 | 13-33 | | | 0.9-0.36 | |
| *Neonates* | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Propafenone (NP) (PO) | 1 | 1[11] | 2 | 6.8-3.8 | 2.1 | 40 | 6.8-3.8 | | | 19-33 | |
| Propafenone (NP) (IV) | 1 | 1[11] | 5 | 17 | 13 | 77 | 14 | 2.0 | 77 | 0.80 | 0.45 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Klamerus *et al.*, 1996; [2]Dilger *et al.*, 2000; [3]Antal et al ,1982; [4]Abernethy *et al.*, 1985 (2); [5]Larsson *et al.*, 1984; [6]Cutler *et al.*, 1981; [7]Briant *et al.*, 1983; Held and Regardh,1986; Larsson *et al.*, 1984; [8]Antal et al ,1982; Abernethy *et al.*, 1985 (2); [9]Briant *et al.*, 1983; Held and Regardh,1986; [10]Cohen *et al.*, 1999; [11]Ito *et al.*, 1998.

Data describing the kinetics of propafenone were available a very limited number of individuals of neonates, infants and children (n<3 in most cases). Compared to healthy adults, the oral clearance values for the 3 subgroups were considerably lower (children: 11-fold; infants: 4-fold; neonates: 26-fold), while intravenous clearances showed much smaller

differences (children: 2.5-fold; infants: 1.6-fold; neonates: 1.3-fold). These data suggest the possibility of an age-related difference in the first-pass metabolism of propafenone.

### III.2.5 Effect of disease on the pharmacokinetics of CYP2D6 probe substrates

Only limited data were available for NP subjects with liver disease (Table 10) and these suggested lower clearance values combined with lower variability. The kinetics of encainide in EM and PM patients with liver disease were available for EMs and PMs and were compared to general healthy EMs and showed a greatly reduced oral clearance of encainide in EMs but a smaller reduction of the intravenous clearance in the same patients (1.3-fold, data not shown). Data were avilable for only one PM patient with liver disease who showed negligible metabolism of encainide.

**Table 10. Effect of disease on the pharmacokinetics of CYP2D6 probe substrates after oral and intravenous administration.**

| Drug/ Phenotype | Ns | Np | n | $X_W$ | $SD_W$ | $CV_N$ | $GM_W$ | $GSD_W$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Liver Disease* | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Propafenone (NP) (IV) | 1 | 1[1] | 8 | 9.4 | 3.4 | 37 | 8.8 | 1.4 | 37 | 1.3 | 1.05 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| Encainide (NP) (PO) | 1 | 1[2] | 6 | 1600 | 730 | 46 | 1500 | 1.6 | 46 | 6.1 | 0.47 |
| Encainide (EM) (PO) | 2 | 2[3] | 14 | 1500 | 840 | 54 | 1300 | 1.7 | 60 | 5.4 | 0.85 |
| Encainide (PM) (PO) | 1 | 1[3] | 1 | 0.10 | | | 0.10 | | | 65000 | |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Encainide (EM) (PO) | 1 | 1[3] | 6 | 270 | 130 | 50 | 240 | 1.6 | 50 | 1.7 | 0.90 |
| Encainide (PM) (PO) | 1 | 1[3] | 1 | 1200 | | | 1200 | | | 7.6 | |
| *Renal Disease* | | | | | | | | | | | |
| CLm ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Venlafaxine (NP) (PO) | 2 | 2[4] | 18 | 4.6 | 2.80 | 62 | 3.8 | 1.6 | 53 | 1.5 | 1.1 |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Propafenone (NP) (IV) | 2 | 2[5] | 10 | 11 | 2.8 | 25 | 10.9 | 1.2 | 21 | 1.01 | 0.60 |
| Venlafaxine (NP) (PO) | 2 | 2[4] | 18 | 23 | 20.4 | 88 | 17.1 | 2.1 | 84 | 1.3 | 1.6 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| Encainide (NP) (PO) | 1 | 1[6] | 1 | 2700 | 1225 | 45 | 2500 | 1.54 | 45 | 3.60 | 0.46 |
| Cmax/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Venlafaxine (NP) (PO) | 2 | 2[4] | 18 | 120 | 48 | 40 | 103 | 1.5 | 40 | 0.91 | 0.84 |

**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_W$** Weighted standard deviation (normal distribution); **$CV_N$** Coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_W$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficent of variation; (lognormal distribution); **Ratio $H/S_{LN}$** Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio $CV_{LN}$** Ratio between the variability of healthy adults and subgroup (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Lee *et al.*, 1987; [2]Bergstrand *et al.*, 1986a; [3]Wensing *et al.*, 1991; [4]Troy *et al.*, 1994; [5]Burgess *et al.*, 1989; [6] Bergstrand *et al.*, 1986b.

Comparison of venlafaxine kinetics between patients with renal disease (Table 10) and healthy adults indicated lower metabolic clearance and clearance adjusted to body weight (2 compounds, 28 subjects). The oral clearance for encainide was nearly 4-fold lower with a 2-

fold lower variability, and the corresponding intravenous data were only 1.6-fold lower. The limited Cmax data for patients with renal disease did not demonstrate any significant difference from the healthy adults.

### III.2.6 Variability in the CYP2D6 pathway: pooled analysis

#### *III.2.6.1 Non Phenotyped and Phenotyped Healthy adults*

The overall parameter-specific coefficients of variation (CVs) for oral kinetics related to the polymorphic CYP2D6 metabolic pathway in non-phenotyped and phenotyped healthy adults were calculated by pooling per subgroup/compound to calculate the overall CV for each subgroup. The same analysis was performed on mean and variability ratios comparing EMs with SEMs and PMs (Table 11).

##### *III.2.6.1.1 Non Phenotyped Healthy adults and Extensive Metabolisers*

Interindividual differences for the CYP2D6 pathway in non-phenotyped healthy adults and EMs would be represented best by using the metabolic clearances (100% of CYP2D6 metabolism). The CV values for non-phenotyped individuals (Table 2) (2 compounds, 134 subjects) were about 50% assuming either a normal or lognormal distribution (however, neither assumptions are absolutely correct for a multimodal distribution). Higher variability was found for the metabolic clearance in EMs (5 compounds, 55-59% for both distributions).

There were only small differences between $CV_N$ and $CV_{LN}$ for all the kinetic parameters in non-phenotyped healthy adults. Comparison of $CV_N$ and $CV_{LN}$ in healthy EMs revealed a much greater difference for the largest database (oral clearance, $mlmin^{-1}$, 7 compounds, 138 subjects) with 85% and 70% respectively.

##### *III.2.6.1.2 Poor Metabolisers*

The variability in clearance, AUC and Cmax for PMs was lower than that for EMs with the most reliable values for metabolic and total clearance estimates with 39/52% and 31/33% respectively compared to 50/55% and 70/85% in EMs. A similar conclusion can be drawn for the Cmax analysis ($CV_N/CV_{LN}$) with values of 15/21% (compared to 53/59% in EMs). The difference in internal dose between EMs and PMs based on oral clearances and AUC ranged between 8.6 and 9.1 whereas the equivalent ratio for metabolic clearances was nearly 50. The rise in internal dose for the Cmax data was greatly reduced compared to the steady state markers with an overall value of 3.5.

The data for the SEM subgroup showed a lower variability compared to the EM phenotype with similar values between normal and lognormal assumptions, however these data were obtained with a small database (1–2 compounds per parameter and n <15). Differences in internal dose between EMs and SEMs were 2.6 for metabolic clearance and 2.8/3 for clearance/Cmax.

**Table 11. Interindividual differences for CYP2D6 metabolism in non-phenotyped and phenotyped healthy adults, pooled analysis[a].**

| PK parameter | Nc | Ns | Np | n | Mean $CV_N$ | Mean $CV_{LN}$ | Mean Ratio $EM/PM_{LN}$ | Mean Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| *Non-phenotyped individuals* | | | | | | | | |
| CLm[1] | 2 | 8 | 8 | 134 | 50 | 48 | | |
| CL[1] | 4 | 20 | 18 | 229 | 66 | 63 | | |
| CLm[2] | 2 | 2 | 2 | 16 | 103 | 101 | | |
| CL[2] | 4 | 4 | 4 | 47 | 85 | 68 | | |
| AUC[3] | 3 | 17 | 13 | 244 | 73 | 62 | | |
| Cmax[3] | 6 | 35 | 30 | 445 | 66 | 61 | | |
| *Phenotyped individuals* | | | | | | | | |
| *Chronic exposure* | | | | | | | | |
| CLm EM[1] | 1 | 1 | 1 | 5 | 77 | 77 | | |
| CLm EM[2] | 5 | 6 | 6 | 43 | 55 | 50 | | |
| CL EM[1] | 2 | 3 | 2 | 25 | 59 | 55 | | |
| CL EM[2] | 7 | 17 | 17 | 138 | 85 | 70 | | |
| AUC EM[3] | 4 | 4 | 4 | 29 | 62 | 60 | | |
| CLm SEM[2] | 1 | 1 | 1 | 5 | 33 | 33 | 2.6 | 1.3 |
| CL SEM[2] | 2 | 3 | 2 | 14 | 38 | 35 | 3.0 | 0.59 |
| CLm PM[1] | 1 | 1 | 1 | 4 | 50 | 50 | 46 | 0.63 |
| CLm PM[2] | 4 | 5 | 5 | 35 | 52 | 39 | 52 | 0.96 |
| CL PM[1] | 1 | 1 | 1 | 4 | 32 | 32 | 8.8 | 0.56 |
| CL PM[2] | 6 | 10 | 10 | 61 | 33 | 31 | 9.1 | 0.47 |
| AUC PM[3] | 2 | 2 | 2 | 9 | 16 | 14 | 8.6 | 0.25 |
| *Acute exposure* | | | | | | | | |
| Cmax EM[3] | 8 | 14 | 13 | 102 | 59 | 53 | | |
| Cmax SEM[3] | 2 | 2 | 2 | 10 | 31 | 31 | 2.8 | 0.56 |
| Cmax PM[3] | 5 | 7 | 6 | 41 | 21 | 15 | 3.0 | 0.40 |

[a]**EM** Extensive metabolisers; **SEM** Slow extensive metabolisers; **PM** Poor metabolisers; **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **Mean $CV_N$** Mean coefficient of variation for all compounds (normal distribution); **Mean $CV_{LN}$**, Mean coefficient of variation for all compounds (lognormal distribution); **Mean ratio $EM/PM_{LN}$** Mean ratio between the poor (PM and SEM) and the extensive metabolisers for all compounds (lognormal distribution); **Mean ratio $CV_{LN}$** Mean ratio of the variability between the poor (PM and SEM) and the extensive metabolisers for all compounds (lognormal distribution); [1]Individual Clearance corrected for body weight $((ml\ min)^{-1})\ Kg^{-1}$; [2]Clearance not corrected for body weight $(ml\ min^{-1})$; [3]Mean AUC $[(ng.h\ ml^{-1})]$ and Cmax$[(ng\ ml^{-1})]$ corrected for dose expressed per mean body weight $(mgkg^{-1})$.

### *III.2.6.2 Effect of Ethnicity, age and disease*

For completeness, the overall data on ethnicity, age and disease are given in Table 12; however these values relate to a very limited database. There was no major difference between the normal and lognormal assumption for the CVs, mean and variability ratios for most of the subgroups with the exception of clearances in African American EM and children.

**Table 12. Pooled analysis for interindividual differences in CYP2D6 metabolism, Effect of ethnicity, age and disease[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | Mean Ratio H/S$_{LN}$ | Mean Ratio H/S CV$_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| CLm[1] NP | Asian | PO | 1 | 1 | 1 | 14 | 1.2 | 0.95 |
| CL[1] NP | | PO | 1 | 2 | 2 | 34 | 1.2 | 0.94 |
| CL[2] NP | | PO | 1 | 1 | 1 | 8 | 2.5 | 0.31 |
| CL EM[2] | | PO | 2 | 4 | 4 | 48 | 0.18 | 0.84 |
| CL SEM[2] | | PO | 2 | 2 | 2 | 21 | 0.23 | 0.81 |
| CL PM[2] | | PO | 1 | 1 | 1 | 12 | 0.77 | 0.98 |
| AUC[3] | | PO | 1 | 2 | 2 | 36 | 0.46 | 0.78 |
| AUC EM[3] | | PO | 1 | 1 | 1 | 4 | 0.40 | 0.34 |
| AUC SEM[3] | | PO | 1 | 1 | 1 | 4 | 0.79 | 0.14 |
| AUC PM[3] | | PO | 1 | 1 | 1 | 4 | 2.3 | 0.42 |
| CLm[2] | Black | PO | 1 | 1 | 1 | 10 | 1.1 | 0.75 |
| CL[2] | African | PO | 1 | 1 | 1 | 10 | 1.1 | 0.77 |
| CL[2] | African American (EM) | PO | 1 | 1 | 1 | 18 | 1.8 | 1.3 |
| CL[1] | Children | PO | 1 | 1 | 1 | 173 | 4.0 | 2.6 |
| CLm[2] | Elderly (EM) | PO | 1 | 1 | 1 | 6 | 1.1 | 1.1 |
| AUC[3] | Elderly (EM) | PO | 1 | 1 | 1 | 6 | 0.5 | 1.2 |
| CLm[1] | Elderly | PO | 1 | 1 | 1 | 18 | 1.3 | 0.69 |
| CL[1] | | PO | 2 | 2 | 2 | 30 | 1.3 | 1.9 |
| CL[2] | | PO | 1 | 2 | 1 | 16 | 1.8 | 5.4 |
| AUC[3] | | PO | 2 | 3 | 3 | 23 | 1.4 | 1.7 |
| CL[1] | Liver Disease | PO | 1 | 1 | 1 | 6 | 6.1 | 0.47 |
| CL[2] | Liver Disease EM | PO | 1 | 1 | 1 | 14 | 5.4 | 0.85 |
| CL[1] | Renal Disease | PO | 2 | 4 | 4 | 28 | 1.3 | 1.1 |
| CLm[1] | | PO | 1 | 1 | 1 | 18 | 1.4 | 1.4 |
| CL[2] | | PO | 1 | 1 | 1 | 6 | 3.6 | 0.46 |
| Cmax[3] | Asian NP | PO | 3 | 4 | 4 | 64 | 1.4 | 0.51 |
| | Asian EM | PO | 3 | 6 | 6 | 62 | 0.86 | 0.57 |
| | Asian SEM | PO | 3 | 3 | 3 | 25 | 1.1 | 0.32 |
| | Asian PM | PO | 2 | 2 | 2 | 16 | 1.7 | 0.50 |
| | Elderly | PO | 3 | 5 | 6 | 62 | 1.1 | 1.0 |
| | Elderly (EM) | PO | 1 | 1 | 1 | 6 | 0.5 | 1.9 |
| | Renal Disease | PO | 1 | 2 | 2 | 18 | 0.91 | 0.84 |

**EM** Extensive metabolisers; **SEM** Slow Extensive metabolisers; **PM** Poor metabolisers; **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **Mean ratio H/S$_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio CV$_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight ((ml min$^{-1}$Kg$^{-1}$); [2]Clearance not corrected for body weight (ml min$^{-1}$); [3]Mean AUC and Cmax corrected for dose expressed per mean body weight (mgkg$^{-1}$).

## III.3 CYP2D6-related uncertainty factors

Uncertainty factors for substrates metabolised primarily by CYP2D6 were calculated for the various groups of the population to cover 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ percentiles of each subgroup using data for the oral route of exposure (Table 14) and assuming that the uncertainty factor is to allow for differences compared with the geometric mean of the general healthy adults.

The CYP2D6-related uncertainty factors necessary to cover 95% of the population, based on clearance and AUC for oral exposure, exceeded 3.16 for nearly all groups (Table 13).

Both, non-phenotyped individuals and EMs would require similar CYP2D6-related uncertainty factors of about 4 cover 99% of each population, whereas SEMs and PMs would need defaults up to 6.6 and 18 respectively. The most susceptible group were children with pathway-related uncertainty factors of 22, 31 and 45 necessary to cover the 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ percentiles of this subpopulation. Neonates and infants would also require higher factors, but the database was too small to provide even an approximation of the values necessary.

The relationship between the percentage of CYP2D6 metabolism of a substrate in EMs and the mean ratios between EMs and PMs (Figure 3) would allow the calculation of CYP2D6-related factors to cover the various percentiles (95$^{th}$, 97.5$^{th}$ and 99$^{th}$ centiles) for the PMs using data on 16 CYP2D6 probe substrates (Figure 4). Exponential relationships between the uncertainty factors for the 95$^{th}$ centiles and the percentage of CYP2D6 metabolism of a substrate in EMs were found. This would allow the prediction of CY2D6-related uncertainty factors taking into account the percentage of the dose metabolised by CYP2D6 in EMs (Table 13). 25% of an oral dose of a compound handled by CYP2D6 would be the limit for which the 3.16 would cover PMs up to the 99$^{th}$ centile (pathway-related uncertainty factors of 3.14).

**Figure 4. Relationship between the percentage of CYP2D6 metabolism after oral administration in extensive metabolisers and CYP2D6-related default uncertainty factors (95$^{th}$ percentile) for poor metabolisers.**

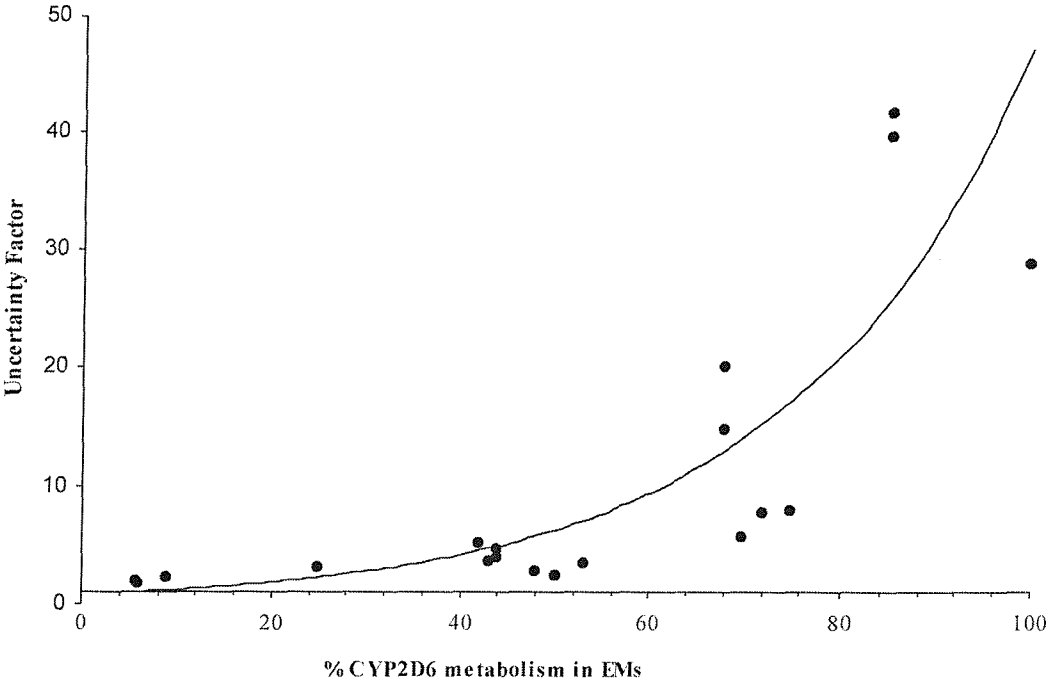



**Table 13. CYP2D6-related uncertainty factors and percentage of CYP2D6 metabolim in EMs.**

| % CYP2D6 metabolism | 95$^{th}$ centile | 97.5$^{th}$ centile | 99$^{th}$ centile |
|---|---|---|---|
| 10 | 1.6 | 1.7 | 1.9 |
| 20 | 2.2 | 2.4 | 2.7 |
| 25 | 2.5 | 2.8 | 3.1 |
| 30 | 3.0 | 3.3 | 3.7 |
| 40 | 4.1 | 4.5 | 5.1 |
| 50 | 5.7 | 6.2 | 7.0 |
| 60 | 7.8 | 8.6 | 9.7 |
| 70 | 11 | 12 | 13 |
| 80 | 15 | 17 | 18 |

**% CY2D6 metabolism** Percentage of an oral dose metabolised by CYP2D6 in extensive metabolisers of debrisoquine; **95$^{th}$ centile** CYP2D6-related uncertainty factors to cover poor metabolisers of debrisoquine to the 95$^{th}$ centile; **97.5$^{th}$ centile** CYP2D6-related uncertainty factors to cover poor metabolisers of debrisoquine to the 97.5$^{th}$ centile; **99$^{th}$ centile** CYP2D6-related uncertainty factors to cover poor metabolisers of debrisoquine to the 99$^{th}$ centile.

**Table 14 .CYP2D6-related uncertainty factors for chronic and acute oral exposure. in subgroups of the human population[a].**

| Subgroup | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ | CYP2D6 related uncertainty factors (lognormal distribution) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | $95^{th}$ | $97.5^{th}$ | $99^{th}$ |
| *Chronic exposure* | | | | | | | | | | | |
| Healthy NP | $CL^1$ , $CL^2$ , $AUC^3$ | 8 | 41 | 35 | 520 | 63 | | | 2.6 | 3.1 | 3.8 |
| Healthy EM | $CL^1$ , $CL^2$ , $AUC^3$ | 9 | 24 | 23 | 192 | 66 | | | 2.7 | 3.3 | 4.1 |
| Healthy SEM | $CL^2$ | 2 | 3 | 2 | 14 | 35 | 3.0 | 0.60 | 5.2 | 5.8 | 6.6 |
| Healthy PM | $CL^1$ , $CL^2$ , $AUC^3$ | 7 | 13 | 13 | 74 | 29 | 9.0 | 0.45 | 15 | 16 | 18 |
| Healthy African NP | $CL^2$ | 1 | 1 | 1 | 10 | 64 | 1.1 | 0.77 | 2.9 | 3.5 | 4.3 |
| Healthy African EM | $CL^2$ | 1 | 1 | 1 | 18 | 120 | 1.8 | 1.3 | 8.2 | 11 | 15 |
| Healthy Asian NP | $CL^1$ , $CL^2$ , $AUC^3$ | 4 | 5 | 5 | 78 | 66 | 1.0 | 0.90 | 2.4 | 2.8 | 3.5 |
| Healthy Asian EM | $CL^2$ , $AUC^3$ | 3 | 3 | 5 | 52 | 35 | 0.20 | 0.80 | <1 | <1 | <1 |
| Healthy Asian SEM | $CL^2$ , $AUC^3$ | 3 | 3 | 3 | 25 | 24 | 0.32 | 0.70 | <1 | <1 | <1 |
| Healthy Asian PM | $CL^2$ , $AUC^3$ | 2 | 2 | 2 | 16 | 41 | 1.2 | 0.84 | 2.1 | 2.4 | 2.7 |
| Children | $CL^1$ | 1 | 1 | 1 | 173 | 140 | 4.0 | 2.6 | 22 | 31 | 45 |
| Elderly | $CL^1$ , $CL^2$ , $AUC^3$ | 5 | 7 | 6 | 69 | 88 | 1.4 | 2.6 | 5.0 | 6.3 | 8.4 |
| Eldelry EM | $AUC^3$ | 1 | 1 | 1 | 6 | 74 | 0.50 | 1.2 | 1.5 | 1.8 | 2.3 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy NP | $Cmax^3$ | 6 | 35 | 30 | 445 | 61 | | | 2.5 | 3.0 | 3.7 |
| Healthy EM | | 8 | 14 | 13 | 102 | 53 | | | 2.3 | 2.7 | 3.2 |
| Healthy SEM | | 2 | 2 | 2 | 10 | 31 | 2.8 | 0.6 | 4.6 | 5.1 | 5.7 |
| Healthy PM | | 5 | 7 | 6 | 41 | 15 | 3.0 | 0.4 | 3.8 | 4.0 | 4.2 |
| Healthy Asian NP | | 3 | 4 | 4 | 64 | 32 | 1.4 | 0.51 | 2.3 | 2.6 | 2.9 |
| Healthy Asian EM | | 3 | 6 | 6 | 62 | 34 | 0.86 | 0.57 | 1.5 | 1.6 | 1.9 |
| Healthy Asian SEM | | 3 | 3 | 3 | 25 | 20 | 1.1 | 0.32 | 1.5 | 1.6 | 1.7 |
| Healthy Asian PM | | 2 | 2 | 2 | 16 | 26 | 1.7 | 0.50 | 2.6 | 2.8 | 3.1 |
| Elderly | | 3 | 6 | 5 | 62 | 50 | 1.1 | 1.0 | 2.5 | 2.9 | 3.4 |
| Elderly EM | | 1 | 1 | 1 | 6 | 77 | 0.46 | 1.9 | 1.4 | 1.8 | 2.3 |

[a]**EM** Extensive metabolisers; **PM** Poor metabolisers; **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Mean coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$** Mean ratio of geometric means between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Mean ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and C max corrected for dose expressed per mean body weight ($mgkg^{-1}$).

## IV. Discussion

This chapter provides an analysis of the interindividual differences in CYP2D6 metabolism in relation to the adequacy of the 3.16 toxicokinetic default uncertainty factor used for risk assessment. Based on this analysis, CYP2D6-related uncertainty factors were developed for various subgroups of the human population. The polymorphic basis of this pathway complicates regulatory issues because the general healthy adult population will include a subgroup of potentially susceptible individuals (assuming that the parent compound is the active toxic moiety).

The overall analysis resulted in a large database for the oral route of exposure with parameters reflecting both chronic exposure (clearances and AUC) and acute exposure (Cmax) (Table 13) for general healthy adults including non-phenotyped individuals (NPs), EMs, SEMs and PMs. The NPs and EMs were used as the reference populations to compare with the data for any subgroup of the population (non-phenotyped or phenotyped individuals). Interindividual differences after oral exposure were large for both subgroups (>60% for clearances and AUCs and >50% for Cmax), whereas the intravenous data indicated a much lower variability (25-30%). These observations can be explained by the fact that CYP2D6 substrates may undergo high first-pass extraction and metabolism and this would increase the variability for the oral route, whereas for high clearance compounds the variability after intravenous dosage would depend largely on liver bood flow. Another important factor that would increase the variability in both non-phenotyped and EM groups is the polyallelic nature of the CYP2D6 polymorphism involving up to 13 alleles and the EM subgroup would potentially consist of individuals owning from 2 to 13 copies (ultra rapid metbolisers) of the CYP2D6 locus (Ingelman-Sundberg *et al.,* 1995). The only *in vivo* kinetic data for ultra rapid metabolisers (13 copies of the gene) were for debrisoquine and nortryptiline in a single subject, who showed a 5-fold decrease in AUC and a 3-5-fold increase in clearance compared to other EMs (2-4 copies of the gene) (Dalen *et al.,* 1998; Dalen *et al.,* 1999). Whereas ultra rapid metbolisers would be at reduced risk if the parent compound were the active form, they would be a vulnerable group if CYP2D6 resulted in bioactivation.

Comparisons between EMs and the poor metaboliser phenotypes (SEMs and PMs) revealed a large increase in internal dose for probe substrates in PMs for the oral route of exposure (ratio >9) and an intermediate rise in SEMs (ratio >3.5): lower differences were found for the intravenous route (ratio of 4.5 and 1.1 respectively). The variability for both of these subgroups was much lower than that for non-phenotyped individuals and EMs. A possible explanation for the lower in variability for both poor metaboliser subgroups also lies in the polyallelic nature of the CYP2D6 isoform, since SEMs can possess a small and consistent number of copies (1 to 2) compared to EMs, together with a mutation (-1496 C to G) of the CYP2D6 gene (60% of SEMs) (Raimundo *et al.,* 2000) whereas PMs would be uniformly deficient of any active protein or would have only one copy.

The interethnic differences did not show that either African (non-phenotyped) or Asian (non-phenotyped, EMs, SEMs and PMs) healthy adults would constitute a potential susceptible subgroup for CYP2D6 substrates. This conclusion is supported by the low frequency of poor metabolisers in both ethnic minorities (1-2%). Data for non-phenotyped elderly, liver disease patients (EMs and PMs) and renal disease patients indicated a higher internal dose due to impaired metabolism.

The very limited database describing the pharmacokinetics of oral propafenone in various stages of early life (neonates, infants and children) demonstrated large differences in clearance rates compared to healthy adults. This was supported by a substantial database on desipramine in children. However, clearances for the intravenous route were similar to non-phenotyped healthy adults probably due to similar liver blood flow. Although, the neonates in the study of Ito et al (1998) were defined as PMs because no active metabolite was found in their plasma after oral propafenone, but authors speculated that the patients could be either PMs or immature EMs (Ito *et al.,* 1998). A recent *in vivo* study based on urinary excretion data involving 52 infants demonstrated that the acquisition of the CYP2D6 phenotype was achieved by 15 days of age (Leeder et al., 2000).

Assuming that the parent compound was the active form, the only subgroups adequately covered by the 3.16 general default were the Asian and African ethnic minorities by the comparison with the general healthy adult group. CYP2D6-related uncertainty factors, ranging from 2.7, 3.3, 4.1 in EMs, 15, 16 and 18 in PMs would be necessary to cover 95%, 97.5% or 99% of each subpopulation. Exponential relationships ($R^2$=0.8) were found between the extent of CYP2D6 metabolism of a substrate and the ratio of internal dose between EMs and PMs, and consequently the extent of CYP2D6 metabolism and the uncertainty factors required to cover the various percentiles of PMs (Figure 4). The extent to which CYP2D6 is responsible for the metabolism of a substrate is critical in the estimation of the CYP2D6-related uncertainty factors and these uncertainty factors would apply to contaminants primarily handled by this pathway, bearing in mind that they are actually taking into account the worst scenario case for CYP2D6 metabolism (>60% metabolism). This relationship (figure 4) can also be used to derive uncertainty factors for compounds handled partially by CYP2D6 and shows that the 3.16 kinetic default factor would cover PMs (3.14, 99$^{th}$ centile) for substrates that were metabolised up to 25% by CYP2D6 metabolism in EMs.

Finally, this analysis has assumed that PMs are the susceptible subgroup. This would be true if the parent compound was the proximate toxicant, so that an increase in internal dose would increase the risk of adverse effects. The EM subgroup (92% of the Caucasian population) would be at greater risk, if the toxic species were a CYP2D6-mediated metabolite; in this case PMs would have lower internal dose of the toxicant and would be less at risk. Examples of this scenario include some organophosphorothioates, such as chlorpyrifos, parathion and diazinon that are activated by CYP2D6 (and other CYP isoforms) to the corresponding toxic phosphate ester or "oxon" which is a potent acetylcholinesterase inhibitor (Sams *et al.,* 2000). For such compounds, the PM status would confer a degree of protection.

In the future readily available *in vitro* techniques can be used to identify the various CYP isoform(s) responsible for the metabolism of a particular compound. Therefore, it would be important to incorporate in regulatory procedures, data describing at least *in vitro* metabolism of the contaminant under assessment to allow identification of the CYP isoform(s) involved in its metabolism, as well as the consequences of metabolism

(because either EMs or PMs could be the more sensitive subgroup). Risk assessors and risk managers could then make decisions about the appropriate pathway-related uncertainty factor relevant to that compound.

# Chapter V Human variability in CYP3A4 metabolism and CYP3A4-related uncertainty factors

## I.Introduction

Amongst the various CYP gene families, the CYP3A subfamily accounts for the majority of drug metabolising enzymes present in the adult human liver and intestine and consists of at least three functional genes: CYP3A4, CYP3A5, CYP3A7 located on chromosome 7. These isoforms possess high sequence homology (85%) but differ in substrate specificity and expression and CYP3A4 has been recognised as the most abundant of them representing 30-40% of the total CYPs in the liver and small intestine. In the liver iself, it represents 50% of the total CYPs in midzonal and centrolobular regions whereas the intestinal CYP3A is present in the enterocytes lining the lumen of the small intestine (de Wildt *et al.,* 1999).

The CYP3A4 isoform has been shown to oxidise at least partly 50% of all known drugs and cover a whole range of structurally unrelated substrates like antihistamines, anticonvulsants, antimicrobials, antifungals, immunosupressants, benzodiazepines, antihypertensives, anti-arrhythmics, antidepressants, analgesics, anaesthesics and also metabolise procarcinogens such as aflatoxin B1 (Shimada and Guengerich, 1989). Chlorpyrifos, parathion and diazinon, three pesticides are also partially oxidised by the CYP3A4 isoform (and CYP2D6 see previous chapter) to their toxic metabolites, which are potent acetylcholinesterase inhibitors (Sams *et al.,* 2000). Endogenous substrates including many steroids such as testosterone (2-β-, 6-β and 15-β-hydroxylation), 6-β-hydroxylation for androstanedione, cortisol, progesterone, estradiol are also oxidised by CYP3A4 (de Wildt *et al.,* 1999).

Since CYP3A4 is such a ubiquitous enzyme with catalytic activities for such a wide range of structural diversity, its importance in risk assessment is very substantial. This chapter will therefore describe the analysis of human variability in kinetics for the CYP3A4 pathway of metabolism to quantify inter-individual differences in the healthy adult population, and characterise the magnitude of any differences in potentially susceptible subgroups of the population. The results of these analyses will provide a basis to derive CYP3A4-related uncertainty factors.

## II.Methods

The methods used in this chapter are presented in chapter II.

## III.Results

### III.1. Metabolism data for CYP3A4 probe substrates

CYP3A4 substrates, that were totally absorbed from the gastrointestinal tract, have been selected on the basis of their in vivo metabolism: alprazolam, budesonide, Diltiazem, felodipine, lidocaine, nifedipine, nisoldipine, terfenadine, triazolam and zolpidem. A summary of the metabolism for each selected CYP3A4 substrate is presented in table 1.

#### III.1.1 Alprazolam

Alprazolam metabolism has been investigated using human liver microsomes and CYP3A expressing B-lymphoblastoid cells and the 1' and 4-hydroxylation were strongly correlated with the CYP3A4 isoform (Gorski *et al.*, 1999). Only 20% of the dose of alprazolam is excreted unchanged in the urine and the CYP3A4 dependent metabolites such as 1'-hydroxy and 4-hydroxy alprazolam (17 and 1%) and derivatives accounted for the remaining fraction of the dose (Smith and Kroboth, 1987).

#### III.1.2 Budesonide

Budesonide, a synthetic glucocorticosteroid, has been shown to metabolised by CYP3A enzymes since its 16$\alpha$ and $\beta$ hydroxylation were inhibited by antibodies raised against the CYP3A subfamily but not by CYP1A antibodies (Jonsson *et al.*,1995). Moreover, only traces of the R and S unchanged budesonide were found in the urine after

intravenous administration and about 70% and 30% of an oral dose were recovered in the urine and faeces respectively (Ryrfeldt *et al.*, 1984; Ryrfeldt *et al.*, 1982).

### III.1.3 Cyclosporin

Cyclosporin metabolism is inhibited by anti P450 3A polyclonal antibodies and CYP3A accounted for more than 80% of the liver cyclosporin oxidase activity (Combalbert *et al.*, 1989). However, it is partially absorbed by the gastrointestinal tract and only the intravenous data have been analysed.

### III.1.4 Calcium channel blockers: diltiazem, felodipine, nifedipine and nisoldipine

The N-demethylation of diltiazem, a commonly used calcium channel antagonist, has been shown to be handled by CYP3A4 in human liver microsomes as well as in primary cultures of human hepatocytes (Pichard *et al.*, 1990). Only 8% of an oral dose was recovered in the urine after 24 hours of collection, concluding on faecal excretion, with N-demethylation metabolites and derivatives represented more than 60% of the total urinary metabolites (Yeung *et al.*, 1990).

Similarly, felodipine, nifedipine and nisoldipine also constitute CYP3A4 probe substrates since their in vitro metabolism in liver microsomes and a yeast clone system expressing the CYP3A4 isoform have been shown to be mediated via this enzyme (Guengueric *et al.*, 1991). After oral administration, felodipine is excreted to a major extent with 70% of the total radioactivity recovered as metabolites in the urine with no quantifiable parent compound. Oral nifedipine is largely excreted in the urine as its acid metabolite with respectively 55 +/-14% of the dose after 24 hours and no unchanged drug in the urine while urinary oxidated metabolites of oral nisoldipine constituted 64 % of the dose (Renwick *et al.*, 1988; Scherling *et al.*, 1988).

### III.1.5 Lidocaine

Monoethylglycinexylidide has been shown to constitute the first step of lidocaine metabolism and this reaction is mediated by the cytochrome P4503A4 isoform in human liver microsomes (Bargetzi *et al.*, 1989). Lidocaine metabolism is extensive in the liver and monoethylglycinexylidide and derivatives (glycinexylidide, 4-hydroxy-2,6-dimethylaniline) constitute more than 80% of the dose recovered after oral administration (Keenaghan and Boyes,1972).

### III.1.6 Terfenadine

Terfenadine biotransformation in human liver microsomes is CYP3A4 dependent with a methyl oxidation yielding the major acid metabolite followed by an oxidative dealkylation. Over 99% of the dose is recovered in the urine (40%) and the faeces (61%) as metabolites and 70% of the total urinary excretion accounts for the acid metabolite and its hydrolysis product while 48% of the faecal radioactivity accounts for the former (Jurima-Romet *et al.*, 1994; Okerholm *et al.*, 1981; Garteiz *et al.*, 1982).

### III.1.7 Triazolam

Triazolam hydroxylase activity has been characterised in liver microsomes as catalysed by the CYP3A4 isoform (Kronbach *et al.*, 1989). This drug is readily absorbed after oral administration with 85% recovered in the urine and 8% in the faeces. The two main metabolites (1 and 4-hydroxylate) correspond to 69% and 11% of the total urinary metabolites respectively (Eberts *et al.*, 1981).

### III.1.8 Zolpidem

The biotransformation of zolpidem to its alcohol derivatives rapidly converted to carboxylic acids, constitutes the main pathway of metabolism in humans and is significantly inhibited by anti-CYP3A antibodies (Pichard *et al.*, 1995). The carboxylic metabolites resulting from methyl-oxidation on the phenyl and imidazopyridine moieties represent 52% and 12% of the dose after oral dosing respectively giving a minimum of 64% of the dose metabolised via the CYP3A4 metabolic route while unchanged zolpidem only represents 0.5% (Bianchetti *et al.*, 1988).

**Table 1. Metabolism data for the CYP3A4 probe substrates in healthy adult volunteers [a].**

| Drug | n | Dose (mg) | Route | % CYP3A4 metabolism |
|---|---|---|---|---|
| Alprazolam[1] | 16 | 4 | PO | 80* |
| Budesonide[2] | 3 | 0.5 | PO | >90* |
| Diltiazem[3] | 3 | 20 | PO | >60[Δ] |
| Felodipine[4] | 3 | 25 | PO | 70* |
| Lidocaine[5] | 2 | 250 | PO | >80* |
| Nifedipine[6] | 59 | 10 | PO | >60 * |
| Nisoldipine[7] | 12 | 12 | PO | >64* |
| Terfenadine[8] | 6 | 60-180 | PO | >71 [Δ] |
| Triazolam[9] | 6 | 0.88 | PO | >70* |
| Zolpidem[10] | 3 | 20 | PO | >63* |

[a] **n** - number of subjects; **PO** - oral administration; **IV** - intravenous administration; *Expressed as the percentage of the dose recovered as CYP3A4 dependent metabolites in the urine. [Δ]Expressed as the percentage of the total amount recovered in the urine.

[1]Smith and Kroboth, 1987; [2]Ryrfeldt *et al.*, 1982; [3]Yeung *et al.*, 1990. [4]Weidolf *et al.*, 1984; [5]Keenaghan and Boyes,1972; [6]Renwick *et al.*, 1988; [7]Sherling *et al.*, 1988; [8]Garteiz *et al.*, 1982; Okerholm *et al.*, 1981; [9]Eberts *et al.*, 1981; [10]Bianchetti *et al.*, 1988.

## III.2 Kinetic data for probe substrates handled by CYP3A4 in healthy adults

The tables (Tables 2-14) present the weighted mean analysis for normal and lognormal data. Human variability is described as the coefficient of variation for both distributions ($CV_N$ for normal and $CV_{LN}$ for lognormal) and is given as a single value unless differences are observed between the distributions in which case both values are given.

### III.2.1 Metabolic clearances

Published metabolic clearances in healthy adults were available for nifedipine, triazolam and minor CYP3A4 substrates for which the isoform mediated specific oxidation reactions (alfentanil and venlafaxine) (Table 2). After oral administration, the variability in metabolic clearances for CYP3A4 was 44% for the clearance adjusted to body weight (1 compound and 8 subjects) and was 54% for the clearance ($mlmin^{-1}$) (2 compounds and 24 subjects) and both distributional assumptions. The intravenous data were limited to alfentanil and the variability was lower than the oral one at 38% (14 subjects).

**Table 2. Interindividual differences in metabolic clearances for compounds eliminated via CYP3A4 after oral and intravenous administration to healthy adult volunteers[a].**

| Drug | CYP3A4 Pathway | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | | |
| Triazolam | 1 and 4 Hydroxylation | 1 | 1[1] | 8 | 2.5 | 1.1 | 44 | 2.3 | 1.5 | 44 |
| CL ($ml min^{-1}$) | | | | | | | | | | |
| Nifedipine | Oxidation | 1 | 1[2] | 10 | 530 | 280 | 58 | 460 | 1.7 | 58 |
| Venlafaxine | N-demethylation | 2 | 1[3] | 14 | 67 | 33 | 50 | 60 | 1.6 | 50 |
| *Intravenous administration* | | | | | | | | | | |
| CL ($ml min^{-1}$) | | | | | | | | | | |
| Alfentanil | Oxidation | 1 | 1[4] | 14 | 51 | 19 | 38 | 48 | 1.4 | 38 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Weighted arithmetic mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Weighted geometric mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficient of variation (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Kinirons *et al.*, 1996; [2]Schellens *et al.*, 1991; [3]Lessard *et al.*, 1999; [4]Krivoruk *et al.*, 1994.

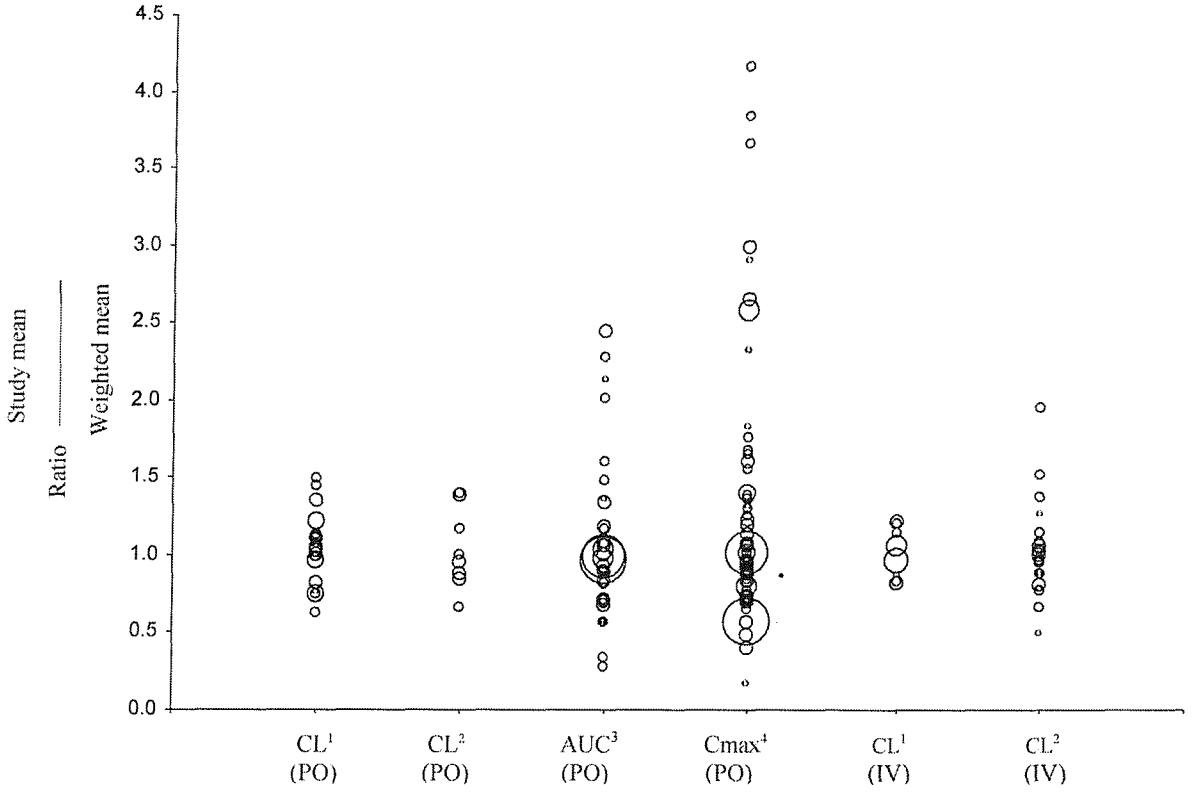
### III.2.2 Markers of chronic exposure (clearances , AUCs) and acute exposure (Cmax)

Variability in kinetics for each probe substrate and after oral and intravenous administration to healthy adult volunteers were analysed for both the normal ($CV_N$) and lognormal ($CV_{LN}$) distribution. Results were tabulated as markers of chronic exposure (clearance adjusted to body weight, clearance, AUC) and markers of acute exposure (Cmax).

#### *III.2.2.1 Variability between studies*

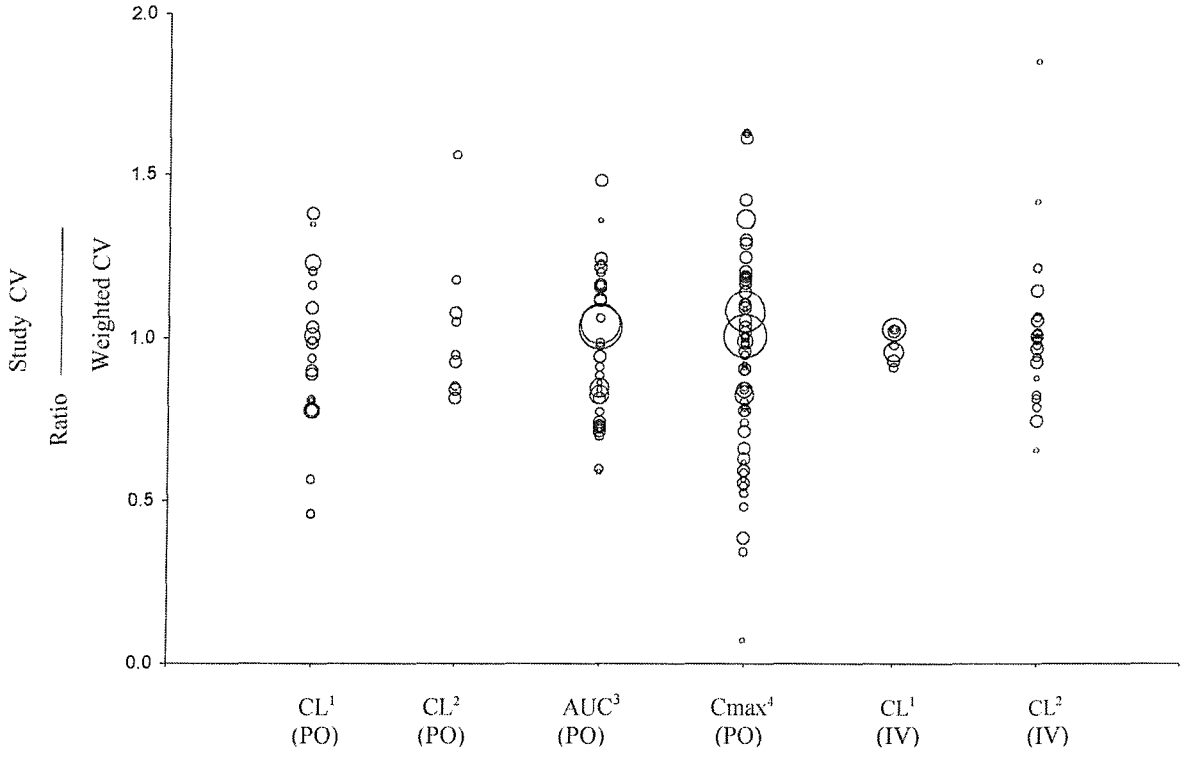
Figures 1 and 2 present the variability between studies (geometric means and $CV_{LN}$ respectively) for all the kinetic parameters (clearances, AUC and Cmax) and both routes of exposure (oral and intravenous). The ratios of geometric means and $CV_{LN}$ from individual studies were included within a 20-30% range of the overall mean for most clearances whereas the AUC data was more variable for smaller studies. The Cmax data was much more variable and most outliers were found for nifedipine studies (4 studies, ratios of 2.6 (n=27), 4.2 (n=7), 3.7 (n=10), 3.8 (n=10)) and nisoldipine studies (2.9 (n=6) and 0.39 (n=12)).

**Figure 1. Inter-study variation in kinetic parameters for compounds handled by CYP3A4 after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study means versus weighted means.**




The overall weighted mean for each compound (shown as the largest circle) has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle. [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}$; [3]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [4]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$; $CL^1$ (PO)-data for alprazolam (10studies), diltiazem (3 studies), nisoldipine (2 studies), triazolam (4 studies); $CL^2$(PO)-data for for alprazolam (5 studies), felodipine (3 studies), nifedipine (2 studies), zolpidem (2 studies); $AUC^3$(PO) -data for alprazolam (2 studies), diltiazem (6 studies), felodipine (3 studies), nifedipine (5 studies), nisoldipine (13 studies), triazolam (7 studies), zolpidem (2 studies); $Cmax^4$(PO) -data for alprazolam (15 studies), diltiazem (6 studies), felodipine (6 studies), nifedipine (8 studies), nisoldipine (13 studies), terfenadine (2 studies), triazolam (11studies), zolpidem (4 studies); $CL^1$(IV) -data for alprazolam (2 studies), cyclosporin (2 studies), lidocaine (7 studies), nifedipine (2 studies), triazolam (2 studies), zolpidem (2 studies); $CL^2$(IV) -data for budesonide (2 studies), diltiazem (2 studies), felodipine (3 studies), lidocaine (5 studies) ,nifedipine (2 studies).

**Figure 2. Inter-study variation in kinetic parameters for compounds handled by CYP3A4 after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations**




The overall weighted mean for each compound (shown as the largest circle) has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle.[1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}$; [3]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [4]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$; $CL^1$ (PO)-data for alprazolam (10studies), diltiazem (3 studies), nisoldipine (2 studies), triazolam (4 studies); $CL^2$(PO)-data for for alprazolam (5 studies), felodipine (3 studies), nifedipine (2 studies), zolpidem (2 studies); $AUC^3$(PO) -data for alprazolam (2 studies), diltiazem (6 studies), felodipine (3 studies), nifedipine (5 studies), nisoldipine (13 studies), triazolam (7 studies), zolpidem (2 studies); $Cmax^4$(PO) -data for alprazolam (15 studies), diltiazem (6 studies), felodipine (6 studies), nifedipine (8 studies), nisoldipine (13 studies), terfenadine (2 studies), triazolam (11studies), zolpidem (4 studies); $CL^1$(IV) -data for alprazolam (2 studies), cyclosporin (2 studies), lidocaine (7 studies), nifedipine (2 studies), triazolam (2 studies), zolpidem (2 studies); $CL^2$(IV) -data for budesonide (2 studies), diltiazem (2 studies), felodipine (3 studies), lidocaine (5 studies) ,nifedipine (2 studies).

### *III.2.2.2 Interindividual differences*

Interindividual differences for the markers of chronic oral exposure (Table 3 and 6) mostly ranged from 30-66% for both distributional assumptions and all the kinetic parameters studied (clearance adjusted to body weight, clearance and AUC data).

However, the CVs for nisoldipine clearance ($mlminkg^{-1}$) were outliers with 94/80% ($CV_N/CVL_N$). Overall, the variability was similar between the kinetic parameters with 54/48 % for the clearance adjusted to body weight (8 compounds, 261 subjects), 50/47% for the AUC (10 compounds, 650 subjects), 42%/41% for the clearance (4 compounds, 129 subjects) (Table 6). The intravenous data were less variable for both clearances ($mlminkg^{-1}$ and $mlmin^{-1}$) and ranged from 16-51% ($CV_N$) and 16-48% ($CV_{LN}$) with a mean of 34/32% (9 compounds, 221 subjects) and 28% (5 compounds and 143 subjects) respectively (Table 4 and 6).

The variability in Cmax (acute oral exposure, Table 5 and Table 6), based on an extensive database (10 compounds, 938 subjects), was comparable with that of clearances and AUC with 48/43% (values range from 25 to 62% ($CV_N$) and 24-61% ($CV_{LN}$).

**Table 3. Interindividual differences in the pharmacokinetics of compounds eliminated via CYP3A4 after oral administration to healthy adult volunteers[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL(mlmin$^{-1}$kg$^{-1}$) | | | | | | | | | |
| Alprazolam | 10 | 9[1] | 137 | 1.1 | 0.4 | 32 | 1.1 | 1.3 | 30 |
| Diltiazem | 3 | 3[2] | 25 | 36 | 15 | 41 | 33 | 1.4 | 38 |
| Felodipine | 1 | 1[3] | 10 | 35 | 14 | 41 | 33 | 1.5 | 41 |
| Nifedipine | 1 | 1[4] | 10 | 11 | 5.7 | 52 | 9.7 | 1.6 | 49 |
| Nisoldipine | 2 | 2[5] | 19 | 340 | 310 | 94 | 240 | 2.0 | 80 |
| Terfenadine | 1 | 1[6] | 13 | 1.3 | 0.87 | 66 | 1.1 | 1.8 | 66 |
| Triazolam | 4 | 3[7] | 44 | 6.8 | 3.1 | 45 | 6.1 | 1.5 | 43 |
| Zolpidem | 1 | 1[8] | 3 | 5.4 | 3.1 | 57 | 4.6 | 1.7 | 57 |
| CL(mlmin$^{-1}$) | | | | | | | | | |
| Alprazolam | 5 | 5[9] | 61 | 70 | 23 | 32 | 66 | 1.4 | 32 |
| Felodipine | 3 | 3[10] | 30 | 8400 | 3300 | 39 | 7600 | 1.5 | 39 |
| Nifedipine | 2 | 2[11] | 18 | 860 | 491 | 57 | 700 | 1.7 | 60 |
| Zolpidem | 2 | 2[12] | 20 | 360 | 140 | 38 | 330 | 1.4 | 38 |
| AUC/dose (nghml$^{-1}$)[a] | | | | | | | | | |
| Alprazolam | 2 | 2[13] | 24 | 14700 | 6600 | 45 | 14000 | 1.5 | 42 |
| Budesonide | 1 | 1[14] | 11 | 21 | 13 | 61 | 18 | 1.8 | 61 |
| Diltiazem | 6 | 6[15] | 60 | 640 | 280 | 44 | 560 | 1.5 | 43 |
| Felodipine | 3 | 3[16] | 32 | 207 | 91 | 44 | 190 | 1.5 | 42 |
| Lidocaine | 1 | 1[17] | 9 | 280 | 100 | 35 | 98 | 1.5 | 42 |
| Nifedipine | 5 | 5[18] | 187 | 1200 | 609 | 49 | 1100 | 1.6 | 48 |
| Nisoldipine | 13 | 8[19] | 130 | 66 | 39 | 58 | 52 | 1.6 | 47 |
| Terfenadine | 1 | 1[20] | 14 | 16 | 8 | 52 | 14 | 1.6 | 52 |
| Triazolam | 7 | 6[21] | 52 | 1500 | 800 | 55 | 1000 | 1.4 | 38 |
| Zolpidem | 2 | 2[22] | 131 | 8700 | 5050 | 58 | 7600 | 1.7 | 57 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Weighted arithmetic mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Weighted geometric mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficient of variation (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight (mgkg$^{-1}$).

[1]Juhl *et al.*, 1984, Ochs *et al.*, 1986, Blyden *et al.*, 1988; Ciraulo *et al.*, 1988, Scavone *et al.*, 1988, Friedman *et al.*, 1991, Kritjansson and Thorsteinsson, 1991(2), Wright *et al.*, 1997, Wong *et al.*, 1998 (a) ; [2]Schwartz *et al.*, 1987, Yeung *et al.*, 1990, Saenz Campos *et al.*, 1995; [3]Dunselman *et al.*, 1989; [4]Van Bortel *et al.*, 1989; [5]Van Harten, 1988c, Ottosson *et al.*, 1989; [6]Wong *et al.*, 1998(b); [7]Ochs *et al.*, 1987 (2), Kroboth *et al.*, 1995, Kinirons *et al.*, 1996; [8]Durol *et al.*, 1997; [9]Greenblatt *et al.*, 1988, Lin *et al.*, 1988, Greenblatt *et al.*, 1992, Greenblatt *et al.*, 1998(a), Amchin *et al.*, 1998; [10]Edgar *et al.*, 1985(a)(b), Edgar *et al.*, 1987(b); [11]Banzet *et al.*, 1983, Schellens *et al.*, 1991; [12]Greenblatt *et al.*, 1998(b), Drover *et al.*, 1999; [13]Schmith *et al.*, 1991, Scavone *et al.*, 1992; [14]Dahlstrom *et al.*, 1996; [15]Boyd *et al.*, 1989, Bianchetti *et al.*, 1991, Tawashi *et al.*, 1991b, Christrup *et al.*, 1992, Bianchetti *et al.*, 1995, Brorson *et al.*, 1994; [16]Smith *et al.*, 1987, Hardy *et al.*, 1988, Landahl *et al.*, 1988; [17]Isohanni *et al.*, 1999; [18]Ene and Roberts,1987, Garnier Moiroux *et al.*, 1987, Schellens *et al.*, 1988, Ashan *et al.*, 1993, Soons *et al.*, 1993; [19]Pasanisi *et al.*, 1985, Levine *et al.*, 1988, Van Harten, 1989(a), (b)(2), (c), Baksi *et al.*, 1991, Chandler *et al.*, 1992 (4), Bailey *et al.*, 1993, Shionoiri *et al.*, 1995; [20]Okerholm *et al.*, 1981; [21]Eberts *et al.*, 1981, Kroboth *et al.*, 1985, Robin *et al.*, 1993, Kosuge *et al.*, 1997, Otani *et al.*, 1997, Yasui *et al.*, 1997 (2); [22]Bianchetti *et al.*, 1988, Piergies *et al.*, 1996.

**Table 4. Interindividual differences in the clearances of compounds eliminated via CYP3A4 after intravenous administration to healthy adult volunteers[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| $CL(mlmin^{-1}kg^{-1})$ | | | | | | | | | |
| Alprazolam | 2 | 2[1] | 67 | 0.92 | 0.28 | 31 | 0.87 | 1.3 | 31 |
| Cyclosporin | 2 | 2[2] | 13 | 8.6 | 2.0 | 23 | 8.8 | 1.3 | 23 |
| Diltiazem | 1 | 1[3] | 12 | 21 | 8.0 | 38 | 20 | 1.4 | 38 |
| Lidocaine | 7 | 7[4] | 58 | 15 | 4.4 | 30 | 13 | 1.3 | 29 |
| Nifedipine | 2 | 2[5] | 13 | 7.6 | 2.9 | 39 | 7.0 | 1.4 | 38 |
| Nisoldipine | 1 | 1[6] | 8 | 11 | 3.2 | 29 | 10.7 | 1.3 | 29 |
| R-Budesonide | 1 | 1[7] | 6 | 28 | 10 | 37 | 26 | 1.4 | 37 |
| Triazolam | 2 | 1[8] | 24 | 2.3 | 0.6 | 25 | 2.2 | 1.3 | 24 |
| Zolpidem | 2 | 1[9] | 20 | 4.5 | 5.2 | 51 | 3.8 | 1.6 | 48 |
| $CL(mlmin^{-1})$ | | | | | | | | | |
| Budesonide | 2 | 2[10] | 18 | 1400 | 320 | 23 | 1300 | 1.3 | 23 |
| Diltiazem | 2 | 2[1] | 15 | 1100 | 540 | 47 | 1030 | 1.5 | 45 |
| Felodipine | 1 | 1[12] | 8 | 902 | 140 | 16 | 890 | 1.2 | 16 |
| Lidocaine | 5 | 2[13] | 66 | 1200 | 360 | 30 | 1100 | 1.3 | 31 |
| Nifedipine | 2 | 2[14] | 18 | 550 | 130 | 24 | 530 | 1.3 | 24 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Weighted arithmetic mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Weighted geometric mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficient of variation (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Fleishaker *et al.*, 1989, Bertz *et al.*, 1997; [2]Legg *et al.*, 1988, Gupta *et al.*, 1990; [3]Hermann *et al.*, 1983; [4]Fuschsfofen *et al.*,1978, Zito *et al.*, 1978, Bauer *et al.*, 1982, Goldberg *et al.*, 1982, Ochs *et al.*, 1983, Ujhelyi *et al.*, 1993, Isohanni *et al.*, 1998; [5]Van Bortel *et al.*, 1989, Rashid *et al.*, 1995; [6]Van Harten *et al.*, 1988a; [7]Ryrfeldt *et al.*, 1984; [8]Derry *et al.*, 1995 (2); [9]Bianchetti *et al.*, 1988(2); [10]Ryrfeldt *et al.*, 1982, Thorsson *et al.*, 1998; [11]Montamat *et al.*, 1989, Tawashi *et al.*, 1991a; [12]Cohen *et al.*, 1990; [13]Abernethy and Greenblatt, 1984 (4), Simon *et al.*, 1997; [14]Kleinbloesem *et al.*, 1986, Robertson *et al.*, 1988.

**Table 5. Interindividual variation in the maximum concentration (Cmax/dose ($ngml^{-1}$)) corrected to the mean body weight for CYP3A4 probe substrates after oral administration to healthy volunteers[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | |
| Alprazolam | 15 | 14[1] | 192 | 1300 | 320 | 25 | 1100 | 1.3 | 24 |
| Budesonide | 1 | 1[2] | 11 | 4.8 | 2.6 | 55 | 21 | 1.8 | 61 |
| Diltiazem | 6 | 6[3] | 57 | 120 | 54 | 47 | 100 | 1.5 | 42 |
| Felodipine | 6 | 5[4] | 62 | 56 | 24 | 43 | 49 | 1.5 | 42 |
| Lidocaine | 1 | 1[5] | 9 | 106 | 45 | 42 | 270 | 1.4 | 35 |
| Nifedipine | 8 | 8[6] | 212 | 330 | 180 | 54 | 220 | 1.5 | 42 |
| Nisoldipine | 13 | 9[7] | 128 | 11 | 7.0 | 62 | 8.7 | 1.6 | 52 |
| Terfenadine | 2 | 2[8] | 27 | 1.6 | 0.9 | 55 | 1.4 | 1.7 | 53 |
| Triazolam | 11 | 9[9] | 96 | 640 | 240 | 38 | 530 | 1.5 | 40 |
| Zolpidem | 4 | 4[10] | 144 | 2200 | 1200 | 60 | 1900 | 1.7 | 54 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Weighted arithmetic mean (normal distribution); **$SD_W$** Weighted standard deviation (normal distribution); **$CV_N$** Coefficient of variation (normal distribution); **$GM_W$** Weighted geometric mean (lognormal distribution); **$GSD_W$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficient of variation (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Juhl *et al.*, 1984, Blyden *et al.*, 1988, Ciraulo *et al.*, 1988, Greenblatt *et al.*, 1988, Lin *et al.*, 1988, Friedman *et al.*, 1991, Kritjansson and Thorsteinsson, 1991(2), Schmith *et al.*, 1991, Greenblatt *et al.*, 1992, Scavone *et al.*, 1992, Wright *et al.*, 1997, Amchin *et al.*, 1998, Greenblatt *et al.*, 1998(a), Wong *et al.*, 1998(a); [2]Dahlstrom *et al.*, 1996; [3]Yeung *et al.*, 1990, Bianchetti *et al.*, 1991, Tawashi *et al.*, 1991b, Christrup *et al.*, 1992, Bianchetti *et al.*, 1995, Saenz-Campos *et al.*, 1995; [4]Edgar *et al.*, 1985(a,b), Edgar *et al.*, 1987(b), Smith *et al.*, 1987, Hardy *et al.*, 1988, Landahl *et al.*, 1988; [5]Ishoanni *et al.*, 1999; [6]Banzet *et al.*, 1983, Ene and Roberts,1987, Garnier-Moiroux *et al.*, 1987, Schellens *et al.*, 1988, Van Bortel *et al.*, 1989, Ashan *et al.*, 1993, Soons *et al.*, 1993 Rashid *et al.*, 1995; [7]Pasanisi *et al.*, 1985, Levin *et al.*, 1988, Van Harten *et al.*, 1988a, Van Harten *et al.*, 1989c, b(2), Baksi *et al.*, 1991, Chandler *et al.*, 1992(4), Bailey *et al.*, 1993 Shionoiri *et al.*, 1995; [8]Okerholm *et al*,1981, Wong *et al.*, 1998(b); [9]Eberts *et al.*, 1981, Kroboth *et al.*, 1985, Ochs *et al.*, 1987 (2), Robin *et al.*, 1993, Kroboth *et al.*, 1995, Kinirons *et al.*, 1996, Kosuge *et al.*, 1997, Otani *et al.*, 1997, Yasui *et al.*, 1997 (2); [10]Bianchetti *et al.*, 1988, Piergies *et al.*, 1996, Durol *et al.*, 1997, Greenblatt *et al.*, 1998(b).

**Table 6. Interindividual differences for CYP3A4 metabolism in healthy adults, overall pooled analysis[a].**

| PK parameter | Nc | Ns | Np | n | Mean $CV_N$ | Mean GSD | Mean $CV_{LN}$ |
|---|---|---|---|---|---|---|---|
| *Oral Administration* | | | | | | | |
| CLm[1] | 1 | 1 | 1 | 8 | 44 | 1.5 | 44 |
| CLm[2] | 2 | 2 | 2 | 24 | 54 | 1.7 | 54 |
| CL[1] | 8 | 23 | 21 | 261 | 54 | 1.6 | 48 |
| CL[2] | 4 | 12 | 11 | 129 | 42 | 1.4 | 41 |
| AUC[3] | 10 | 41 | 35 | 650 | 50 | 1.6 | 47 |
| Cmax[4] | 10 | 67 | 59 | 938 | 48 | 1.6 | 43 |
| *Intravenous Administration* | | | | | | | |
| CLm[2] | 1 | 1 | 1 | 14 | 38 | 1.4 | 38 |
| CL[1] | 9 | 20 | 18 | 221 | 34 | 1.4 | 32 |
| CL[2] | 5 | 12 | 9 | 125 | 28 | 1.3 | 26 |

**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; n,number of subjects; **Mean $CV_N$** Mean coefficient of variation for all compounds (normal distribution); **Mean $CV_{LN}$** Mean coefficient of variation for all compounds (lognormal distribution); [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}$; [3]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [4]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$.

## III.3 Kinetic data in subgroups of the population

Kinetic data for CYP3A4 metabolism in subgroups of the population were abstracted and compared to the geometric mean and variability from the healthy adult data. Data were available for Asian healthy adults, African healthy adults, children (>1 year, <16 years), the elderly (>70 years), and patients with liver and kidney diseases.

### II.3.1 Interethnic differences

Interethnic differences (Table 7 and pooled analysis table 12) showed an overall 1.5-fold increase in internal dose in healthy Asian adults compared to healthy adults associated with higher variability for most parameters.

The data for Africans and Mexicans demonstrated similar differences to those for healthy Asian adults and compared to healthy adults with a 1.3-fold and 1.8-fold higher internal dose. Coefficients of variation were similar for both subgroups (30-40%) (Table 7 and 12).

**Table 7. Pharmacokinetics of CYP3A4 probe substrates: comparison between general healthy adults, healthy Asian adults, healthy African adults, healthy Mexican adults after oral and intravenous administration[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Asian* | | | | | | | | | | | |
| *Oral administration* | | | | | | | | | | | |
| CL($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Alprazolam | 4 | 3[1] | 29 | 0.95 | 0.26 | 27 | 0.91 | 1.3 | 26 | 1.2 | 0.87 |
| Triazolam | 1 | 1[2] | 8 | 3.5 | 0.8 | 23 | 3.4 | 1.3 | 23 | 1.8 | 0.53 |
| CL($mlmin^{-1}$) | | | | | | | | | | | |
| Alprazolam | 2 | 1[3] | 28 | 49 | 11 | 23 | 48 | 1.3 | 23 | 1.3 | 1.5 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Nifedipine | 5 | 4[4] | 60 | 2200 | 1200 | 55 | 1900 | 1.7 | 54 | 1.7 | 1.1 |
| Zolpidem | 1 | 1[5] | 9 | 12600 | 6500 | 51 | 11200 | 1.6 | 51 | 1.5 | 1.1 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Alprazolam | 6 | 4[6] | 57 | 1300 | 220 | 17 | 1200 | 1.2 | 21 | 1.1 | 0.85 |
| Nifedipine | 6 | 5[7] | 68 | 600 | 400 | 66 | 390 | 1.7 | 53 | 1.8 | 1.26 |
| Triazolam | 1 | 1[2] | 8 | 1500 | 470 | 33 | 1400 | 1.4 | 33 | 2.6 | 0.82 |
| *Intravenous administration* | | | | | | | | | | | |
| CL($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Nifedipine | 1 | 1[8] | 8 | 4.8 | 2.4 | 50 | 4.3 | 1.6 | 50 | 1.6 | 1.3 |
| *African* | | | | | | | | | | | |
| Oral Administration | | | | | | | | | | | |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Nifedipine **N** | 1 | 1[9] | 11 | 2200 | 680 | 48 | 2100 | 1.3 | 31 | 1.9 | 0.65 |
| Zolpidem **BA** | 1 | 1[10] | 10 | 9900 | 5700 | 58 | 8600 | 1.7 | 58 | 1.1 | 1.0 |
| Zolpidem **NA** | 1 | 1[10] | 10 | 10400 | 3200 | 30 | 9900 | 1.3 | 30 | 1.3 | 0.54 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Nifedipine **N** | 1 | 1[9] | 11 | 550 | 400 | 73 | 450 | 1.9 | 73 | 2.1 | 0.58 |
| *Mexican* | | | | | | | | | | | |
| *Oral administration* | | | | | | | | | | | |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Nifedipine | 1 | 1[11] | 12 | 2100 | 790 | 37 | 2001 | 1.4 | 37 | 1.8 | 1.3 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Nifedipine | 1 | 1[11] | 12 | 810 | 440 | 55 | 710 | 1.7 | 55 | 3.3 | 1.3 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_W}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_W}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **NA**: North African subjects; **BA**: Black African subjects; **N**: Nigerian subjects.

[1]Otani *et al.*, 1997(2), Furukori *et al*, 1998, Yasui *et al.*, 1998; [2]Kinirons *et al.*, 1996; [3]Lin *et al.*, 1988 (2); [4]Da-Guang *et al.*, 1990 (2), Ashan *et al.*, 1991; Ashan *et al.*, 1993, Azuma *et al.*, 1996; [5]Bianchetti *et al.*, 1988; [6]Lin *et al.*, 1988 (2), Otani *et al.*, 1997(2), Furukori *et al*, 1998, Yasui *et al.*, 1998; [7]Da-Guang *et al.*, 1990 (2), Ashan *et al.*, 1991, Ashan *et al.*, 1993, Rashid *et al.*, 1995, Azuma *et al.*, 1996; [8]Rashid *et al.*, 1995; [9]Sowunmi *et al.*, 1995; [10]Bianchetti *et al.*, 1988; [11]Hoyo-Vadillo *et al.*, 1989.

## III.3.2 Children

The oral (clearances, AUC, Cmax) and intravenous (clearance) data for children (Table 8 and Table 12) showed a 1.5-fold decrease in internal dose compared to healthy adults and the variability was overall similar to that in healthy adults.

**Table 8. Pharmacokinetics of compounds eliminated via CYP3A4 metabolism: comparison between healthy adults and children after oral and intravenous administration[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Children* | | | | | | | | | | | |
| *Oral administration* | | | | | | | | | | | |
| CL($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Alprazolam | 1 | 1[1] | 3 | 1.06 | 0.27 | 26 | 1.0 | 1.3 | 25 | 1.0 | 1.2 |
| Felodipine | 1 | 1[2] | 6 | 80 | 48 | 60 | 68 | 1.7 | 60 | 0.48 | 1.5 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Zolpidem | 1 | 1[3] | 7 | 5600 | 3000 | 53 | 4900 | 1.6 | 53 | 0.65 | 0.94 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Triazolam | 1 | 1[4] | 9 | 340 | 120 | 35 | 320 | 1.4 | 35 | 0.61 | 0.89 |
| Zolpidem | 1 | 1[3] | 7 | 1500 | 610 | 42 | 1300 | 1.5 | 42 | 0.70 | 0.78 |
| *Intravenous administration* | | | | | | | | | | | |
| CL($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Lidocaine | 1 | 1[5] | 12 | 25 | 7.1 | 29 | 24 | 1.3 | 29 | 0.55 | 1.0 |
| R-budesonide | 1 | 1[6] | 6 | 34 | 7.0 | 21 | 33 | 1.2 | 21 | 0.78 | 0.56 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); **$SD_w$**Weighted standard deviation (normal distribution); **$CV_N$** Coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficent of variation; (lognormal distribution); **Ratio $H/S_{LN}$** Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio $CV_{LN}$** Ratio between the variability of healthy adults and subgroup (Lognormal distribution)**; (n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$)

[1]De Vane *et al.*, 1998; [2]Blowey *et al.*, 1996; [3]Bianchetti *et al.*, 1988; [4]Karl *et al.*, 1997; [5]Pedersen *et al.*, 1987; [6]Michael *et al.*, 1992.

### III.3.3 The elderly

The comparison of geometric means between elderly and healthy adults (Table 9 and pooled analysis table 12) revealed an overall 1.5-, 2-fold and 1.2-fold increase in internal dose for markers of chronic exposure (oral and intravenous, clearances and AUC) and acute exposure (Cmax) respectively. The variability was similar to that in healthy adults for most parameters.

**Table 9. Pharmacokinetics of CYP3A4 probe substrates in the elderly after oral and intravenous administration: Comparison with healthy adults[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Elderly* | | | | | | | | | | | |
| *Oral administration* | | | | | | | | | | | |
| CL($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Alprazolam | 3 | 1[1] | 26 | 0.59 | 0.18 | 31 | 0.56 | 1.4 | 31 | 1.9 | 1.0 |
| Diltiazem | 1 | 1[2] | 10 | 22 | 8.6 | 40 | 20 | 1.5 | 40 | 1.7 | 1.0 |
| CL($mlmin^{-1}$) | | | | | | | | | | | |
| Felodipine | 1 | 1[3] | 11 | 4600 | 1000 | 22 | 4500 | 1.2 | 22 | 1.7 | 0.56 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Diltiazem | 1 | 1[4] | 16 | 430 | 194 | 45 | 400 | 1.5 | 45 | 0.71 | 1.1 |
| Felodipine | 2 | 2[5] | 23 | 240 | 120 | 49 | 350 | 1.5 | 40 | 1.9 | 0.97 |
| Nifedipine | 1 | 1[6] | 10 | 4400 | 3000 | 68 | 3700 | 1.8 | 68 | 3.3 | 1.4 |
| Nisoldipine | 3 | 3[7] | 33 | 101 | 64 | 63 | 84 | 1.8 | 61 | 1.6 | 1.3 |
| Zolpidem | 1 | 1[8] | 14 | 14000 | 7400 | 54 | 12000 | 1.7 | 54 | 1.6 | 0.96 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Alprazolam | 3 | 1[1] | 26 | 1200 | 330 | 28 | 1100 | 1.3 | 27 | 1.0 | 1.1 |
| Diltiazem | 1 | 1[4] | 16 | 51 | 29 | 47 | 43 | 1.6 | 47 | 0.43 | 1.1 |
| Felodipine | 3 | 3[9] | 34 | 73 | 38 | 51 | 55 | 1.5 | 45 | 1.1 | 1.1 |
| Nifedipine | 1 | 1[6] | 10 | 420 | 260 | 61 | 360 | 1.8 | 61 | 1.7 | 1.4 |
| Nisoldipine | 3 | 3[7] | 33 | 34 | 27 | 80 | 26 | 2.0 | 76 | 3.0 | 1.5 |
| Zolpidem | 1 | 1[8] | 14 | 2800 | 1070 | 38 | 2600 | 1.4 | 38 | 1.4 | 0.71 |
| *Intravenous administration* | | | | | | | | | | | |
| CL($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Alprazolam | 1 | 1[10] | 25 | 0.77 | 0.32 | 41 | 0.71 | 1.5 | 41 | 1.2 | 1.3 |
| Lidocaine | 3 | 2[11] | 59 | 7.0 | 2.3 | 32 | 6.6 | 1.3 | 30 | 2.0 | 1.0 |
| CL($mlmin^{-1}$) | | | | | | | | | | | |
| Diltiazem | 1 | 1[12] | 12 | 1100 | 346 | 31 | 1080 | 1.3 | 31 | 0.95 | 0.68 |
| Nifedipine | 1 | 1[13] | 6 | 350 | 83 | 24 | 340 | 1.3 | 24 | 1.6 | 1.0 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Felodipine | 1 | 1[14] | 11 | 3500 | 1800 | 53 | 3100 | 1.6 | 53 | 2.1 | 1.4 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); **$SD_w$** Weighted standard deviation (normal distribution); **$CV_N$** Coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficent of variation; (lognormal distribution); **Ratio $H/S_{LN}$** Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio $CV_{LN}$** Ratio between the variability of healthy adults and subgroup (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$)

[1]Kroboth *et al.*, 1990(3); [2]Schwartz *et al.*, 1987; [3]Dunselman *et al.*, 1989; [4]Caille *et al.*, 1991; [5] Landahl *et al.*, 1988, Bainbridge *et al.*, 1993; [6]Garnier-Moiroux *et al.*, 1987; [7] Van Harten *et al.*, 1989(b), Baksi *et al.*, 1991, Davidsson *et al.*, 1995; [8]Bianchetti *et al.*, 1988; [9]Landahl *et al.*, 1988, Dunselman *et al.*, 1989, Bainbridge *et al.*, 1993; [10]Bertz *et al.*, 1997; [11]Drayer *et al.*, 1983, Cusson *et al.*, 1985 (2); [12]Montamat *et al.*, 1989; [13]Robertson *et al.*, 1988; [14]Landahl *et al.*, 1988.

### III.3.4 Patients with liver disease and renal disease

The data for patients with liver disease (Table 10 and pooled analysis table 12) demonstrated an overall 2.5-3.5-fold increase in internal dose for all kinetic parameters and for both routes of exposure compared to healthy adults, the coefficients of variation were mostly similar to that in healty adults.

**Table 10. Pharmacokinetics of CYP3A4 probe substrates in patients with liver disease after oral and intravenous administration: comparison with healthy adults[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Liver Disease* | | | | | | | | | | | |
| *Oral administration* | | | | | | | | | | | |
| CL(mlmin$^{-1}$kg$^{-1}$) | | | | | | | | | | | |
| Alprazolam | 1 | 1[1] | 17 | 0.56 | 0.32 | 57 | 0.49 | 1.7 | 57 | 2.2 | 1.9 |
| Felodipine | 1 | 1[2] | 9 | 42 | 17 | 0.40 | 6.2 | 1.6 | 48 | 5.3 | 0.85 |
| Nisoldipine | 1 | 1[3] | 7 | 83 | 86 | 103 | 83 | 2.3 | 103 | 2.9 | 1.3 |
| AUC/dose (ngml$^{-1}$ h)[a] | | | | | | | | | | | |
| Nifedipine | 1 | 1[4] | 7 | 2400 | 500 | 20 | 2400 | 1.2 | 20 | 2.1 | 0.43 |
| Triazolam | 1 | 1[5] | 6 | 4900 | 1719 | 35 | 4600 | 1.4 | 35 | 4.6 | 0.92 |
| Zolpidem | 1 | 1[6] | 8 | 37000 | 33000 | 90 | 27000 | 2.2 | 90 | 3.6 | 1.6 |
| Cmax/dose (ngml$^{-1}$)[a] | | | | | | | | | | | |
| Alprazolam | 1 | 1[1] | 17 | 1300 | 380 | 30 | 1200 | 1.3 | 29 | 1.1 | 1.2 |
| Felodipine | 1 | 1[2] | 9 | 130 | 73 | 58 | 110 | 1.7 | 58 | 2.2 | 1.4 |
| Nifedipine | 1 | 1[3] | 7 | 830 | 300 | 36 | 780 | 1.4 | 36 | 3.6 | 0.85 |
| Nisoldipine | 2 | 2[7] | 15 | 70 | 40 | 59 | 57 | 1.7 | 59 | 6.5 | 1.1 |
| Triazolam | 1 | 1[5] | 6 | 1050 | 430 | 41 | 970 | 1.5 | 41 | 1.8 | 1.0 |
| Zolpidem | 1 | 1[6] | 8 | 4400 | 1900 | 43 | 4010 | 1.5 | 43 | 2.1 | 0.81 |
| *Intravenous administration* | | | | | | | | | | | |
| CL(mlmin$^{-1}$kg$^{-1}$) | | | | | | | | | | | |
| Lidocaine | 1 | 1[8] | 11 | 2.6 | 0.80 | 30 | 2.5 | 1.3 | 30 | 5.1 | 0.97 |
| Nisoldipine | 1 | 1[9] | 7 | 4.5 | 1.3 | 30 | 4.3 | 1.3 | 30 | 2.5 | 1.02 |
| CL(mlmin$^{-1}$) | | | | | | | | | | | |
| Nifedipine | 1 | 1[10] | 7 | 230 | 109 | 47 | 210 | 1.6 | 47 | 2.5 | 2.0 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); $SD_w$Weighted standard deviation (normal distribution); $CV_N$ Coefficient of variation (normal distribution); $GM_W$ Geometric weighted mean (lognormal distribution); $GSD_w$ Weighted geometric standard deviation (lognormal distribution); $CV_{LN}$ Coefficent of variation; (lognormal distribution); **Ratio** $H/S_{LN}$ Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $CV_{LN}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight (mgkg$^{-1}$)

[1]Juhl *et al.*, 1984; [2]Regardh *et al.*, 1989; [3]Van Harten *et al.*, 1988(c); [4]Ene and Roberts, 1987; [5]Robin *et al.*, 1993; [6]Bianchetti *et al.*, 1988; [7]Van Harten *et al.*, 1988b, Davidsson *et al.*, 1995; [8]Fuschsfofen *et al.*,1978; [9]Davidsson *et al.*, 1995; [10]Kleinbloesem *et al.*, 1986.

There was a 1.5-fold and 2.2 fold increase in oral AUC (5 compounds, 68 subjects) and Cmax (5 compounds, 63 subjects) respectively for patients with renal disease compared to healthy adults. However both oral clearances were in contradiction with this result (data based on only 13 and 8 subjects respectively) (Table 11 and 12 for pooled analysis). The intravenous data did not show any differences between the two groups nor did the variability for all parameters analysed.

**Table 11. Pharmacokinetics of CYP3A4 probe substrates in patients with renal disease after oral and intravenous administration: comparison with healthy adults[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | | |
| CL($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Alprazolam | 1 | 1[1] | 7 | 1.1 | 0.40 | 35 | 1.1 | 1.4 | 35 | 1.0 | 1.2 |
| Nifedipine | 1 | 1[2] | 6 | 36 | 19 | 53 | 32 | 1.7 | 53 | 0.30 | 1.1 |
| CL($mlmin^{-1}$) | | | | | | | | | | | |
| Nifedipine | 1 | 1[3] | 8 | 1200 | 1200 | 99 | 840 | 2.3 | 99 | 0.84 | 1.7 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Diltiazem | 1 | 1[4] | 10 | 1400 | 330 | 23 | 1400 | 1.3 | 23 | 2.5 | 0.6 |
| Felodipine | 3 | 3[5] | 25 | 290 | 130 | 46 | 260 | 1.5 | 46 | 1.4 | 1.1 |
| Nisoldipine | 2 | 2[6] | 11 | 65 | 19 | 29 | 54 | 1.4 | 34 | 1.0 | 0.7 |
| Triazolam | 1 | 1[7] | 11 | 2300 | 2200 | 93 | 1700 | 2.2 | 93 | 1.7 | 2.4 |
| Zolpidem | 1 | 1[8] | 11 | 14000 | 9200 | 66 | 12000 | 1.8 | 66 | 1.5 | 1.2 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Diltiazem | 1 | 1[4] | 10 | 110 | 36 | 32 | 107 | 1.4 | 32 | 1.1 | 0.8 |
| Felodipine | 3 | 3[5] | 25 | 61 | 25 | 41 | 53 | 1.5 | 41 | 1.1 | 1.0 |
| Nifedipine | 1 | 1[2] | 6 | 540 | 83 | 38 | 530 | 1.2 | 15 | 2.5 | 0.4 |
| Nisoldipine | 2 | 2[6] | 11 | 23 | 7.1 | 31 | 19 | 1.5 | 41 | 2.2 | 0.5 |
| Triazolam | 1 | 1[7] | 11 | 4040 | 1800 | 45 | 3700 | 1.5 | 45 | 7.0 | 1.3 |
| *Intravenous administration* | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Lidocaine | 1 | 1[9] | 6 | 12 | 2.4 | 20 | 12 | 1.2 | 20 | 1.1 | 0.67 |
| Zolpidem | 2 | 2[10] | 20 | 5.1 | 5.5 | 108 | 3.7 | 2.1 | 85 | 1.0 | 1.8 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| Diltiazem | 1 | 1[4] | 7 | 410 | 210 | 51 | 370 | 1.6 | 51 | 2.8 | 0.88 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Felodipine | 1 | 1[11] | 5 | 1700 | 660 | 33 | 1600 | 1.5 | 39 | 1.1 | 1.07 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric mean between healthy adults and subgroup (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$)

[1]Ochs *et al.*, 1986; [2]Van Bortel *et al.*, 1989; [3]Martre *et al.*, 1985; [4]Tawashi *et al.*, 1991; [5]Edgar *et al.*, 1989, Larsson *et al.*, 1990, Buur *et al.*, 1991; [6]Van Harten *et al.*, 1989(c); Shionoiri *et al.*, 1995; [7]Kroboth *et al.*, 1985; [8]Fillastre *et al.*, 1993; [9]Collinsworth *et al.*,1975; [10]Bianchetti *et al.*, 1988; [11]Buur *et al.*, 1991.

**Table 12. Pooled analysis for inter-individual differences in CYP3A4, effects of ethnicity and age[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio H/S $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL[1] | Asian | PO | 2 | 5 | 4 | 37 | 25 | 1.5 | 0.68 |
| CL[1] | | IV | 1 | 1 | 1 | 8 | 50 | 1.6 | 1.3 |
| CL[2] | | PO | 1 | 2 | 1 | 28 | 23 | 1.4 | 1.55 |
| AUC[3] | | PO | 2 | 6 | 5 | 69 | 53 | 1.6 | 1.1 |
| AUC[3] | North African | PO | 1 | 1 | 1 | 10 | 30 | 1.3 | 0.54 |
| AUC[3] | Black African | PO | 2 | 2 | 2 | 21 | 42 | 1.4 | 0.85 |
| AUC[3] | Mexican | PO | 1 | 1 | 1 | 12 | 37 | 1.8 | 1.3 |
| CL[1] | Elderly | PO | 2 | 4 | 2 | 36 | 35 | 1.8 | 1.0 |
| CL[1] | | IV | 2 | 4 | 3 | 84 | 35 | 1.6 | 1.1 |
| CL[2] | | PO | 1 | 1 | 1 | 11 | 22 | 1.7 | 0.56 |
| CL[2] | | IV | 2 | 2 | 2 | 18 | 27 | 1.2 | 0.82 |
| AUC[3] | | PO | 5 | 8 | 8 | 96 | 53 | 1.6 | 1.1 |
| AUC[3] | | IV | 1 | 1 | 1 | 11 | 53 | 2.1 | 1.4 |
| CL[1] | Children | PO | 2 | 2 | 2 | 9 | 39 | 0.69 | 1.34 |
| CL[1] | | IV | 2 | 2 | 2 | 18 | 25 | 0.65 | 0.75 |
| AUC[3] | | PO | 1 | 1 | 13 | 7 | 53 | 0.65 | 0.94 |
| CL[1] | Liver Disease | PO | 3 | 3 | 3 | 33 | 66 | 3.2 | 1.3 |
| CL[1] | | IV | 2 | 2 | 2 | 18 | 30 | 3.6 | 1.0 |
| AUC[3] | | PO | 3 | 1 | 3 | 21 | 40 | 3.3 | 0.86 |
| CL[2] | | IV | 1 | 1 | 1 | 7 | 47 | 2.5 | 2.0 |
| CL[1] | Renal disease | PO | 2 | 2 | 2 | 13 | 43 | 0.5 | 1.1 |
| CL[1] | | IV | 2 | 2 | 2 | 26 | 41 | 1.0 | 1.1 |
| CL[2] | | PO | 1 | 1 | 13 | 8 | 99 | 0.84 | 1.7 |
| CL[2] | | IV | 1 | 1 | 14 | 7 | 51 | 2.8 | 0.88 |
| AUC[3] | | PO | 5 | 8 | 8 | 68 | 47 | 1.5 | 1.1 |
| AUC[3] | | IV | 1 | 1 | 1 | 5 | 39 | 1.1 | 1.1 |
| Cmax[4] | Asian | PO | 3 | 13 | 10 | 133 | 33 | 1.7 | 0.96 |
| | Nigerian | | 1 | 1 | 1 | 11 | 73 | 2.1 | 0.58 |
| | Mexican | | 1 | 1 | 1 | 12 | 55 | 3.3 | 1.3 |
| | Children | | 2 | 2 | 2 | 16 | 38 | 0.65 | 0.83 |
| | Elderly | | 6 | 12 | 10 | 133 | 47 | 1.2 | 1.1 |
| | Liver disease | | 6 | 7 | 7 | 62 | 43 | 2.4 | 1.0 |
| | Renal disease | | 5 | 8 | 8 | 63 | 33 | 2.2 | 0.73 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$** Mean ratio of geometric means between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}$; [3]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [4]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$.

### III.4 Derivation of pathway-related uncertainty factors for CYP3A4 metabolism

CYP3A4-related default uncertainty factors were calculated for all groups of the population using the data for the oral route of exposure (Table 13). The 3.16 would cover more than 99% of heathy adults and children with uncertainty factors of 2.1, 2.4 and 2.8 (chronic exposure) and 2.0, 2.2 and 2.6 (acute exposure) whereas only 95% of subjects from ethnic minorities (Asain, Mexican, and African) and the elderly would be covered. Overall, patients with liver disease would constitute the most susceptible subgroups and require factors of 7.7, 9.1, 11 for the oral route whereas values for patients with renal disease would be much lower (2.8,3.3 and 3.9).

## IV.Discussion

This chapter aimed to investigate the inter-individual differences in CYP3A4 metabolism for ten major substrates to allow for the calculation of CYP3A4-related uncertainty factors. Two large databases describing the pharmacokinetics of drugs handled by CYP3A4 were analysed for healthy adults using parameters reflecting chronic exposure (oral and intravenous clearances/AUC data for 1040 and 346 subjects respectively) and oral acute exposure (Cmax data for 938 subjects). Inter-individual variability in kinetics for markers of chronic exposure in healthy adults was larger for the oral route of exposure with an average of 46% (30% for the intravenous route) and was associated with CYP3A4-related uncertainty factors below the 3.16 kinetic default with values of 2.1, 2.4 and 2.8 (95, 97.5 and $99^{th}$ centile). These differences in variability between the oral and intravenous route of exposure probably arise from the fact that CYP3A4 is expressed in the intestine (de Wildt *et al.*, 1999); the variability in kinetics estimated for the oral route would reflect the CYP3A4 activity in both the liver and the intestine. Two important issues relative to these inter-individual differences in CYP3A4 activity have given rise to debate over the last five years: P-glycoprotein and genetic polymorphism (Wacher *et al.*, 1995; Suzuki and Sugiyama, 2000).

**Table 13 .CYP3A4-related default factors in subgroups of the human population for chronic and acute oral exposure.**

| Subgroup (Route) | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ | CYP3A4-related uncertainty factors (Lognormal distribution) 95th | 97.5th | 99th |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | | |
| Healthy (PO) | CL[1], CL[2], AUC[3] | 10 | 76 | 67 | 1040 | 46 | | | 2.1 | 2.4 | 2.8 |
| Healthy Asian (PO) | CL[3], AUC[3] | 5 | 13 | 10 | 134 | 39 | 1.5 | 1.1 | 2.9 | 3.3 | 3.9 |
| Healthy North African (PO) | AUC[3] | 1 | 1 | 1 | 10 | 30 | 1.3 | 0.5 | 2.1 | 2.3 | 2.6 |
| Healthy Black African (PO) | AUC[3] | 2 | 2 | 21 | 21 | 42 | 1.5 | 1.5 | 2.9 | 3.3 | 3.8 |
| Healthy Mexican (PO) | AUC[3] | 1 | 1 | 1 | 12 | 37 | 1.8 | 1.3 | 3.2 | 3.6 | 4.1 |
| Elderly (PO) | CL[1],CL[3] | 8 | 13 | 11 | 143 | 46 | 1.7 | 1.0 | 3.4 | 3.9 | 4.6 |
| Children (IV) | CL[1], AUC[3] | 3 | 3 | 3 | 16 | 45 | 0.7 | 1.2 | 1.4 | 1.6 | 1.8 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy | | 10 | 67 | 59 | 938 | 43 | | | 2.0 | 2.2 | 2.6 |
| Healthy Asian | | 3 | 13 | 10 | 133 | 33 | 1.73 | 0.96 | 2.9 | 3.2 | 3.7 |
| Healthy Mexican | Cmax[4] | 1 | 1 | 12 | 12 | 55 | 3.30 | 1.30 | 7.7 | 9.0 | 10.9 |
| Elderly | | 2 | 2 | 2 | 16 | 38 | 0.65 | 0.8 | 1.2 | 1.3 | 1.5 |
| Children | | 6 | 12 | 10 | 133 | 47 | 1.20 | 1.1 | 2.5 | 2.9 | 3.4 |

**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Mean coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$) ; [3]Mean AUC and C max corrected for dose expressed per mean body weight ($mgkg^{-1}$).

In the intestine, there are overlapping substrate specificities between CYP3A4 and the MDR 1 (multi drug resistance) P-glycoprotein, an ATP-binding cassette transmembrane transporter (Wacher *et al.,* 1995). CYP3A4 substrates can either be a substrate, an inhibitor or an enhancer of the P-glycoprotein (Wacher *et al.,* 1995; Suzuki and Sugiyama, 2000). Both proteins are expressed in enterocytes and authors have proposed that this may decrease drug/xenobiotic oral biovailability and absorption (Suzuki and Sugiyama, 2000). These data show that the mean absorption rate and bioavailability would be affected by inhibition of P-glycoprotein without affecting dramatically the variability in CYP3A4 activity.

Another source of variability for the oral route and the CYP3A4 pathway has been shown with the presence of both allelic variants with altered catalytic activities and of protein variants (Eseilt *et al.,* 2001; Sata *et al.,* 2000). Ozdemir *et al* (2000) analysed data from Kasuba et al (1998) and Ohlman *et al.,* 1993 to test the genetic contribution to CYP3A4 hepatic variability using repeated administrations of midazolam (as a hepatic marker of the latter enzyme) and day-night changes in cyclosporin pharmacokinetics respectively. The results showed that the genetic contribution accounted for 96% of the enzyme activity with 95% confidence limits of 92% and 98% for midazolam and that the genetic contribution for cyclosporin was much higher at night than during the day and clearly other factors such as liver blood flow, food consumption would not influence cyclosporin kinetics as much as during the day (Ozdemir *et al.,* 2000; Kalow, 2001).

CYP3A4*2 has been shown to have lower intrinsic clearance for nifedipine compared to the wild type enzyme using a baculovirus-directed cDNA expression system (Sata *et al.,* 2000). It was the first report of a potential functional polymorphism from missense mutations in CYP3A4 genes (Sata *et al.,* 2000), however these *in vitro* assays would need to be investigated *in vivo* to quantify differences in clearances between phenotypes, and to investigate the clinical relevance of such polymorphism. Another polymorphism has been found in the 5' promotor region of the CYP3A4 gene (CYP3A4*1 B) and was associated with high frequencies in black Americans (55%, n=186), low in white Americans (3.6% in n=273) and non-existent in Japanese and Chinese Americans (0.0%; n = 77 and 78 respectively) (Ball *et al.,* 1999; Sata *et al.,* 2000). Although the frequency of this polymorphism was high in black Americans there were no differences in the pharmacokinetics of nifedipine between homozygous and heterozygous individuals, and it

was concluded that this polymorphism would not play a major role in determining constitutive CYP3A4 expression (Ball *et al.,* 1999).

From this body of evidence a genetic basis accounting for human variability in CYP3A4 metabolism is clear but its contribution to the variability in the *in vivo* pharmacokinetics of CYP3A4 probe substrates remains to be clarified.

The comparison between subgroups and general healthy adults using CYP3A4 probe substrates revealed consistent 1.5- 2-fold lower systemic clearance in South Asians, Mexicans, Africans and the elderly, and these subgroups would require CYP3A4-related uncertainty factors of 3.9, 3.8, 4.1 and 4.6 respectively ($99^{th}$ centile). The rationale for the observed interethnic differences in CYP3A4 activity would clearly involve lower hepatic metabolism in both South Asian and African compared to general healthy adults (Rashid *et al.,* 1995; Johnson *et al.,* 2000). Interethnic differences have also been suggested to involve gut metabolism/P-glycoprotein in a study with cyclosporin, African and Hispanics (although cyclosporin is not well absorbed in the first place) (Lindholm *et al.,* 1992, Johnson, 2000).

The differences between the elderly and general healthy adults have been investigated using *in vitro* assays for erythromycin N-demethylation with liver specimens from patients of different age groups (27-83) and gender (Hunt *et al.,* 1992). CYP3A4 activity was not demonstrated to be affected by age, and the age-related alteration of CYP3A4 activity was considered as secondary to changes in liver blood flow, drug binding and distribution (Hunt *et al.,* 1992). Although, these interethnic and age differences in CYP3A4 metabolism have been well documentated in our database; more studies would be required to characterise precisely the involvement of hepatic and gut metabolism, P-glycoprotein and genetic polymorphism.

Children showed higher clearances for CYP3A4 probe substrates than healty adults and this can be associated with faster metabolism in this subgroup (Renwick *et al.,* 2000). Unfortunately, no *in vivo* kinetic data were available for neonates. However, low reduction of CYP3A4 *in vitro* activity has been documented during the first 2 months of life since the neonatal form CYP3A7 is expressed (Cresteil *et al.,* 1998; de Wildt *et al.,* 1999). Because

of the general lack of data for CYP3A4/CYP3A7 in neonates, contaminants such as pesticides that are handled by CYP3A4 could be of most concern.

Patients with liver disease demonstrated overall 3-fold lower systemic clearance for CYP3A4 probe substrates compared to heathy adults, and such differences would be expected because this isoform represents more 50% of all CYPs in the liver.

This chapter has dealt with the analysis of human variability in CYP3A4 metabolism and showed that the current 3.16 kinetic default would cover at least 99% of healthy adults. However, sources of variability that have not yet been fully characterised include gut metabolism, overlapping substrate specificities between CYP3A4 and P-glycoprotein and the presence of genetic polymorphisms. Potential susceptible subgroups would include South Asians, and the elderly for whom the kinetic default would cover less than 95% of each subpopulation. Neonates are also a potentially susceptible group but the expression of the foetal and neonatal CYP3A7 may provide an alternative enzyme for the metabolim of CYP3A4 substrates. The absence of data for neonates is of concern because CYP3A4 is involved in the metabolism of many environmental contaminants and pesticides together with the polymorphic CYP2D6 (which is also immature in neonates)(Eaton et al., 2000; Chapter IV).

# Chapter VI: Human variability in Phase I, Phase II metabolism and renal excretion

The previous result chapters have described the analysis of human variability in kinetics for three major pathways in humans (Glucuronidation, CYP2D6, CYP3A4) to derive pathway-related default uncertainty factors for each pathway and both healthy adults and other subgroups of the population (depending on availability of the data).

Most Phase I, Phase II pathways and renal excretion have also been analysed using the same method as presented in Chapter II. This chapter aims to present the summary data for all these pathways since the size of the database was too large to describe the individual data for each probe substrate (Appendix I) in a thesis format. The metabolism of the probe substrates, the summary kinetic data for all the available subgroups of the population and the pathway-related uncertainty factors will be presented. These results will be discussed in the final discussion dealing with the applications of these analyses for chemical risk assessment (chapter VIII).

## I. Phase I Metabolism

### I.1 Differences between studies

Bubble graphs representing differences between indivdiual studies and the overall weighted mean/coefficient of variation for each phase I pathway and parameter analysed are presented in Appendix I .

### I.2 Interindividual differences

#### I.2.1 CYP1A2

##### *I.2.1.1 Metabolism data for CYP1A2 probe substrates*

The literature search identified four probe substrates for the CYP1A2 pathway: caffeine, theophylline, paraxanthine and theobromine. A comprehensive review of the metabolism for each of these substrates in humans and the different test species used in toxicity testing

has been published (Dorne *et al.*, 2001; Walton *et al.*, 2001).

Four CYP1A2 probe substrates have been selected: caffeine, theophylline, theobromine and paraxanthine and are completely absorbed from the gastrointestinal tract.

Caffeine is primarily transformed via 3 major N-demethylation reactions (1-, 3- or 7-N-demethylation) producing theobromine, paraxanthine and theophylline, which are further metabolised via N-demethylation or C-8 oxidation and excreted in the urine (Lelo *et al.*, 1986a). Studies using liver microsomes have shown that the CYP1A2 isoform mediated the N-demethylation reactions with high affinity, and that the CYP2E1 isoform catalysed the 1- and 7–N-demethylations with a low affinity. Over 90% of an oral dose of caffeine undergoes a combination of 3-N-demethylation (79.6%) and 1- and 7–N-demethylation (10.8 and 3.7%), the products of which are recovered as urinary metabolites (Lelo *et al.*, 1986a; Gu *et al*, 1992; Chung and Cha, 1997).

Theophylline undergoes C-8-oxidation as the major metabolic route accounting for 49% its urinary excretion, together with oxidative 1- and 3-N-demethylation (18% and 25% respectively). In humans, these reactions are mediated by the CYP1A2 isoform at pharmacological concentrations, whereas CYP2E1 mediates C-8-oxidation at high concentrations (Birkett *et al.*, 1985; Gu *et al.*, 1992; Fuhr *et al.*, 1992; Zhang and Kaminsky, 1995).

Paraxanthine is metabolised extensively with more than 80% of an oral dose excreted in the urine as products of 7-N-demethylation (66.8%), 1-N-demethylation (5.2%) and C-8-oxidation (7.7 %). An *in vitro* study using human liver microsomes showed that both N-demethylation reactions were catalysed by the PAH-inducible CY1A2 isoform (Lelo *et al.*, 1989; Campbell *et al.*, 1987b).

Theobromine is metabolised (90% of an oral dose) via CYP1A2 mediated reactions: 3-N-demethylation (>60%), 7-N-demethylation (20%) and C-8-oxidation (<15%). Minor involvements of CYP2A6 and CYP2E1 in 7-N-demethylation and C-8-oxidation were demonstrated in human hepatic microsomes, but because CYP1A2 is expressed in human liver more prominently than these other isoforms, it is likely to predominate *in vivo* (Birkett *et al.*, 1985; Campbell *et al.*, 1987a; Gates and Miners, 1999).

R-warfarin did not fulfil the metbolism criteria, because less than 60% of an oral dose was recovered as CYP1A2 metabolites in the urine and faeces (Kaminsky and Zhang, 1997; Heimark *et al.*, 1992). Nevertheless, the 6-hydroxylation is specifically mediated by CYP1A2 and the corresponding metabolic clearance after intravenous (iv) dosing has been abstracted.

### *I.2.1.2 Human variability in kinetics*

The analysis of human variability for the CYP1A2 has been published in detail (Dorne *et al.*, 2001).

#### *I.2.1.2.1 Healthy adults*

When pooling the data for each substrate and each parameter, the resultant coefficient of variation ranged from 30 to 56% (Table 1). The most reliable estimation of the variability reflecting chronic oral exposure is given by the oral clearance adjusted to body weight with a value of 32/28% based on data for all four probe substrates and 326 healthy adult volunteers similar to the equivalent specific metabolic clearance parameter for the lognormal data (4 compounds, 29%). The variability for the AUC (adjusted to body weight) data was comparable at 41/36%. The clearance ($mlmin^{-1}$) and its metabolic equivalent were more variable (56%) but were derived from only 1 probe substrate and 10 volunteers. The data for the intravenous route gave similar values to that for the oral route with 34/29% for the metabolic clearance (adjusted to body weight), 38/33% for the equivalent clearance and 30/27% for the AUC.

The Cmax variability (21/20%) based on 3 compounds and 99 healthy adults, was lower than for the clearance and the AUC.

**Table 1. Interindividual differences in CYP1A2 metabolism for Healthy adults and subgroups of the population, pooled analysis[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_N$ | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | |
| CLm[1] | Healthy | PO | 4 | 6 | 6 | 47 | 42 | 29 | | |
| CLm[1] | | IV | 2 | 4 | 3 | 28 | 34 | 29 | | |
| CLm[2] | | IV | 1 | 1 | 1 | 6 | 59 | 59 | | |
| CL[1] | | PO | 4 | 25 | 25 | 326 | 32 | 28 | | |
| CL[1] | | IV | 2 | 14 | 13 | 112 | 38 | 33 | | |
| CL[2] | | PO | 1 | 1 | 1 | 10 | 56 | 56 | | |
| AUC[3] | | PO | 3 | 4 | 4 | 43 | 41 | 36 | | |
| AUC[3] | | IV | 2 | 3 | 2 | 22 | 30 | 27 | | |
| CL[1] | Smokers | PO | 2 | 5 | 4 | 53 | 31 | 29 | 0.61 | 0.81 |
| CL[1] | | IV | 1 | 1 | 1 | 8 | 24 | 24 | 1.0 | 0.99 |
| AUC[3] | | PO | 1 | 1 | 1 | 6 | 40 | 40 | 0.49 | 1.6 |
| AUC[3] | | IV | 1 | 2 | 1 | 14 | 31 | 31 | 0.62 | 1.6 |
| CL[1] | Black Zimbabwean | IV | 1 | 1 | 1 | 16 | 27 | 27 | 1.6 | 1.7 |
| CL[1] | Neonates | PO | 1 | 1 | 1 | 5 | 18 | 18 | 8.96 | 0.50 |
| CL[1] | | IV | 2 | 7 | 6 | 251 | 39 | 35 | 6.2 | 1.1 |
| CL[1] | Infants | PO | 2 | 3 | 3 | 37 | 81 | 86 | 1.3 | 0.74 |
| CL[1] | | IV | 1 | 3 | 2 | 43 | 36 | 33 | 2.2 | 1.3 |
| CL[1] | Children | PO | 1 | 1 | 1 | 3 | 32 | 32 | 0.66 | 0.88 |
| CL[1] | | IV | 1 | 12 | 7 | 195 | 36 | 34 | 0.82 | 1.4 |
| CL[1] | Elderly | PO | 1 | 1 | 1 | 19 | 15 | 15 | 1.2 | 0.42 |
| CL[1] | | IV | 2 | 7 | 6 | 59 | 40 | 40 | 1.4 | 1.4 |
| AUC[3] | | PO | 1 | 1 | 1 | 8 | 48 | 48 | 0.74 | 0.87 |
| CL[1] | Elderly smokers | PO | 1 | 1 | 1 | 11 | 15 | 15 | 1.2 | 0.42 |
| CL[1] | Pregnant women | PO | 1 | 2 | 2 | 14 | 55 | 47 | 2.3 | 1.3 |
| CL[1] | | IV | 1 | 3 | 3 | 14 | 26 | 23 | 1.2 | 0.92 |
| CL[1] | Liver Disease | PO | 1 | 9 | 6 | 116 | 71 | 60 | 2.6 | 1.7 |
| CL[1] | | IV | 2 | 11 | 7 | 113 | 63 | 53 | 2.2 | 1.3 |
| CL[1] | Renal Disease | IV | 2 | 5 | 4 | 36 | 39 | 36 | 2.7 | 1.1 |
| *Acute exposure* | | | | | | | | | | |
| Cmax[3] | Healthy | PO | 2 | 8 | 8 | 99 | 21 | 20 | | |
| | Healthy Smokers | | 1 | 1 | 1 | 6 | 35 | 35 | 0.97 | 1.5 |
| | Neonates | | 1 | 2 | 2 | 16 | 8 | 7 | 0.75 | 0.27 |
| | Infants | | 1 | 1 | 1 | 20 | 38 | 38 | 0.55 | 2.1 |
| | Elderly | | 2 | 2 | 2 | 27 | 16 | 16 | 0.36 | 1.1 |
| | Elderly smokers | | 1 | 1 | 1 | 11 | 14 | 14 | 0.56 | 0.79 |
| | Pregnant women | | 1 | 1 | 1 | 8 | 72 | 72 | 1.1 | 3.1 |
| | Liver Disease | | 1 | 3 | 1 | 27 | 17 | 16 | 0.97 | 0.68 |

[a]**Nc** umber of compounds; **Ns**,Number of studies; **Np**,Number of publications; **n**.Number of subjects; **Mean ratio $H/S_{LN}$**, Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$**, ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight ((ml $min^{-1}Kg^{-1}$); [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and Cmax corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### *I.2.1.2.2 Subgroups*

An overall analysis for the subgroups is presented in Table 1 (data based only on Caffeine and theophylline). The comparison of geometric means between healthy adults and subgroups revealed a 1.5- 2.5 fold increase in internal dose for black Zimbabwean (1.6-fold, intravenous clearance, 16 subjects), pregnant women (2.3-fold, oral clearance), infants

(1.3-fold overall), liver disease (2-fold for both intravenous and oral clearance), renal disease (1.5-fold for intravenous clearance).

The neonates were the only individuals for whom there was a dramatic increase in internal dose compared to healthy adults , this being 9-fold for the oral clearance (n=5) and 6.2-fold for the intravenous clearance.

All other subgroups showed lower internal dose (1.3-1.6-fold for children and 1.6-fold for smokers) or values similar to that in healthy adults (elderly, and elderly smokers).

The analysis of Cmax did not show any difference between subgroups and healthy adults except for pregnant women for whom variability was three times higher than that in healthy adults.

### *II.1.2.3 CYP1A2-related uncertainty factors*

Data reflecting chronic oral exposure (clearances and AUC) were sufficient in healthy adults to derive default uncertainty factors for the CYP1A2 pathway and respective values of 1.8, 2.0 and 2.0 would cover the 95$^{th}$, 97.5$^{th}$ or 99$^{th}$centiles of the healthy adult population (Table 2).

CYP1A2-related defaults for subgroups of the population were derived from both oral and intravenous data and pregnant women, infants and neonates were shown to be the most susceptible subgroups with uncertainty factors up to 6.5, 7.5 and 14 (99$^{th}$ centile) respectively. Patients with liver disease were also identified as a potentially susceptible subgroup with values of 7.0, 8.5, 10.5 (oral clearance, data not shown) (95$^{th}$, 97.5$^{th}$ or 99$^{th}$centiles) whereas patients with renal disease would only require factors of 2.8, 3.1 and 3.6.

CYP1A2-related uncertainty factors were below a value of 2 (99$^{th}$ centile) for all other subgroups (healthy adult smokers, elderly non-smokers and smokers, children).

**Table 2. CYP1A2 related uncertainty factors in subgroups of the human population[a].**

| Subgroup | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ | CYP1A2 related default factors (lognormal distribution) 95th | 97.5th | 99th |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | | |
| Healthy (PO) | CL[1], CL[2], AUC[3] | 4 | 30 | 30 | 379 | 30 | | | 1.6 | 1.8 | 2.0 |
| Healthy (IV) | CL[1], AUC[3] | 2 | 17 | 15 | 134 | 32 | | | 1.7 | 1.8 | 2.1 |
| Healthy Smokers (PO) | CL[1], AUC[3] | 2 | 6 | 5 | 59 | 36 | 0.61 | 1.05 | 1.1 | 1.2 | 1.4 |
| Healthy Black (IV) | CL[1] | 1 | 1 | 1 | 16 | 27 | 1.6 | 1.1 | 2.5 | 2.7 | 3.0 |
| Neonates (PO) | CL[1] | 1 | 1 | 1 | 5 | 18 | 9.0 | 0.50 | 12 | 13 | 14 |
| Neonates (IV) | CL[1] | 2 | 7 | 6 | 251 | 35 | 6.2 | 1.1 | 11 | 12 | 14 |
| Infants (PO) | CL[1] | 2 | 3 | 3 | 37 | 86 | 1.3 | 0.74 | 4.5 | 5.7 | 7.5 |
| Infants (IV) | CL[1] | 1 | 3 | 2 | 43 | 33 | 2.2 | 1.3 | 3.7 | 4.1 | 4.6 |
| Children (PO) | CL[1] | 1 | 1 | 1 | 3 | 32 | 0.66 | 0.88 | 1.1 | 1.2 | 1.4 |
| Children (IV) | CL[1] | 1 | 12 | 7 | 195 | 34 | 0.82 | 1.4 | 1.4 | 1.6 | 1.8 |
| Elderly (PO) | CL[1] | 2 | 2 | 2 | 27 | 25 | 1.06 | 0.55 | 1.5 | 1.7 | 1.8 |
| Elderly Smokers (PO) | CL[1] | 1 | 1 | 1 | 11 | 15 | 1.2 | 0.42 | 1.5 | 1.5 | 1.6 |
| Pregnant women (PO) | CL[1] | 1 | 2 | 2 | 14 | 47 | 2.3 | 1.3 | 4.7 | 5.4 | 6.4 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy (PO) | Cmax[3] | 2 | 8 | 8 | 99 | 20 | 1.0 | 1.0 | 1.4 | 1.5 | 1.6 |
| Healthy Smokers (PO) | | 1 | 1 | 1 | 6 | 35 | 0.97 | 1.5 | 1.7 | 1.9 | 2.1 |
| Neonates (PO) | | 1 | 2 | 2 | 16 | 6.0 | 0.75 | 0.27 | <1 | <1 | <1 |
| Infants (PO) | | 1 | 1 | 1 | 20 | 38 | 0.55 | 2.1 | 1.0 | 1.1 | 1.3 |
| Elderly (PO) | | 2 | 2 | 2 | 27 | 16 | 0.36 | 1.1 | <1 | <1 | <1 |
| Elderly Smokers (PO) | | 1 | 1 | 1 | 11 | 14 | 0.56 | 0.79 | <1 | 0.7 | 0.8 |
| Pregnant women (PO) | | 1 | 1 | 1 | 8 | 72 | 11 | 3.1 | 1.6 | 2.0 | 2.5 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Mean coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and C max corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### I.2.2 CYP2C9

#### *I.2.2.1 Metabolism data for the probe substrates*

Two probe substrates were found to be metabolised primarily by the CYP2C9 isoform: the S-enantiomer of Warfarin and Tolbutamide. Tolbutamide is oxidised to its 4-hydroxy derivative via CYP2C9 (>80%) and further metabolised to carboxy-tolbutamide via Alcohol dehydrogenase CYP2C9/10 (Bach *et al.,* 1988; Relling *et al.,* 1990; Thomas and Ikeda, 1966; Veronese *et al.,* 1990) making the major contribution. S-Warfarin is mainly metabolised to 6- and 7-hydroxy-warfarin (80-85%) via CYP2C9 (Rettie e*t al.,* 1992; Takahashi *et al.,* 1998).

#### *I.2.2.2 Human variability in kinetics*

The data describing the human variability in kinetics for the CYP2C9 pathway are presented in Table 3. Inter-individual differences in healthy adults ranged from 12 to 43% (normal distribution) and 12 to 38% (lognormal distribution) for all kinetic parameters after oral administration. The overall variability was 25% (2 compounds, 21 subjects), 40/38% (2 compounds, 100 subjects) and 21/18% (2 compounds, 38 subjects) for the clearance adjusted to body weight, clearance and AUC respectively. The coefficient of variation for the intravenous metabolic clearance ($mlmin^{-1}$) (tolbutamide, 7 subjects) was 34%, but the intravenous plasma clearance was less variable (26%). The variability in Cmax was similar to that for clearances and AUC (Table 3).

The data for elderly and Chinese subjects did not show any difference compared to healthy adults. Tolbutamide clearances (oral and intravenous) for patients with liver disease were 2-fold higher than in healthy adults and the variability was similar (data based on only 5 subjects) (Table 5)

#### *I.2.2.3 CYP2C9-related uncertainty factors*

Due to the lack of the data for this pathway, CYP2C9-related uncertainty factors could only be calculated for healthy adults and the elderly. These pathway-related defaults were below the 3.16 kinetic default for both markers of chronic and acute exposure with values of 1.7 1.9 and 2.2 ($CV_{LN}$= 32%, 2 compounds and 169 subjects) and 1.6, 1.7

and 1.9 ($CV_{LN}$= 26%, 2 compounds, 30 subjects) covering 95, 97.5 and 99% of the population respectively.

**Table 3. Pooled analysis for interindividual differences in CYP2C9 metabolism, Healthy adults, elderly and patients with liver disease[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_N$ | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio H/S $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| CLm[2] | Healthy | IV | 1 | 1 | 1 | 7 | 34 | 34 | | |
| CL[1] | | PO | 2 | 4 | 4 | 31 | 24 | 23 | | |
| CL[2] | | PO | 2 | 8 | 6 | 100 | 40 | 38 | | |
| CL[2] | | IV | 2 | 2 | 2 | 16 | 26 | 26 | | |
| AUC[3] | | PO | 2 | 3 | 3 | 38 | 21 | 18 | | |
| CL[2] | Elderly | PO | 1 | 1 | 1 | 12 | 30 | 30 | 0.74 | 1.1 |
| CL[2] | Liver Disease | PO | 1 | 1 | 1 | 5 | 21 | 21 | 0.44 | 0.96 |
| CL[2] | Liver Disease | IV | 1 | 1 | 1 | 5 | 22 | 22 | 0.61 | 0.57 |
| Cmax[3] | Heathy | PO | 2 | 3 | 3 | 30 | 29 | 26 | | |
| | Elderly | | 1 | 1 | 1 | 12 | 38 | 38 | 0.83 | 2.2 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **Mean ratio $H/S_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight ((ml $min^{-1}Kg^{-1}$); [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and Cmax corrected for dose expressed per mean body weight ($mgkg^{-1}$).

## I.2.3 CYP2C19

### *I.2.3.1 Metabolism data for the probe substrates*

Three substrates have been identified as probe substrates for CYP2C19 (omeprazole, Hexobarbital, S-mephenytoin) on the basis that at least 60% of an oral dose was metabolised by CYP2C19 in extensive metabolisers of S-mephenytoin (EMs).

Omeprazole has been shown to be metabolised by 2 main routes: a 5'-hydroxylation mediated by CYP2C19 followed by a further oxidation to the acid, and a suplhoxidation mediated by CYP3A4 followed by an oxidation to the acid derivative (Renberg et al., 1989; Karam *et al.,* 1996). More than 80% of the metabolites were recovered as the 5-hydroxy metabolites and derivatives in the urine and this constituted at least 50% of the dose (Renberg et al., 1989). Another 16% are excreted in the faeces for which metabolites have not been characterised (Lind *et al.,* 1987). The CYP2C19 pathway is predominant in EMs

and can be considered to account for at least 60% of an oral dose of omeprazole whereas the CYP3A4 pathway is predominant in Poor metabolisers (PMs) (Bottiger *et al.*, 1997).

S-mephenytoin is nearly solely metabolised (91% of an oral dose) to its 4-hydroxy derivative via CYP2C19 (Kupfer *et al.*, 1981; Shimada *et al.*, 1986).

R-hexobarbital metabolism is mediated by CYP2C19 through the formation of 3'-hydroxy- and 3'-keto-hexobarbital and 1,5-dimethylbarbituric acid and these metabolites account for 90% of the excreted drug in EMs (Adedoyin *et al.*, 1994).

### *I.2.3.2 Human variability in kinetics*

#### *I.2.3.2.1 Healthy adults*

Variability for chronic oral exposure ranged from 33 to 77% ($CV_N$) and 32 to 68% ($CV_{LN}$) for non-phenotyped (NP) individuals with 46/44% for the best clearance estimate (3 compounds, 71 subjects) (Table 4). The variability for the intravenous route ranged from 25-76% ($CV_{LN}$) and was similar to the variability after oral administration with an average of 50%. Similar values were found for the Cmax analysis at 49/45% (2 compounds, 77 subjects). The range of variability for the EM data was also similar to that for NP. However, the best clearance estimate ($mlmin^{-1}$) was more variable with 80% ($CV_{LN}$) (3 compounds, 77 subjects) whereas variability for Cmax was 54% (2 compounds, 31 subjects). The small databases for PMs and SEMs are difficult to interpret because there was a wide range of differences in internal dose for PMs compared to EMs (3.1-86 for AUC and clearances, 5-fold for Cmax); only 4 subjects were available for SEMs. However, both subgroups showed consistent lower variability than EMs.

**Table 4. Interindividual differences for CYP2C19 metabolism in non-phenotyped and phenotyped healthy adults after oral and intravenous administration, pooled analysis[a].**

| PK parameter | Nc | Ns | Np | n | Mean $CV_N$ | Mean $CV_{LN}$ | Mean Ratio $EM/PM_{LN}$ | Mean Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | |
| *Non-phenotyped individuals* | | | | | | | | |
| CL[1] | 3 | 4 | 4 | 71 | 46 | 44 | | |
| CL[2] | 2 | 2 | 2 | 16 | 33 | 32 | | |
| AUC[3] | 1 | 4 | 4 | 61 | 77 | 68 | | |
| Cmax[3] | 2 | 5 | 5 | 77 | 49 | 45 | | |
| *Intravenous administration* | | | | | | | | |
| CL[1] | 1 | 3 | 3 | 40 | 26 | 25 | | |
| CL[2] | 1 | 4 | 4 | 35 | 60 | 76 | | |
| AUC[3] | 1 | 1 | 1 | 10 | 58 | 58 | | |
| *Phenotyped individuals* | | | | | | | | |
| *Chronic exposure* | | | | | | | | |
| CLm EM[2] | 1 | 1 | 1 | 13 | 78 | 78 | | |
| CL EM[1] | 1 | 1 | 1 | 5 | 35 | 35 | | |
| CL EM[2] | 2 | 3 | 3 | 27 | 77 | 80 | | |
| AUC EM[3] | 1 | 3 | 3 | 24 | 45 | 43 | | |
| CL SEM[2] | 1 | 1 | 1 | 4 | 13 | 13 | 3.8 | 0.36 |
| CLm PM[2] | 1 | 1 | 1 | 6 | 50 | 50 | 46 | 0.64 |
| CL PM[1] | 1 | 1 | 1 | 5 | 17 | 17 | 20 | 0.47 |
| CL PM[2] | 1 | 1 | 1 | 6 | 24 | 24 | 86 | 0.31 |
| AUC PM[3] | 1 | 2 | 2 | 10 | 20 | 20 | 3.1 | 0.46 |
| *Acute exposure* | | | | | | | | |
| Cmax EM[3] | 2 | 4 | 4 | 31 | 52 | 54 | | |
| Cmax SEM[3] | 1 | 1 | 1 | 4 | 13 | 14 | 1.9 | 0.28 |
| Cmax PM[3] | 1 | 2 | 2 | 11 | 25 | 24 | 5.3 | 0.49 |

[a]**EM** Extensive metabolisers of mephenytoin.; **SEM** Slow extensive metabolisers of mephenytoin; PM.Poor metabolisers of mephenytoin.; **Nc** Number of compounds; **Ns** Number of studies: **Np**.Number of publications; **n**, Number of subjects; **Mean $CV_N$** Mean coefficient of variation for all compounds (normal distribution); **Mean $CV_{LN}$** Mean coefficient of variation for all compounds (lognormal distribution); **Mean ratio $EM/PM_{LN}$** Mean ratio between the poor (PM and SEM) and the extensive metabolisers for all compounds (lognormal distribution); **Mean ratio $CV_{LN}$** Mean ratio of the variability between the poor (PM and SEM) and the extensive metabolisers for all compounds (lognormal distribution); [1]Individual Clearance corrected for body weight ((ml $min)^{-1}$) $Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC [(ng.h $ml^{-1}$)] and Cmax[(ng $ml^{-1}$)] corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### *I.2.3.2.2 Subgroups of the population*

The small database for phenotyped healthy Asian adults (EM and PM mostly) showed consistent increases in internal dose between the EMs and PMs for all three groups (Chinese, Korean, Japanese) compared to general healthy adult EMs, with values ranging from 1.1 (Asian EMs) to 2.6 and 12-20 (Asian PMs) for clearances/AUC and 1.5 to1.7, 5.3 to 5.8 for Cmax. Variability was generally higher in Asian EMs (1.5 to 2.7-fold), except in Korean adults, and was lower in Asian PMs compared to general healthy adult EMs. Although consistent differences were found for Asian groups, these

conclusions were based on only small numbers of subjects (4-12 per parameter) (Table 5).

Data for the elderly were based on only 10 subjects and showed an increase (1.8-fold) in internal dose associated with lower variability than in healty adults (Table 5).

The data for children were associated with an increase in internal dose and variability for the oral route (1.6-fold) but the intravenous data did not show any difference in internal dose and was associated with lower variability than in healthy adults (Table 5).

Large differences between the oral and intravenous route were observed for patients with liver disease (including EMs for the oral route) with a 9- to 15-fold and a 1.3 to1.6-fold increase in internal dose respectively compared to healthy EM adults. The variability data were inconsistent (Table 5).

The data for renal disease patients showed a lower internal dose for the intravenous clearance but a higher internal dose for Cmax (1.4-fold), both parameters were associated with lower variability than in healthy adults (Table 5).

**Table 5. Pooled analysis for interindividual differences in CYP2C19 metabolism, Effect of ethnicity, age and disease[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_N$ | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio H/S $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| $CL^2$ EM | Chinese | PO | 1 | 1 | 1 | 4 | 58 | 58 | 1.2 | 0.69 |
| $CL^2$ PM | | PO | 1 | 1 | 1 | 4 | 16 | 16 | 17 | 0.19 |
| AUC $EM^3$ | | PO | 1 | 1 | 1 | 8 | 68 | 68 | 2.2 | 1.6 |
| AUC $PM^3$ | | PO | 1 | 1 | 1 | 4 | 42 | 42 | 12 | 0.98 |
| $CL^2$ EM | Korean | PO | 1 | 1 | 1 | 8 | 33 | 31 | 2.6 | 0.87 |
| $CL^2$ PM | | PO | 1 | 1 | 1 | 8 | 15 | 15 | 20 | 0.42 |
| $CL^1$ EM | Japanese | PO | 1 | 1 | 1 | 9 | 95 | 96 | 1.5 | 2.7 |
| $CL^1$ PM | | PO | 1 | 1 | 1 | 6 | 38 | 38 | 17 | 1.1 |
| AUC $EM^3$ | | PO | 1 | 2 | 2 | 11 | 60 | 59 | 1.1 | 1.4 |
| AUC $SEM^3$ | | PO | 1 | 2 | 2 | 10 | 48 | 51 | 2.8 | 1.2 |
| AUC $PM^3$ | | PO | 1 | 2 | 2 | 12 | 27 | 28 | 12 | 0.65 |
| $CL^1$ | Children | IV | 1 | 1 | 1 | 13 | 56 | 56 | 1.1 | 0.73 |
| $AUC^3$ | | PO | 1 | 1 | 1 | 25 | 86 | 86 | 1.6 | 1.3 |
| $CL^2$ | Elderly | PO | 1 | 1 | 1 | 10 | 39 | 39 | 1.8 | 0.52 |
| $CL^1$ | Liver Disease | IV | 1 | 3 | 3 | 31 | 51 | 47 | 1.3 | 1.9 |
| $CL^2$ | | PO | 1 | 1 | 1 | 8 | 44 | 44 | 8.5 | 1.2 |
| $CL^2$ | | IV | 1 | 1 | 1 | 10 | 28 | 31 | 1.6 | 0.41 |
| $AUC^3$ | | PO | 1 | 1 | 1 | 8 | 21 | 21 | 13 | 0.32 |
| $CL^2$ | Liver Disease (EM) | PO | 1 | 1 | 1 | 18 | 240 | 240 | 15 | 3.1 |
| $CL^1$ | Renal Disease | IV | 1 | 1 | 1 | 12 | 39 | 39 | 0.6 | 0.51 |
| $Cmax^3$ | Korean EM | PO | 1 | 1 | 1 | 8 | 40 | 38 | 1.7 | 0.77 |
| | Korean PM | | 1 | 1 | 1 | 8 | 20 | 20 | 5.3 | 0.4 |
| | Japanese EM | | 1 | 2 | 2 | 15 | 74 | 64 | 1.5 | 1.3 |
| | Japanese SEM | | 1 | 1 | 1 | 6 | 59 | 59 | 2.5 | 1.2 |
| | Japanese PM | | 1 | 2 | 2 | 12 | 31 | 34 | 5.8 | 0.69 |
| | Children | | 1 | 1 | 1 | 25 | 63 | 63 | 0.6 | 0.94 |
| | Elderly | | 1 | 1 | 1 | 10 | 36 | 36 | 0.71 | 0.92 |
| | Liver Disease | | 1 | 3 | 3 | 26 | 39 | 38 | 2.6 | 0.56 |
| | Liver Disease (EM) | | 1 | 1 | 1 | 18 | 59 | 59 | 3 | 1.1 |
| | Renal Disease | | 1 | 1 | 1 | 12 | 48 | 48 | 1.4 | 0.71 |

[a]**EM**, Extensive metabolisers of mephenytoin ; **SEM**, Slow Extensive metabolisers of mephenytoin; **PM**, Poor metabolisers of mephenytoin; **Nc**,Number of compounds; **Ns**,Number of studies; **Np**,Number of publications; **n**,Number of subjects; **Mean ratio $H/S_{LN}$**, Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** , ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight ((ml $min^{-1}Kg^{-1}$); [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and Cmax corrected for dose expressed per mean body weight ($mgkg^{-1}$).

**Table 6 .CYP2C19-related uncertainty factors in subgroups of the human population for the oral route of exposure[a].**

| Subgroup | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ | CYP2C19 related uncertainty factors (lognormal distribution) 95th | 97.5th | 99th |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | | |
| Healthy NP | CL[1], CL[2], AUC[3] | 3 | 7 | 7 | 91 | 43 | | | 2.0 | 2.3 | 2.6 |
| Healthy EM | CL[1], CL[2], AUC[3] | 3 | 7 | 7 | 56 | 60 | | | 2.5 | 3.1 | 3.8 |
| Healthy SEM | CL[2] | 1 | 1 | 1 | 4 | 13 | 3.8 | 0.36 | 4.7 | 4.9 | 5.1 |
| Healthy PM | CL[1], CL[2], AUC[3] | 3 | 4 | 4 | 21 | 20 | 31 | 0.42 | 45 | 48 | 52 |
| Healthy Chinese EM | CL[2], AUC[3] | 1 | 2 | 2 | 12 | 65 | 1.9 | 1.3 | 5.0 | 6.1 | 7.6 |
| Healthy Chinese PM | CL[2], AUC[3] | 1 | 2 | 2 | 8 | 29 | 15 | 0.59 | 23 | 25 | 28 |
| Healthy Korean EM | CL[1] | 1 | 1 | 1 | 8 | 31 | 2.6 | 0.87 | 4.3 | 4.7 | 5.3 |
| Healthy Korean PM | CL[1] | 1 | 1 | 1 | 8 | 15 | 20 | 0.42 | 26 | 27 | 28 |
| Healthy Japanese EM | CL[1], AUC[3] | 1 | 3 | 3 | 20 | 76 | 1.3 | 2.0 | 4.0 | 5.1 | 6.6 |
| Healthy Japanese SEM | AUC[3] | 1 | 2 | 2 | 10 | 51 | 2.8 | 1.2 | 6.2 | 7.2 | 8.6 |
| Healthy Japanese PM | CL[1], AUC[3] | 1 | 3 | 3 | 18 | 31 | 14 | 0.80 | 23 | 25 | 29 |
| Children | CL[2] | 1 | 1 | 1 | 25 | 86 | 1.6 | 1.3 | 5.4 | 6.9 | 9.0 |
| Elderly | CL[2] | 1 | 1 | 1 | 10 | 39 | 1.8 | 0.52 | 3.4 | 3.8 | 4.3 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy NP | Cmax[3] | 2 | 5 | 5 | 77 | 45 | | | 2.0 | 2.3 | 2.7 |
| Healthy EM | | 2 | 4 | 4 | 31 | 54 | | | 2.3 | 2.7 | 3.2 |
| Healthy SEM | | 1 | 1 | 4 | 14 | 14 | 1.9 | 0.28 | 2.4 | 2.5 | 2.6 |
| Healthy PM | | 2 | 2 | 11 | 25 | 24 | 5.3 | 0.49 | 7.8 | 8.4 | 9.2 |
| Healthy Korean EM | | 1 | 1 | 1 | 8 | 38 | 1.7 | 0.77 | 3.1 | 35 | 4.0 |
| Healthy Korean PM | | 1 | 1 | 1 | 8 | 20 | 5.3 | 0.4 | 7.3 | 7.8 | 8.4 |
| Healthy Japanese EM | | 1 | 2 | 2 | 15 | 64 | 1.5 | 1.3 | 3.9 | 4.7 | 5.9 |
| Healthy Japanese SEM | | 1 | 1 | 1 | 6 | 59 | 2.5 | 1.2 | 6.1 | 7.3 | 8.9 |
| Healthy Japanese PM | | 1 | 2 | 2 | 12 | 34 | 5.8 | 0.69 | 10 | 11 | 13 |
| Children | | 1 | 1 | 1 | 25 | 63 | 0.60 | 0.94 | 1.6 | 1.9 | 2.3 |
| Elderly | | 1 | 1 | 1 | 10 | 36 | 0.71 | 0.92 | 1.3 | 1.4 | 1.6 |

[a]**EM** Extensive metabolisers of Mephenytoin; **PM** Poor metabolisers of debrisoquin; **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Mean coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and C max corrected for dose expressed per mean body weight ($mgkg^{-1}$).

Data for patients with liver disease showed an increase in internal dose for both clearances (1.3-fold and 6-fold) and higher variability than that in healthy adults with 26/37% and 60% respectively (1 compound, 71 and 10 subjects). Similarly, data for patients with renal disease showed a 2-fold increase for both internal dose and variability (1 compound, 13 subjects) (Table 7).

### *I.2.4.3 CYP2E1 related uncertainty factors*

CYP2E1-related uncertainty factors were low for both healthy adults and elderly (trimethadione only, 22 subjects) with values up to 1.8 and 2.3 respectively to cover up to the 99$^{th}$ centile of each subgroup. Patients with liver disease and patients with renal disease would need defaults of 3.9, 4.5, 5.3 and 5.4, 6.1 and 7.0 respectively (data not shown, trimethadione only).

**Table 7. Pooled analysis for interindividual differences in CYP2E1 metabolism, Healthy adults, elderly and patients with liver and patients with renal disease[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_N$ | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio H/S $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| CLm[2] | Healthy | PO | 1 | 5 | 3 | 91 | 33 | 32 | | |
| CL[1] | | PO | 2 | 14 | 10 | 182 | 23 | 23 | | |
| CL[2] | | PO | 2 | 6 | 6 | 81 | 33 | 29 | | |
| CL[1] | Elderly | PO | 1 | 2 | 1 | 22 | 25 | 26 | 1.3 | 1.4 |
| CL[1] | Liver Disease | PO | 1 | 1 | 6 | 71 | 26 | 37 | 1.3 | 2.0 |
| CL[2] | | PO | 1 | 1 | 1 | 10 | 60 | 58 | 6.1 | 2.3 |
| CL[1] | Renal Disease | PO | 1 | 1 | 1 | 13 | 39 | 39 | 2.9 | 2.1 |
| Cmax[3] | Heathy | PO | 2 | 9 | 6 | 87 | 25 | 16 | | |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **Mean ratio $H/S_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight ((ml $min^{-1}Kg^{-1}$); [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and Cmax corrected for dose expressed per mean body weight ($mgkg^{-1}$).

## I.2.5 Alcohol dehydrogenase (ADH)

### *I.2.5.1 Metabolism of ethanol in humans*

Ethanol was the only substrate available for Alcohol dehydrogenase (ADH) and its elimination is widely recognised to be principally catalysed by the latter enzyme (>80-90%)(Lands, 1998). CYP2E1 and CYP1A2 have also been shown to contribute to a minor extent (5%) (Lands, 1998).

### *I.2.5.3 Human variability in kinetics*

The coefficients of variation for metabolism via ADH were consistent between both routes and the different kinetic parameters reflecting chronic and acute exposure with values ranging between 20 and 30% for both distributions (Table 8).

Interindividual differences for oriental individuals were lower than those in healthy adults and ranged between 11 and 21%. Differences in internal dose were not significant with only a slight decrease for individuals with the ADH- phenotyped (1.2-fold). The elderly data did not show any increase in internal dose for either the AUC or Cmax. However, a 2-fold greater variability was observed for both parameters compared to healthy adults (Table 8).

**Table 8. Interindividual differences ethanol handled via alcohol dehydrogenase: Comparison between healthy adults, healthy orientals and elderly after oral and intravenous administration [a].**

| Parameter (Route) | Ns | Np | n | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| ***Healthy adults*** | | | | | | | | | |
| *Oral administration* | | | | | | | | | |
| ER[1] | 4 | 4 | 145 | 20 | 1.8 | 1.2 | 18 | | |
| AUC[4] | 11 | 8 | 136 | 29 | 3.2 | 1.3 | 30 | | |
| AUC[4] (Sigma ADH) | 1 | 1 | 10 | 22 | 0.9 | 1.3 | 23 | | |
| Cmax[d] | 9 | 7 | 112 | 23 | 1.3 | 1.2 | 21 | | |
| *Intravenous administration* | | | | | | | | | |
| CL[2] | 2 | 1 | 12 | 31 | 273 | 1.3 | 29 | | |
| AUC[c] | 1 | 1 | 24 | 25 | 4.8 | 1.3 | 25 | | |
| ***Orientals (Oral administration)*** | | | | | | | | | |
| ER[1] | 5 | 2 | 154 | 21 | 2.1 | 1.2 | 21 | 0.87 | 1.2 |
| ER[1] (ADH+) | 4 | 1 | 114 | 11 | 1.5 | 1.1 | 14 | 1.2 | 0.74 |
| ER[1] (ADH-) | 4 | 1 | 166 | 14 | 1.7 | 1.1 | 11 | 1.2 | 0.62 |
| AUC[3] (Sigma ADH) | 1 | 1 | 10 | 12 | 0.9 | 1.1 | 11 | 1.1 | 0.50 |
| ***Elderly (Oral administration)*** | | | | | | | | | |
| AUC[3] | 2 | 1 | 29 | 75 | 2.7 | 1.9 | 73 | 0.82 | 2.4 |
| Cmax[3] | 2 | 1 | 29 | 43 | 1.5 | 1.5 | 46 | 0.88 | 2.1 |

[a] **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$CV_N$** coefficient of variation (normal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$**, Variability ratio between healthy adults and subgroup (lognormal distribution); **Sigma ADH** Sigma phenotype for the ADH gene (slow metabolism); **ADH+** fast phenotype for ADH; **ADH-** slow phenotype for ADH, **ER[1]** Elimination rate in $mgmin^{-1}kg^{-1}$; **CL[2]** Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); [3]AUC/dose and Cmax/dose with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### *I.2.5.4 ADH-related uncertainty factors*

ADH-related default uncertainty factors were lower than the 3.16 kinetic default factor for healthy adults and oriental healthy adults with maximum values of 1.8 ($99^{th}$ centile). However the elderly would require values up to 4.4 ($99^{th}$ centile)(Table not shown).

## I.2.6 Hydrolysis

### *I.2.6.1 Metabolism data for the probe substrates*

Substrates that were well absorbed from the GI tract and for which hydrolysis is a major route of metabolism were aspirin, fosinopril and flumazenil. Cocaine, etodimate, esmolol, and flestolol were also totally hydrolysed, but are only partially absorbed from the GI tract, only the intravenous data have been analysed. The metabolism data for these compounds are summarised in Table 9.

**Table 9. Metabolism data for probe substrates metabolised via hydrolysis in healthy adult volunteers** [a]

| Drug | Route | % metabolism via hydrolysis |
|---|---|---|
| Aspirin[1] | PO | 90-100 |
| Cocaine[2] | IV | >60 |
| Esmolol[3] | IV | 80 |
| Etodimate[4] | IV | 75-90 |
| Flestolol[5] | IV | >80 |
| Flumazenil[6] | PO | 80% |
| Fozinopril[7] | PO | 75% |

[a] **n**- number of subjects; **PO** - oral administration; **IV** –intravenous administration; *Expressed as the percentage of the dose recovered as hydrolysis dependent metabolites in the urine.

[1]Montgomery *et al.*, 1986; [2]Stewart *et al.*, 1979; [3]Achari *et al.*, 1986; [4]Ghonheim *et al.*, 1979; [5]Achari *et al.*, 1987 [6]Klotz and Kanto, 1988; [7]Singhvi et al., 1988.

### *I.2.6.2 Human variability in kinetics*

Variability for metabolism via hydrolysis ranged between 25% and 30% overall for both the oral and intravenous routes, kinetic parameters and normal/lognormal assumptions (Table 10). The intravenous data showed similar variability for both systemic clearances although the variability in metabolic clearance was slightly higher (this was only based on 1 compound and 11 subjects).

The comparison between healthy adults and Chinese from a single intravenous study describing the kinetics of fozinopril (Hu et *al.*, 1997) showed a 2-fold lower metabolic clearance and total clearance associated with an increase in variability (Table 10).

No major differences were observed between children, the elderly and healthy adults with a slightly higher clearance and variability for both subgroups (Table 10).

Patients with liver disease showed 1.5 to 2-fold lower intravenous clearances compared to healthy adults, but the variability data were inconsistent across the different parameters. A similar observation was made for the intravenous clearance for patients with renal disease but the variability was similar to that in heathy adults (Table 10).

**Table 10. Interindividual differences for metabolism via hydrolysis (oral and intravenous route) in subgroups of the population: Comparison between healthy adults, Asian healthy adults, children, elderly, patients with liver disease and patients with renal disease, pooled analysis[a].**

| PK parameter/Route | Nc | Ns | Np | n | Mean $CV_N$ | Mean $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| *Healthy* | | | | | | | | |
| $CL^1$(PO) | 1 | 2 | 1 | 15 | 19 | 19 | | |
| $AUC^3$(PO) | 3 | 20 | 11 | 151 | 31 | 29 | | |
| $CLm^1$(IV) | 1 | 1 | 1 | 11 | 33 | 33 | | |
| $CL^1$(IV) | 7 | 18 | 18 | 123 | 28 | 24 | | |
| $CL^2$(IV) | 3 | 10 | 9 | 71 | 29 | 26 | | |
| *Chinese* | | | | | | | | |
| $CLm^1$(IV) | 1 | 1 | 1 | 12 | 54 | 54 | 1.8 | 1.3 |
| $CL^1$(IV) | 1 | 1 | 1 | 12 | 43 | 43 | 1.9 | 2.0 |
| *Children* | | | | | | | | |
| $CL^1$ (IV) | 3 | 3 | 3 | 43 | 45 | 40 | 0.80 | 1.29 |
| *Elderly* | | | | | | | | |
| $AUC^3$ (PO) | 2 | 4 | 3 | 31 | .42 | 35 | 0.66 | 1.20 |
| *Liver disease* | | | | | | | | |
| $CL^1$ (IV) | 2 | 2 | 2 | 21 | 30 | 30 | 1.3 | 0.82 |
| $CL^2$ (IV) | 1 | 2 | 2 | 11 | 56 | 48 | 2.2 | 2.6 |
| $AUC^3$ (PO) | 1 | 1 | 1 | 4 | 42 | 42 | 1.1 | 1.9 |
| *Renal disease* | | | | | | | | |
| $CL^2$ (IV) | 1 | 3 | 1 | 13 | 30 | 30 | 1.7 | 0.82 |
| *Acute exposure* | | | | | | | | |
| Cmax [3] Healthy | 3 | 24 | 14 | 179 | 32 | 30 | | |
| Cmax [3] Elderly | 2 | 4 | 3 | 31 | 37 | 40 | 44 | 1.1 |
| Cmax [3] Liver disease | 2 | 2 | 2 | 12 | 46 | 43 | 76 | 1.2 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$, Variability ratio between healthy adults and subgroup (lognormal distribution); $\mathbf{CL^1}$: Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); $\mathbf{CL^2}$: Total clearance adjusted to body weight ($mlmin^{-1}$);[3]**AUC/dose** and **Cmax/dose** with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### *I.2.6.3 Hydrolysis-related uncertainty factors*

The database describing oral kinetics in healthy adults, children and elderly provided similar uncertainty factors for hydrolysis which were below 2 to cover up to 99% of these populations (Table 11).

**Table 11 . Hydrolysis-related uncertainty factors in subgroups of the human population for chronic and acute oral exposure[a].**

| Subgroup (Route) | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ | Hydrolysis-related uncertainty factors (Lognormal distribution) 95th | 97.5th | 99th |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | | |
| Healthy (PO) | CL[1], AUC[3] | 4 | 22 | 12 | 166 | 28 | | | 1.6 | 1.7 | 1.9 |
| Healthy (IV) | CL[1], CL[2] | 7 | 28 | 27 | 194 | 25 | | | 1.5 | 1.6 | 1.8 |
| Chinese (IV) | CL[1] | 1 | 1 | 1 | 12 | 43 | 2.0 | 2.0 | 3.8 | 4.3 | 5.0 |
| Children (IV) | CL[1] | 3 | 3 | 3 | 43 | 40 | 0.80 | 1.3 | 1.5 | 1.7 | 2.0 |
| Elderly (PO) | AUC[3] | 2 | 4 | 3 | 31 | 35 | 0.66 | 1.2 | 1.2 | 1.3 | 1.5 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy (PO) | Cmax[3] | 3 | 24 | 14 | 179 | 30 | | | 1.6 | 1.8 | 2.0 |
| Elderly (PO) | | 2 | 4 | 3 | 31 | 40 | 0.44 | 1.1 | <1 | <1 | <1 |

[a]**Nc**, Number of compounds; **Ns**, Number of studies; **Np**, Number of publications; **n**, Number of subjects; **$CV_{LN}$**, mean coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$**, Mean ratio between healthy adults and subgroup (lognormal distribution); **Mean ratio $CV_{LN}$**, Mean ratio of the variability between healthy adults and subgroup (lognormal distribution); [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and Cmax corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### *II.2.1.3 Human variability in kinetics*

#### *II.2.1.3.1 Healthy adults*

Data describing variability in oral kinetics for N-acetyltransferase substrates were only available for phenotyped healthy adults (FAs, IAs and SAs)(Table 12). Interindividual differences for FAs were consistent between the different parameters with 29/35% for the metabolic clearances adjusted to body weight (1 compound, 33 subjects), 32/31% for the equivalent total clearance (2 compounds, 142 subjects), 38% for the clearance in $mlmin^{-1}$(2 compounds, 33 subjects). Data describing the metabolic clearance ($mlmin^{-1}$) and the AUC were slightly less variable at21% and 26% respectively (1 compound 7 and 16 subjects). Variability in Cmax was higher at 37% (data only based on 7 subjects)

No significant differences in internal dose or variability were observed between FAs and IAs (21 subjects, 1 compound). SAs showed an overall 3-fold higher internal dose based on both clearance and AUCs. Metabolic clearance data were similar with a 4-fold decrease for the best estimate (1 compound, 73 subjects). The variability for SAs was either lower than that for FAs or similar, ranging from 11% to 41% for the lognormal data.

#### *II.2.1.3.2 Subgroups of the population*

The very small dataset for FA and IA chinese healthy adults (5 and 4 subjects) does not allow a conclusion on interethnic differences but no real differences were demonstrated and variability was very low for both Chinese groups. The data for Japanese healthy adults demonstrated a 2- and 3-fold lower total clearance for both FAs (33 subjects) and SAs (5 subjects) respectively, together with similar variability to FA healthy adults (Table 12).

The data for FA children were comparable to FA healthy adults for both clearance and variability whereas the SA clearance was about one half than that in FA adults and associated with a lower variability (data based on 1 compound and 25 subjects) for both subgroups (Table 12).

In the elderly, data for the fast phenotype showed a 1.1- and 1.3-fold decrease in metabolic and total clearance for FA (8 and 56 subjects) associated with a higher variability compared to FA healthy adults. Both metabolic and total clearances (9 and 105 subjects) in SAs were 5-and 4-fold lower whereas the variability was comparable to that in FA healthy adults (Table 12).

### *II.2.1.4 NAT-related uncertainty factors*

Uncertainty factors for compounds handled by the polymorphic N-acetyltransferase pathway were calculated for each subgroup of the population. Most SA subgroups of the population (healthy adults, Japanese, elderly) would constitute potentially susceptible subgroups and values of 5, 7 and 8 would cover 99% of each subpopulation (Table 13).

**Table 12. Interindividual differences for the N-acetyltransferase pathway of metabolism in phenotyped healthy adults, Asian healthy adults, children and elderly (fast, intermediate and slow acetylators), pooled analysis[a].**

| PK parameter | Nc | Ns | Np | n | Mean $CV_N$ | Mean $CV_{LN}$ | Mean Ratio $FA/SA_{LN}$ | Mean Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| ***Chronic exposure*** | | | | | | | | |
| *Healthy adults* | | | | | | | | |
| $CLm^1$ FA | 1 | 5 | 4 | 33 | 29 | 35 | | |
| $CLm^2$FA | 1 | 1 | 1 | 7 | 21 | 21 | | |
| $CL^1$FA | 2 | 9 | 6 | 142 | 32 | 31 | | |
| $CL^2$FA | 2 | 4 | 3 | 33 | 38 | 38 | | |
| $AUC^3$FA | 1 | 2 | 1 | 16 | 26 | 26 | | |
| $CLm^1$ IA | 1 | 3 | 2 | 21 | 35 | 34 | 0.78 | 0.97 |
| $CL^1$IA | 1 | 3 | 3 | 21 | 35 | 32 | 1.1 | 1.4 |
| $CLm^1$ SA | 1 | 1 | 1 | 7 | 15 | 15 | 1.6 | 0.7 |
| $CLm^2$ SA | 1 | 6 | 4 | 73 | 60 | 41 | 3.9 | 1.2 |
| $CL^1$ SA | 2 | 10 | 6 | 243 | 31 | 30 | 2.9 | 1.1 |
| $CL^2$ SA | 2 | 4 | 3 | 197 | 15 | 11 | 3.2 | 0.28 |
| $AUC^3$ SA | 1 | 2 | 1 | 32 | 32 | 33 | 3.6 | 1.3 |
| *Asian Heathy adults* | | | | | | | | |
| $CLm^2$ FA | 1 | 1 | 1 | 5 | 12 | 12 | 0.5 | 0.31 |
| $CL^2$ FA C | 1 | 1 | 1 | 5 | 12 | 12 | 1.0 | 0.30 |
| $CLm^2$ IA | 1 | 1 | 1 | 4 | 6.8 | 6.8 | 0.8 | 0.20 |
| $CL^2$ IA C | 1 | 1 | 1 | 4 | 10 | 10 | 1.6 | 0.25 |
| $CLm^2$ FA | 1 | 2 | 1 | 33 | 34 | 34 | 1.8 | 0.94 |
| $CL^2$ SA J | 1 | 1 | 1 | 5 | 35 | 39 | 2.8 | 1.1 |
| *Children* | | | | | | | | |
| $CL^1$ FA | 1 | 2 | 2 | 46 | 20 | 28 | 0.74 | 0.80 |
| $CL^1$ SA | 1 | 2 | 2 | 44 | 10 | 11 | 1.6 | 0.32 |
| *Elderly* | | | | | | | | |
| $CLm^1$ FA | 1 | 1 | 1 | 8 | 33 | 33 | 1.1 | 0.94 |
| $CLm^1$ SA | 1 | 1 | 1 | 9 | 32 | 32 | 5.4 | 0.89 |
| $CL^1$ FA | 2 | 4 | 2 | 56 | 38 | 37 | 1.3 | 1.3 |
| $CL^1$ SA | 2 | 4 | 3 | 105 | 30 | 29 | 3.9 | 1.1 |
| *Acute exposure* | | | | | | | | |
| Cmax $^3$FA | 1 | 1 | 1 | 7 | 37 | 37 | | |
| Cmax $^3$SA | 1 | 1 | 1 | 7 | 17 | 17 | 1.0 | 0.47 |

[a]**FA**, Fast acetylators.; **IA,** Intermediate Acetylators; **SA,** Slow Acetylators; **C** Chinese; **J** Japanese; **Nc**, Number of compounds; **Ns**,Number of studies; **Np**,Number of publications; **n**, Number of subjects; **Mean $CV_N$**, Mean coefficient of variation for all compounds (normal distribution); **Mean $CV_{LN}$**, Mean coefficient of variation for all compounds (lognormal distribution); **Mean ratio $FA/SA_{LN}$**, Mean ratio between the slow (IA and SA) and the Fast acetylators for all compounds (lognormal distribution); **Mean ratio $CV_{LN}$**, Mean ratio of the variability between the slow (IA and SA) and the Fast acetylators for all compounds (lognormal distribution); [1]Individual Clearance corrected for body weight $((ml\ min)^{-1})\ Kg^{-1}$; [2]Clearance not corrected for body weight $(ml\ min^{-1})$; [3]Mean AUC $[(ng.h\ ml^{-1})]$ and Cmax$[(ng\ ml^{-1})]$ corrected for dose expressed per mean body weight $(mgkg^{-1})$.

**Table 13. N-acetyltransferase-related uncertainty factors in subgroups of the human population for chronic and acute oral exposure[a].**

| Subgroup (Route) | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $FA/SA_{LN}$ | Ratio $CV_{LN}$ | N-acetyltransferase related uncertainty factors (Lognormal distribution) 95th | 97.5th | 99th |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | | |
| Healthy FA | $CL^1$, $CL^2$, $AUC^3$ | 2 | 15 | 10 | 191 | 32 | | | 1.7 | 1.8 | 2.1 |
| Healthy IA | $CL^1$ | 1 | 3 | 3 | 21 | 32 | 1.1 | 1.4 | 1.8 | 2.0 | 2.3 |
| Healthy SA | $CL^1$, $CL^2$, $AUC^3$ | 2 | 16 | 10 | 472 | 22 | 3.1 | 0.77 | 4.4 | 4.8 | 5.2 |
| Healthy Chinese FA | $CL^2$ | 1 | 1 | 1 | 5 | 12 | 1.0 | 0.30 | 1.2 | 1.3 | 1.3 |
| Healthy Chinese IA | $CL^2$ | 1 | 1 | 1 | 4 | 10 | 1.6 | 0.25 | 1.9 | 1.9 | 2.0 |
| Healthy Japanese FA | $CL^2$ | 1 | 1 | 1 | 33 | 34 | 1.8 | 0.94 | 3.1 | 3.4 | 3.9 |
| Healthy Japanese SA | $CL^2$ | 1 | 1 | 1 | 5 | 39 | 2.8 | 1.1 | 5.2 | 5.9 | 6.7 |
| Children FA | $CL^1$ | 1 | 2 | 2 | 44 | 28 | 0.74 | 0.80 | 1.2 | 1.3 | 1.4 |
| Children SA | $CL^1$ | 1 | 2 | 2 | 46 | 11 | 1.6 | 0.32 | 1.9 | 2.0 | 2.1 |
| Elderly FA | $CL^1$ | 2 | 4 | 2 | 56 | 37 | 1.3 | 1.3 | 2.3 | 2.5 | 2.9 |
| Eldelry SA | $CL^1$ | 2 | 4 | 3 | 105 | 29 | 3.9 | 1.1 | 6.3 | 6.9 | 7.6 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy FA | $Cmax^3$ | 1 | 1 | 1 | 7 | 37 | | | 1.8 | 2.0 | 2.3 |
| Healthy SA | | 1 | 1 | 1 | 7 | 17 | 1.0 | 0.47 | 1.3 | 1.4 | 1.5 |

[a]**FA** Fast Acetylators; **IA** Intermediate acetylators; **SA** Slow acetylators; **Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Mean coefficient of variation (lognormal distribution); **Mean ratio $FA/SA_{LN}$** Mean ratio between the slow (IA and SA) and the Fast acetylators for all compounds (lognormal distribution); **Mean ratio $CV_{LN}$** Mean ratio of the variability between the slow (IA and SA) and the Fast acetylators for all compounds (lognormal distribution); [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance not corrected for body weight (ml $min^{-1}$); [3]Mean AUC and C max corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### II.2.2 Glycine Conjugation

***II.2.2.1 Metabolism data for the probe substrates and human variability in kinetics***

Salicylic acid and benzoate were selected probe substrates for glycine conjugation with more than 84% and 83-90% excreted as salicyluric acid and hippuric acid respectively after an oral dose in healthy adults (Montgomery *et al.,* 1986; Kubota and Ishizaki, 1991).

Interindividual differences for the glycine pathway ranged between 15% and 24% for both routes of exposure with an overall mean of 21% for the oral route (205 subjects), variability for Cmax was lower at 16% (262 subjects). No mean differences were observed between healthy adults, children (20 subjects), elderly adults (30 subjects) or patients with liver disease. However, variability was higher for patients with liver disease, particularly for the intravenous data (30 subjects). Neonates showed a dramatic increase in internal dose (19-fold, data only based on 1 compound and 10 subjects) (Table 14).

### II.2.3 Sulphate Conjugation

***II.2.3.1 Metabolism data for the probe substrates and human variability in kinetics***

Prenalterol was selected as a probe substrate for sulphation since more than 76% of an oral dose was recovered in the urine of healthy adult volunteers (Hoffmann *et al.,* 1982). No other probe substrates were fund for this route of metabolism. However metabolic clearances via sulphation were available for diflunisal, paracetamol and salbutamol.

Data for the sulphation pathway in healthy adults showed that variability was below 30% for the oral route (26-28%, 97 subjects) and was slightly higher for the intravenous route (36%). However the number of subjects was much lower (18) for the latter route. Variability in the elderly was lower than that in healthy adults for both routes of exposure and no differences in internal dose were shown (Table 14).

Pathway related defaults for Glycine and Sulphate conjugation in healthy adults were similar with respective values of 1.4, 1.5, 1.6 (CV=21%) and 1.5, 1.7 and 1.8 (CV= 26%) to cover 95, 97.5 and 99% of the population. Neonates were identified as a potentially sensitive subgroup for the Glycine pathway with defaults of 25, 26 and 28 to cover the former percentiles (data based only on 10 subjects).

**Table 14. Interindividual differences for metabolism via Glycine conjugation and Suphate conjugation (oral and intravenous route) in subgroups of the population, pooled analysis[a].**

| PK parameter/Route | Nc | Ns | Np | n | Mean $CV_N$ | Mean $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|
| ***Glycine conjugation*** | | | | | | | | |
| *Healthy* | | | | | | | | |
| $CL^1$(PO) | 1 | 2 | 1 | 44 | 21 | 21 | | |
| $CL^1$(IV) | 1 | 4 | 1 | 25 | 25 | 24 | | |
| $CL^2$PO) | 1 | 3 | 2 | 24 | 23 | 21 | | |
| $AUC^3$ (PO) | 2 | 16 | 16 | 137 | 24 | 21 | | |
| $AUC^3$(IV) | 1 | 1 | 1 | 7 | 15 | 15 | | |
| Cmax $^3$ (PO) | 2 | 22 | 16 | 262 | 17 | 16 | | |
| *Neonates* | | | | | | | | |
| $AUC^3$(IV) | 1 | 2 | 1 | 10 | 16 | 16 | 19 | 1.1 |
| *Children* | | | | | | | | |
| $CL^1$(PO) | 1 | 2 | 1 | 20 | 28 | 27 | 0.98 | 1.3 |
| Cmax $^3$ (PO) | 1 | 2 | 1 | 20 | 35 | 33 | 1.40 | 2.1 |
| *Elderly* | | | | | | | | |
| $CL^1$(IV) | 1 | 2 | 1 | 21 | 24 | 23 | 1.1 | 0.99 |
| $AUC^3$ (PO) | 1 | 3 | 2 | 19 | 26 | 30 | 1.0 | 1.1 |
| Cmax $^3$ (PO) | 1 | 5 | 4 | 40 | 18 | 19 | 0.85 | 1.2 |
| *Liver Disease* | | | | | | | | |
| $AUC^3$ (PO) | 1 | 1 | 1 | 8 | 43 | 43 | 1.1 | 1.5 |
| $AUC^3$ (IV | 1 | 2 | 1 | 30 | 40 | 37 | 0.48 | 2.5 |
| Cmax $^3$ (PO) | 1 | 1 | 1 | 8 | 36 | 36 | 0.94 | 2.3 |
| ***Sulphate conjugation*** | | | | | | | | |
| *Healthy* | | | | | | | | |
| $CLm^1$ (PO) | 2 | 9 | 7 | 65 | 30 | 26 | | |
| $CLm^1$ (IV) | 1 | 1 | 1 | 10 | 36 | 36 | | |
| $CLm^2$ (PO) | 1 | 3 | 3 | 26 | 28 | 27 | | |
| $CLm^2$ (IV) | 1 | 1 | 1 | 8 | 36 | 36 | | |
| $AUC^3$ (PO) | 1 | 1 | 1 | 6 | 28 | 28 | | |
| Cmax $^3$ (PO) | 1 | 1 | 1 | 6 | 33 | 33 | | |
| *Elderly* | | | | | | | | |
| $CLm^1$(PO) | 1 | 1 | 1 | 8 | 16 | 16 | 1.1 | 0.96 |
| $CLm^1$(IV) | 1 | 3 | 2 | 24 | 23 | 23 | 1.1 | 0.62 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$CV_N$** coefficient of variation (normal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$**, Variability ratio between healthy adults and subgroup (lognormal distribution); **$CL^1$**: Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **$CL^2$**: Total clearance adjusted to body weight ($mlmin^{-1}$);[3]AUC/dose and Cmax/dose with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

# III.Renal excretion

## III.1 Differences between studies

Differences between studies for renal excretion pathway are presented in Appendix 1 for both routes of exposure.

## III.2 Interindividual differences

### III.2.1 Metabolism data

Probe substrates were selected on the basis that renal excretion is the major pathway of primary metabolism, i.e. >60% is excreted as the parent coumpound. Probe substrates which were totally absorbed from the intestine were: Amoxicillin, Ampicillin, Ciprofloxacin, Fluconazole, Lomefoxacin and Ofloxacin. Intravenous data were analysed for Acyclovir, Cefazolin, Cefpirome, Gentamycin, Piperacillin and Trobamycin since oral absorption was variable (<90%). Metabolism data after oral or intravenous administration to healthy adult volunteers are summarised in Table 15 together with the mechanism of renal excretion by which the compounds are handled (glomerular filtration, tubular secretion or a combination of both).

### III.2.2 Human variability in kinetics

#### *III.2.2.1 Healthy adults*

Table 16 presents an overall analysis for the healthy adults for which parameter-specific variability has been pooled for all the substrates. Values for variability in kinetics for all parameters and chronic markers of exposure (renal clearances, clearances and AUC) were between 20% and 25% for the oral route (average 21%) and 23-34% (average 28%) for the intravenous route. The Cmax analysis was similar with values of 27/30% (normal/lognormal).

**Table 15. Metabolism data for the renal excretion probe substrates in healthy adult volunteers [a]**

| Drug | n | Dose (mg) | Route | % Drug in urine | Renal Clearance |
|---|---|---|---|---|---|
| Acyclovir | 6[1] | 500 | IV | 74±13 | GF, TS |
| Amoxicillin | 8[2] | 1000 | PO | 65±11 | GF, TS |
| Ampicillin | 6[3] | 1500 | IV | 80±7.7 | GF, TS |
| Cefazolin | 10[4] | 1000 | IV | 80-95 | GF (TS) |
| Cefpirome | 10[5] | 1000 | IV | 78-100 | GF |
| Ciprofloxacin | 11[6] | 100 | IV | 80±11 | TS |
| Fluconazole | 18[7] | 100-500 | IV/PO | 89±9 | GF |
| Gentamicin | 6[8] | 100 | IV | 82±10 | GF |
| Lomefloxacin | 6[9] | 400 | PO | 76±3 | GF, TS |
| Ofloxacin | 12[10] | 200 | PO | 88±11 | GF, TS |
| Piperacillin | 8[11] | 3000 | IV | 74±9 | TS (GF) |
| Trobamycin | 6[12] | 2.5 | IV | 94±6 | GF |

[a]**n** number of subjects; **PO** oral administration; **IV** intravenous administration,
GF: Glomerular Filtration, TS: Tubular Secretion.

[1]Bridgen *et al.*,1981; [2]Westphal *et al.*,1990; [3]Sjovell *et al.*,1985; [4]Scheld *et al.*,1981; [5]Malerczyk *et al.*,1987; [6]Wise *et al.*,1984; [7]Ripa *et al.*,1993; [8]Hannedouche *et al.*,1986; [9]Stone *et al.*,1988; [10]Silvain *et al.*,1989; [11]Johnson *et al.*,1992; [12]Davis *et al.*,1988.

**Table 16. Interindividual differences for renal excretion in healthy adults, overall pooled analysis[a].**

| PK parameter | Nc | Ns | Np | n | Mean $CV_N$ | Mean GSD | Mean $CV_{LN}$ |
|---|---|---|---|---|---|---|---|
| *Oral Administration* | | | | | | | |
| CLr[1] | 3 | 3 | 3 | 26 | 25 | 1.3 | 23 |
| CLr[3] | 5 | 12 | 11 | 115 | 25 | 1.3 | 25 |
| CL[1] | 3 | 6 | 6 | 48 | 22 | 1.3 | 22 |
| CL[2] | 2 | 4 | 4 | 35 | 22 | 1.2 | 21 |
| CL[3] | 4 | 15 | 10 | 130 | 28 | 1.3 | 24 |
| AUC[4] | 6 | 23 | 19 | 231 | 21 | 1.2 | 20 |
| Cmax[5] | 6 | 44 | 35 | 401 | 30 | 1.3 | 27 |
| *Intravenous Administration* | | | | | | | |
| CLr[1] | 3 | 3 | 3 | 25 | 27 | 1.3 | 26 |
| CLr[2] | 4 | 7 | 6 | 53 | 27 | 1.3 | 23 |
| CLr[3] | 7 | 24 | 22 | 226 | 25 | 1.3 | 27 |
| CL[1] | 9 | 21 | 18 | 367 | 33 | 1.4 | 34 |
| CL[2] | 5 | 11 | 7 | 192 | 29 | 1.4 | 34 |
| CL[3] | 9 | 41 | 39 | 546 | 25 | 1.3 | 23 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **Mean $CV_N$** Mean coefficient of variation for all compounds (normal distribution); **Mean $CV_{LN}$** Mean coefficient of variation for all compounds (lognormal distribution); **CLr** Renal clearance; **CL** Clearance; [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}.1.73m^{-2}$; [3]Clearance expressed in $ml.min^{-1}$; [4]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [5]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$.

### *III.2.2.2 Subgroups of the population*

#### *III.2.2.2.1 Interethnic differences*

The data for interethnic differences were limited (Table 17) and did not show any major consistent differences in internal dose or variability between Asian (Japanese and Indian subjects) and general healthy adults, although the numbers of subjects studied were limited (n<20) (Table 17).

#### *III.2.2.2.2 Neonates, Infants and children*

Renal clearances and total clearances ($mlmin^{-1}kg^{-1}$) for the intravenous route were consistently lower in neonates compared to healthy adults with a 1.5- and 1.7-fold decrease respectively (2 compounds, 41 subjects and 5 compounds, 451 subjects). The variability in renal clearances was higher in neonates (1.6-fold) but similar to healthy adults for both clearances. The Cmax data showed a 1.4-fold decrease in both internal dose and variability compared to healthy adults, however the number of subjects (7) was limited. A single kinetic study for trobamycin in Japanese neonates showed that their clearance rate was 2-fold higher than that in healthy adults and variability was 1.4-fold lower (19 subjects) (Table 17).

The data for the infants were also consistent between the parameters with a 1.3-fold increase in total clearances ($mlmin^{-1}kg^{-1}$ and $mlmin^{-1}1.73m^{-2}$) and a slight (1.2-fold) decrease in variability compared to healthy adults (3 compounds, 29 subjects and 1 compound, 4 subjects). The renal clearance data in this subgroup were similar to those in healthy adults but was associated with greater variability (1.4-fold) (2 compounds, 19 subjects) (Table 17).

The data for children showed a 1.3-1.7 fold decrease in internal dose for all parameters (renal clearance, total clearances and AUC) associated with higher variability than that in healthy adults (1.5-2-fold) except for renal clearance and clearance ($mlmin^{-1}kg^{-1}$) for which it was similar. The Cmax analysis revealed a decrease in internal dose (1.8-fold) and an increase in variability (3-fold, 1 compound, 9 subjects) (Table 17).

#### *III.2.2.2.3 The elderly*

The kinetic data for the elderly (Table 17) were reliable and revealed lower clearances (for both routes of exposure) and higher AUC/Cmax values as compared with the equivalent data in healthy adults. For the oral route of exposure, the increase in internal dose ranged from 1.5-fold to 2.2 fold in the same way as the intravenous data (1.1-2.3-fold). The variability data were less consistent. However, the largest database for both routes of exposure demonstrated a similar variability in the elderly to that in healthy adults (oral, 3 compounds, 64 subjects; intravenous, 4 compounds, 113 subjects).

*III.2.2.2.4 Patients with liver disease*

Patients with liver disease (Table 18) demonstrated lower clearances for all the kinetic parameters and compounds describing the renal excretion pathway. The decrease in internal dose compared to healthy adults ranged from 1.2 to 2.5-fold for the oral route and 1.5-1.6-fold for the intravenous route. The largest database for the oral route described a 1.6-fold increase in internal dose (AUC, 2 compounds, 20 subjects) matching the intravenous data (1.5-fold, clearance adjusted to body weight, 3 compounds, 48 subjects). The variability was generally greater than that in healthy adults with an overall 1.5-fold increase for both routes of exposure.

**Table 17. Pooled analysis for inter-individual differences in renal excretion, effect of ethnicity and age[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio H/S $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL[3] | Asian | PO | 1 | 1 | 1 | 11 | 25 | 0.65 | 1.7 |
| CL[3] | Indian | PO | 1 | 1 | 1 | 12 | 11 | 0.64 | 0.50 |
| AUC[4] | Asian | PO | 2 | 2 | 2 | 19 | 21 | 0.91 | 1.4 |
| CLr[1] | Elderly | PO | 1 | 2 | 2 | 30 | 62 | 1.8 | 2.9 |
| CLr[2] | | IV | 1 | 1 | 1 | 8 | 9 | 1.5 | 0.44 |
| CLr[3] | | PO | 1 | 1 | 1 | 12 | 36 | 2.0 | 0.87 |
| CLr[3] | | IV | 1 | 1 | 1 | 12 | 40 | 2.3 | 1.4 |
| CL[1] | | PO | 1 | 1 | 1 | 20 | 56 | 1.5 | 2.9 |
| CL[1] | | IV | 5 | 6 | 6 | 166 | 42 | 1.7 | 1.1 |
| CL[1]* | | IV | 1 | 2 | 1 | 16 | 25 | 1.1 | 0.83 |
| CL[2] | | IV | 3 | 4 | 4 | 52 | 21 | 1.1 | 0.80 |
| CL[3] | | PO | 3 | 5 | 5 | 64 | 27 | 2.2 | 1.1 |
| CL[3] | | IV | 4 | 6 | 6 | 113 | 33 | 1.3 | 1.1 |
| CLr[1] | Neonates | IV | 2 | 3 | 2 | 41 | 37 | 1.5 | 1.6 |
| CL[1] | | | 5 | 21 | 1 | 451 | 33 | 1.7 | 0.96 |
| CL[1]* | | | 1 | 2 | 2 | 19 | 41 | 0.51 | 1.4 |
| CL[2] | | | 2 | 2 | 2 | 37 | 30 | 2.5 | 0.90 |
| CLr[1] | Infants | IV | 2 | 2 | 2 | 19 | 31 | 0.97 | 1.4 |
| CL[1] | | | 3 | 3 | 3 | 29 | 27 | 0.74 | 0.87 |
| CL[2] | | | 1 | 1 | 1 | 4 | 23 | 0.72 | 0.80 |
| CLr[1] | Children | IV | 1 | 2 | 1 | 18 | 25 | 0.59 | 1.1 |
| CL[1] | | | 4 | 5 | 4 | 72 | 30 | 0.78 | 1.0 |
| CL[2] | | | 1 | 1 | 1 | 6 | 40 | 0.66 | 1.4 |
| CL[3] | | | 2 | 2 | 2 | 40 | 32 | 0.71 | 1.5 |
| AUC[4] | | PO | 1 | 1 | 1 | 9 | 29 | 0.80 | 1.9 |
| Cmax[5] | Asian | PO | 3 | 3 | 3 | 31 | 20 | 0.78 | 0.92 |
| | Indian | | 1 | 1 | 12 | 8 | 17 | 0.60 | 0.62 |
| | Elderly | | 1 | 1 | 1 | 21 | 29 | 1.8 | 1.4 |
| | Elderly* | | 4 | 9 | 9 | 111 | 33 | 1.7 | 1.1 |
| | Neonates | | 1 | 1 | 1 | 7 | 22 | 0.65 | 0.71 |
| | Children | | 1 | 1 | 1 | 9 | 51 | 1.8 | 3.0 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **CV** Coefficient of variation; **Mean ratio $H/S_{LN}$** Mean Ratio be tween healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; **CLr** Renal clearance; **CL** Clearance; [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}.1.73m^{-2}$; [3]Clearance expressed in $ml.min^{-1}$; [4]AUC/dose expressed as ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [5]Cmax/dose expressed as ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); *Japanese

### *III.2.2.2.5 Patients with renal disease*

The database describing the kinetics of the renal excretion pathway in patients with renal disease and healthy adults is presented in Table 18. A decrease in oral and intravenous renal clearances was observed for all parameters ranging from 5-13 fold and associated with a 2-fold increase in variability compared to healthy adults (except for the clearance adjusted to body surface, 5-fold increase). The same pattern was

demonstrated for total clearances for all parameters and routes of exposure (3-5-fold decreasein clearances and 1.3-1.4-fold increase in variability). The Cmax database did not reveal major differences between patients with renal disease and healthy adults with a 1.3-fold increase in internal dose and similar variability for both groups.

**Table 19. Pooled analysis for inter-individual differences in renal excretion, effect of liver and renal disease[a].**

| PK parameter | Group | Route | Nc | Ns | Np | n | $CV_{LN}$ | Mean Ratio $H/S_{LN}$ | Mean Ratio H/S $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| CLr[1] | Liver Disease | PO | 1 | 1 | 1 | 8 | 33 | 1.4 | 0.80 |
| CLr[3] | | PO | 2 | 2 | 2 | 20 | 53 | 1.9 | 1.6 |
| CLr[3] | | IV | 1 | 1 | 1 | 9 | 46 | 1.6 | 1.8 |
| CL[1] | | PO | 1 | 1 | 1 | 8 | 13 | 1.2 | 0.60 |
| CL[1] | | IV | 3 | 5 | 4 | 48 | 41 | 1.5 | 1.2 |
| CL[3] | | PO | 1 | 1 | 1 | 12 | 52 | 2.5 | 2.4 |
| CL[3] | | IV | 1 | 1 | 17 | 9 | 49 | 1.4 | 3.1 |
| AUC[4] | | PO | 2 | 2 | 2 | 20 | 45 | 1.6 | 2.1 |
| CLr[1] | Renal Disease | IV | 1 | 3 | 1 | 17 | 46 | 7.5 | 1.5 |
| CLr[2] | | IV | 1 | 4 | 1 | 24 | 105 | 4.8 | 4.9 |
| CLr[3] | | PO | 2 | 6 | 4 | 45 | 63 | 13 | 1.9 |
| CLr[3] | | IV | 3 | 10 | 4 | 72 | 58 | 8.9 | 2.1 |
| CL[1] | | IV | 4 | 8 | 6 | 141 | 34 | 3.6 | 1.03 |
| CL[2] | | PO | 1 | 9 | 33 | 54 | 28 | 3.2 | 1.4 |
| CL[2] | | IV | 3 | 16 | 6 | 94 | 22 | 3.9 | 1.3 |
| CL[3] | | PO | 2 | 9 | 6 | 68 | 40 | 4.7 | 1.3 |
| CL[3] | | IV | 5 | 19 | 7 | 122 | 32 | 2.9 | 1.4 |
| Cmax[5] | Liver Disease | PO | 3 | 7 | 5 | 59 | 30 | 1.2 | 1.1 |
| | Renal Disease | | 3 | 18 | 10 | 122 | 29 | 1.3 | 1.04 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{CV_{LN}}$ Coefficient of variation (lognormal distribution); **Mean ratio $\mathbf{H/S_{LN}}$** , Mean Ratio be tween healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $\mathbf{CV_{LN}}$**, Ratio between the variability of the subgroup and the healthy volunteers; **CLr**, renal clearance; **CL**, Clearance; [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}.1.73m^{-2}$; [3]Clearance expressed in $ml.min^{-1}$; [4]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [5]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$; *Japanese

## III.3 Renal excretion-related uncertainty factors

Uncertainty factors for renal excretion below a value of 2 would cover more than 99% of the healthy adult population for both chronic and acute exposure (Table 19). These values were adequate for most subgroups of the population except the elderly and neonates for which defaults of up to 4.3 and 3.7 respectively would be required. Patients with liver disease and patients with renal disease would require values of 3.6, 4.1 and 4.8 and 7.1, 7.9, 9.0 respectively to cover the 95$^{th}$, 97.5$^{th}$ and 99$^{th}$ centile of each subgroup. Finally, patients with renal disease would constitute the major sensitive

subgroup and interindividual differences in renal clearances (corresponding to compounds handled via a 100% renal excretion) would involve default uncertainty factors of 34, 41, 51 and 20, 24 and 30 for the oral and intravenous routes respectively.

**Table 19. Renal excretion related uncertainty factors in subgroups of the human population[a].**

| Subgroup (Route) | PK parameter | Nc | Ns | Np | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ | Renal excretion related uncertainty factors (lognormal distribution) $95^{th}$ | $97.5^{th}$ | $99^{th}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Chronic exposure* | | | | | | | | | | | |
| Healthy (PO) | $CL^1$, $CL^2$, $CL^3$, $AUC^4$ | 6 | 48 | 39 | 444 | 21 | | | 1.4 | 1.5 | 1.6 |
| Healthy (IV) | $CL^1$, $CL^2$, $CL^3$ | 10 | 72 | 64 | 1105 | 29 | | | 1.5 | 1.7 | 1.9 |
| Healthy Asian | $CL^3$, $AUC^4$ | 3 | 3 | 3 | 30 | 22 | 0.80 | 1.5 | 1.2 | 1.3 | 1.4 |
| Elderly (PO) | $CL^1$, $CL^3$ | 3 | 6 | 6 | 84 | 34 | 2.0 | 1.6 | 3.5 | 3.8 | 4.3 |
| Elderly (IV) | $CL^1$, $CL^2$, $AUC^4$ | 7 | 16 | 16 | 331 | 36 | 1.5 | 1.0 | 2.7 | 3.0 | 3.4 |
| Neonates (IV) | $CL^1$, $CL^2$ | 6 | 23 | 15 | 488 | 33 | 1.8 | 0.96 | 3.0 | 3.2 | 3.7 |
| Infants (IV) | $CL^1$, $CL^2$ | 3 | 4 | 4 | 33 | 27 | 0.70 | 0.9 | 1.1 | 1.2 | 1.4 |
| Children (IV) | $CL^1$, $CL^2$, $CL^3$ | 4 | 8 | 7 | 118 | 31 | 0.80 | 1.2 | 1.2 | 1.4 | 1.5 |
| *Acute exposure* | | | | | | | | | | | |
| Healthy (PO) | | 6 | 44 | 35 | 401 | 27 | | | 1.5 | 1.7 | 1.9 |
| Healthy Asian | | 3 | 3 | 3 | 31 | 20 | 0.78 | 0.92 | 1.1 | 1.2 | 1.2 |
| Elderly (PO) | $Cmax^4$ | 4 | 9 | 9 | 111 | 33 | 1.7 | 1.1 | 2.85 | 3.2 | 3.5 |
| Neonates (PO) | | 1 | 1 | 1 | 7 | 22 | 0.65 | 0.71 | 1.0 | 1.0 | 1.1 |
| Children (PO) | | 1 | 1 | 1 | 9 | 51 | 1.8 | 3.0 | 3.9 | 4.5 | 5.4 |

[a]**Nc** Number of compounds; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; **$CV_{LN}$** Mean coefficient of variation (lognormal distribution); **Mean ratio $H/S_{LN}$** Mean Ratio between healthy volunteers and subgroup (for the AUC the Ratio S/H was calculated) (lognormal distribution); **Mean ratio $CV_{LN}$** Ratio between the variability of the subgroup and the healthy volunteers; [1]Individual Clearance corrected for body weight (ml $min^{-1}Kg^{-1}$; [2]Clearance corrected to body surface (ml $min^{-1}1.73m^{-2}$); [3]Clearance not corrected for body weight (ml $min^{-1}$); [4]Mean AUC and C max corrected for dose expressed per mean body weight ($mgkg^{-1}$).

# Chapter VII Prediction of human variability in kinetics for xenobiotics handled by multiple pathways

## I.Introduction

The previous result chapters have dealt with the analysis of human variability in kinetics for compounds handled by a single major metabolic route (>60% of an oral dose) to derive pathway-related uncertainty factors for healthy adults and potentially sensitive subgroups of the population. Many environmental contaminants such as pesticides are handled by multiple pathways (Eaton et al., 2000) and quantification of human variability in kinetics for such compounds would provide a basis to derive uncertainty factors for many environmental contaminants.

The purpose of this chapter is therefore to estimate kinetic variability in healthy adults for compounds handled by multiple pathways using published data and compare the results to a latin hypercube (Monte Carlo) predictive model based on quantitative metabolism data and pathway-specific kinetic variability (derived from previous chapters). The validation of such a model would be useful to risk assessors and managers, because it could allow the prediction of variability in kinetics for compounds for which only metabolism is known. Particular issues of concern regarding polymorphic pathways are addressed and two probe drugs (propranolol and diazepam) have been selected to validate the latin hypercube (Monte Carlo) model since both substrates are handled by a combination of pathways including CYP2D6, glucuronidation and CYP1A2 for propranolol and CYP2C19 and CYP3A4 for diazepam. Kinetic data for propranolol and diazeapm are analysed and compared to the predictions from the Monte Carlo model, and implications for deriving uncertainty factors from real data are discussed.

## II.Methods

### II.1 Probe substrates

Data for propranolol and diazepam metabolism were searched in the literature (BIDS, EMBASE and TOXLINE, 1966-Dec 2000) to identify the pathways involved in their metabolism and quantify the involvement of each pathway using urinary excretion data. Kinetic data (clearance and AUC) for healthy adults were also abstracted from the literature and analysed using the same method as described in chapter II to derive an overall coefficient of variation for each compound.

### II.2 Latin Hypercube (Monte Carlo) model

The Latin Hypercube (Monte Carlo) models for propranolol and diazepam were built using the following assumptions:

#### II.2.1 Propranolol

1. Data for propranolol metabolism (see results section for metabolism data) allowed quantification of the percentage of a dose handled by each of the pathways:

-Glucuronidation,
-CYP2D6,
-CYP1A2,
with

$$\alpha_G + \beta_{2D6} + \delta_{1A2} = 1 \qquad (1)$$

where $\alpha_G$, $\beta_{2D6}$ and $\delta_{1A2}$ correspond to the fractions of a dose of propranolol handled by glucuronidation, CYP2D6 and CYP1A2 respectively (1) and the sum of $\alpha_G$, $\beta_{2D6}$ and $\delta_{1A2}$ equal 1 (100% of a dose of propranolol).

The variability in propranolol kinetics ($CV_p$) corresponds to the combination of the specific variability (equations 2 and 3) from each pathway involved in its metabolism (based on $\alpha_G$, $\beta_{2D6}$ and $\delta_{1A2}$) and follows a lognormal distribution f(x) (chapter II). Coefficients of variation for each pathway ($CV_G$, $CV_{2D6}$ and $CV_{1A2}$) equally follow a lognormal distribution ($f_G(x)$ and $f_{2D6}(x)$, $f_{1A2}(x)$).

$CV_p = f(x)$

$CV_G=\alpha_G\ f_G(x)$

$CV_{2D6}=\beta_{2D6}\ f_{2D6}(x)$

$CV_{1A2}=\delta_{1A2}\ f_{1A2}(x)$

The overall coefficient of variation would be given by

$CV_p= f(x) = \alpha_G\ f_G(x) + \beta_{2D6}\ f_{2D6}(x) + \delta_{1A2}\ f_{1A2}(x)$ (3)

**II.2.2 Diazepam**

Data for diazepam metabolism (see results section for metabolism data) allowed quantification of the percentage of a dose handled by each pathway

-CYP2C19,

-CYP3A4,

with

$\alpha_{2C19} + \beta_{3A4} =1$ (4)

where $\alpha_{2C19}$ and $\beta_{3a4}$ correspond to the fractions of a dose of diazepam handled by CYP2C19 and CYP3D4 respectively and the sum of $\alpha_{2C19}$ and $\beta_{3A4}$ equals 1 (100% of a dose of diazepam).

The variability in diazepam kinetics ($CV_D$) corresponds to the combination of the specific variability (equation 5 and 6) from each pathway involved in its metabolism (based on $\alpha_{2C19} + \beta_{3A4}$) and follows a lognormal distribution $f_D(x)$ (chapter II). Coefficients of variation for each pathway ($CV_{2C19}$ and $CV_{3A4}$) equally follow a lognormal distribution ($f_{2C19}(x)$ and $f_{3A4}(x)$).

$CV_D= f_D(x)$

$CV_{2C19}=\alpha_{2C19}\ f_{2C19}(x)$

$CV_{3A4}=\beta_{3A4}\ f_{3A4}(x)$ (5)

The overall coefficient of variation would be given by

$CV_D = f_D(x) = \alpha_{2C19}\ f_{2C19}(x) + \beta_{3A4}\ f_{3A4}(x)$ (3)

### II.2.3 Simulations

Simulations were performed with the @Risk software using the lognormal function (RiskLognorm (GM, GSD)) which when provided a geometric mean (GM) and a geometric standard deviation (GSD) allows the distributions to be plotted.

The Monte Carlo model was designed using the following tables for propranolol (Table 1) and diazepam (Table 2):

**Table 1. Design of the Monte Carlo model for propranolol**

| Pathway | Pathway | Proportion | GM | GSD |
|---|---|---|---|---|
| Glucuronidation | 1 | $\alpha_G$ | $GM_1$ | $GSD_1$ |
| CYP2D6 | 2 | $\beta_{2D6}$ | $GM_2$ | $GSD_2$ |
| CYP1A2 | 3 | $\delta_{1A2}$ | $GM_3$ | $GSD_3$ |

$GSD_1$, $GSD_2$ and $GSD_3$ are pathway specific geometric standard deviations (glucuronidation, CYP2D6 and CYP1A2) obtained from chapter III, IV and VI respectively.

**Table 2. Design of the Monte Carlo model for diazepam**

| Pathway | Pathway | Proportion | GM | GSD |
|---|---|---|---|---|
| CYP2C19 | 1 | $\alpha_{2C19}$ | $GM_1$ | $GSD_1$ |
| CYP3A4 | 2 | $\beta_{3A4}$ | $GM_2$ | $GSD_2$ |

$GSD_1$ and $GSD_2$ are pathway specific geometric standard deviations (CYP2C19 and CYP3A4) obtained from chapter VI and IV respectively.

Simulations were run using Latin hypercube sampling (10000 iterations) a variant a Monte Carlo simulation for which the input distributions are stratified, divided into equal intervals and combined into a single lognormal distribution. Random samples for each distribution are randomly taken from each interval, thereby modelling the overall distribution in fewer iterations when compred with the Monte Carlo method (Guide to using @RISK, 1996).

The sampling and combination of each lognormal distribution has been designed according to:

- The proportions of each pathway involved in the metabolism of propranolol and diazepam.

Simulations were run using two discrete functions A and B associated with each frequency so that:

1.$\alpha_G,\beta_{2D6},\delta_{1A2}$ for propranolol

A= RiskDiscrete({1,2,3},{$\alpha_G,\beta_{2D6},\delta_{1A2}$})

2.$\alpha_{2C19}$ and $\beta_{3A4}$ for diazepam) so that:

B=RiskDiscrete({1,2},{$\alpha_{2C196},\beta_{3A4}$})

Each distribution was sampled at each iteration according to its weight in the final lognormal distribution :

$f_{Propranolol}(x)$ = IF(A=1,RiskLognorm($GM_1$,$GSD_G$), IF(A=2,RiskLognorm($GM_2$,$GSD_{1A2}$), IF(A=3,RiskLognorm($GM_3$,$GSD_{2D6}$))).

$f_{Diazepam}(x)$=IF(A=1,RiskLognorm($GM_1$,$GSD_{2C19}$),IF(A=2,RiskLognorm($GM_2$,$GSD_{3A4}$)).

For each distribution the geometric mean was arbitraly chosen to equal 1 since the geometric standard deviations (GSD) were the variables of interest (specific to each phenotype and pathway).

The lognormal distributions for the overall propranolol and diazepam variability were plotted using a GM of 1 and the GSD calculated from the analyses of published kinetic data in healthy adults and compared to the distributions obtained from the simulations ($f_{Propranolol}(x)$ and $f_{Diazepam}(x)$).

# III.Results

## III.1 Metabolism

### III.1.1 Propranolol

Propranolol is metabolised via three pathways: 16% of an oral dose is glucuronidated (chapter III)), 44% undergoes 4-hydroxylation via CYP2D6 and 40% undergoes N-deisopropylation via CYP1A2 (chapter VI) (Data based on 96 hours urinary recovery). Both oxidation products are conjugated via glucuronidation and sulphation (Walle *et al.,* 1986; Masubuchi *et al.,* 1994; Yoshimoto *et al.,* 1995).

### III.1.2 Diazepam

Diazepam metabolism undergoes two main reactions: (62% of an oral dose undergoes N-demethylation with further hydroxylation to give oxazepam and a 40% undergoes C-3 hydroxylation to give temazepam which is further hydroxylated into oxazepam. Both oxazepam and temazepam are conjugated via glucuronidation (Bertilsson *et al.,* 1989). Andersson *et al* (1994) showed that temazepam formation was carried out mainly by CYP3A isoforms, whereas the formation of N-desmethyldiazepam was mediated by both CYP3A isoforms and S-mephenytoin hydroxylase (CYP2C19). These authors compared their in vitro data with *in vivo* data from Bertilsson *et al.,* 1989, and concluded that half of the N-demthylation is mediated by CYP2C19 and half by CYP3A4 (Andersson *et al.,* 1994).

## III.2 Kinetic data

### III.2.1 Kinetic data for propranolol

Kinetic data for propranolol were available for non-phenotyped healthy adults and the variability ranged from 33% to 62% for the different markers of chronic exposure (Table 3). The weighted mean analysis of these three parameters gave a geometric standard deviation of 1.60 with an overall variability of 50%.

**Table 3. Interindividual differences in the pharmacokinetics of propranolol after oral administration to healthy adult volunteers.**

| Kinetic parameter | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL[1] | 5 | 4[1] | 82 | 55 | 28 | 51 | 48 | 1.6 | 50 |
| CL[2] | 5 | 4[2] | 51 | 1600 | 520 | 32 | 1300 | 1.4 | 33 |
| AUC[3] | 7 | 6[3] | 67 | 310 | 160 | 52 | 190 | 1.8 | 62 |

**Ns** Number of studies; **Np** Number of publications; n number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficient of variation (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation; **CL[1]** Clearance ($ml min^{-1} kg^{-1}$); **CL[2]** Clearance ($ml min^{-1}$); **AUC** ($ng ml^{-1} h^{-1}$) adjusted to body weight ($mg kg^{-1}$).

[1]Lalonde *et al.*,1987, Silber *et al.* 1983, Shiga *et al.*, 1993, Walle *et al.*, 1994 (2); [2]Wood *et al.*,1978, Rigby *et al.*,1985, Dimmitt *et al.*, 1991, Panton *et al.*,1995(2); [3] Lowenthal *et al.*,1974, Schneider *et al.*,1980(2), Rocher *et al.*,1985, Hinderling *et al.*,1995, Vanakovski *et al.*,1995.

### III.2.2 Kinetic data for diazepam

Kinetic data for diazepam were also available for non-phenotyped healthy adults and the variability ranged from 42% to 68% (lognormal distribution) for the different markers of chronic exposure (Table 4). The weighted mean analysis of these three parameters gave an overall variability of 56% (GSD= 1.68, 161 subjects).

**Table 4. Interindividual differences in the pharmacokinetics of diazepam after oral administration to healthy adult volunteers.**

| Kinetic parameter | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL[1] | 8 | 5[1] | 110 | 0.36 | 0.33 | 90 | 0.30 | 1.7 | 58 |
| CL[2] | 4 | 2[2] | 33 | 56 | 32 | 57 | 46 | 1.5 | 42 |
| AUC[3] | 1 | 1[3] | 18 | 12000 | 8300 | 68 | 10200 | 1.9 | 68 |

**Ns** Number of studies; **Np** Number of publications; n number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficient of variation (lognormal distribution); **CL[1]** Clearance ($ml min^{-1} kg^{-1}$); **CL[2]** Clearance ($ml min^{-1}$); **AUC[3]** ($ng ml^{-1} h^{-1}$) adjusted to body weight ($mg kg^{-1}$); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Kumana *et al.*,1987 (2), Mineshita *et al.*,1988, Greenblatt *et al.*,1989, Perucca *et al.*,1994,Caraco *et al.*,1995 (2), Herman *et al.*,1996; [2] Alda *et al.*,1987, Ohnhaus *et al.*,1987(3);[3]Ochs *et al.*, 1982.

## III.3 Monte Carlo models

### III.3.1 Variability in Propranolol kinetics

Lognormal distributions describing human variability for the three pathways involved in propranolol metabolism (glucuronidation, CYP2D6, CYP1A2) were combined to predict the overall variability in propranolol kinetics for healthy Caucasian adults. Three

simulations were run and the geometric standard deviation ranged between 1.58-1.65 with an average of 1.61 (Table 6) which was comparable to that derived from the kinetic data (III.2.1). There was no difference between the variability for the simulated data and the kinetic data. Uncertainty factors to cover the general healthy adult population up to the 95$^{th}$, 97.5$^{th}$ and 99$^{th}$ centile were below 3.16 with values of 2.2, 2.5 and 3.0 respectively.

**Table 6. Simulation of propranolol variability in kinetics after oral administration in healthy adult Caucasian**

| Pathway | Proportion | GM | GSD |
|---|---|---|---|
| Glucuronidation | 0.44 | 1 | 1.42 |
| CYP2D6 | 0.40 | 1 | 1.78 |
| CYP1A2 | 0.16 | 1 | 1.56 |
| Propranolol 1 | 1 | 1 | 1.60 |
| Propranolol 2 | 1 | 1 | 1.65 |
| Propranolol 3 | 1 | 1 | 1.58 |

**Proportion** Proportion of a dose of propranolol metabolised by each pathway (glucuronidation, CYP2D6, CYP1A2) in the healthy adult Caucasian population, **Propranolol** Simulated data (data for three separate 10000 iteration analyses), **GM** Geometric mean, **GSD** Geometric standard deviation for each pathway ((glucuronidation, CYP2D6, CYP1A2) and simulated data (propranolol).

### III.3.3 Variability in Diazepam kinetics

Lognormal distributions describing human variability for the two pathways involved in diazepam metabolism (CYP2C19 and CYP3A4) were combined to predict the overall variability in diazepam kinetics for the healthy adult Caucasian population.

**Table 7. Simulation of the diazepam variability in kinetics after oral administration in healthy adult Caucasian**

| Pathway | Proportion | GM | GSD |
|---|---|---|---|
| CYP2C19 | 0.30 | 1 | 1.53 |
| CYP3A4 | 0.70 | 1 | 1.55 |
| Diazepam 1 | 1 | 1 | 1.60 |
| Diazepam 2 | 1 | 1 | 1.50 |
| Diazepam 3 | 1 | 1 | 1.52 |

**Proportion** Proportion of a dose of propranolol metabolised by each pathway (CYP2C19, CYP3A4) in the healthy adult Caucasian population, **Diazepam** Simulated data (data for three separate 10000 iteration analyses), **GM** Geometric mean, **GSD** Geometric standard deviation for each (CYP2C19, CYP3A4) and simulated data (diazepam).

The simulated geometric standard deviation (Table 6) for diazepam kinetics in the general healthy adult population ranged from 1.50 to 1.60 with an average of 1.54 similar to that derived from the kinetic data (1.67, III.2.2). There was only 6% between the variability for the simulated data (45%) and the published kinetic data (51%); the respective uncertainty

factors were 2.0, 2.3, 2.7 and 2.2, 2.6 and 3.1 to cover 95$^{th}$, 97.5$^{th}$ and 99$^{th}$ centile of the general healthy adult population.

## IV.Discussion

This chapter has explored the possibility of predicting human variability in kinetics for the general Caucasian healthy adult population using Monte Carlo simulation for compounds handled by multiple pathways. Human variability in kinetics was derived from published trials for propranolol (handled by three main pathways: glucuronidation, CYP2D6 and CYP1A2) and diazepam (handled by two main pathways: CYP2C19 and CYP3A4) and compared to the Monte Carlo model, based on quantitative metabolism data and pathway–specific variability derived from previous chapters (chapter III, IV, V and VI).

This chapter has dealt with the feasibility of the use of Monte Carlo analysis to predict human variability in kinetics for compounds handled by multiple pathways.

Two approaches have been looked at:

1.The use of mathematics describing the quantitative involvement of each pathway (with a known variability) handling a particular compound to predict the variability in kinetics.

2. The use of Monte Carlo analysis describing the quantitative involvement of each pathway (with a distribution GM and GSD) handling a particular compound to predict the variability in kinetics.

1. The use of mathematics to predict human variability in kinetics

The coefficient of variation for propranolol ($CV_p$) is given by:

$$CV_p = f(x) = \alpha_G f_G(x) + \beta_{2D6} f_{2D6}(x) + \delta_{1A2} f_{1A2}(x) \quad (1)$$

where $\alpha_{G=}0.16$, $\beta_{2D6} = 0.44$ and $\delta_{1A2=} 0.40$.

The specific variability for each pathway has also been calculated using 29% for glucuronidation, 63% for CYP2D6 and 30% for CYP1A2 (see overall tables from discussion chapter).

CVp can be derived from equation (1)

$CVp = 0.16(0.29) + 0.44(0.63) + 0.4\ (0.3) = 0.44$

The coefficient of variation for diazepam ($CV_D$) is given by:

$CV_D = f_D\ (x) = \alpha_{2C19}\ f_{2C19}(x) + \beta_{3A4}\ f_{3A4}(x)$ (2)

where $\alpha_{2C19} = 0.30$, $\beta_{3A4} = 0.70$. The specific variability for each pathway has also been calculated with, 44% for CYP2C19 and 46% for CYP3A4.

$CV_D$ can be derived from (2)

$CV_D = 0.3(0.44) + 0.7(0.46) = 0.45$

2. The use of Monte Carlo analysis to predict human variability in kinetics

The results obtained from equations 1 and 2 are identical to the results from the Monte Carlo model for diazepam (45%). However, small differences between the results of equation 1 and 2 (44%) and the Monte Carlo model (50%) were observed for propranolol. These differences could have arisen purely by chance since sets of 10 simulations were run for other compounds handled by multiple pathways have also shown these small differences (1-5%). Moreover, the latter result could also be due to the fact that the calculation of the variability using the above equation uses a point estimate (a CV) whereas the Monte Carlo model uses the distribution (GM and GSD).

Overall, the results showed that the kinetic variability and the uncertainty factors ($99^{th}$ centile) derived from published trials in propranolol (50%, 3.0) and diazepam (51%, 3.1) kinetics were similar to the results of the Monte Carlo model with the same values for propranolol and similar values of 45% (2.7) for diazepam.

The use of Monte Carlo models in public health risk assessment has been discussed before (Thompson *et al.,* 1992, Burmaster *et al.,* 1994, Finley *et al.,* 1994) and applied to age-specific distributions for soil ingestion rates, inhalation rates, body weights, skin surface area, tapwater and fish consumption (Finley *et al.,* 1994) as well as exposure assessment of contaminated soils using fruit and vegetable ingestion data (Mc Kone, 1994).

The prediction of human variability in kinetics presented here for compounds handled by multiple pathways (which represent the real situation for a large the majority of xenobiotics) remains a totally new approach. However, the Monte Carlo model developed here would need to be validated for a number of compounds handled by a combination of pathways before it could be confidently applied for chemical risk assessment. There are a number of areas of uncertainty that need to be explored with more precision than the author has attempted in this preliminary study. These would include the quantification of the variability in metabolism for extensive metabolisers based on data for phenotyped individuals (as opposed to non-phenotyped data analysed here) together with the quantification of differences in internal dose between extensive and poor metabolisers. These analyses are currently under way to predict variability in kinetics for phenotyped individuals (polymorphic pathways) for whom frequencies of the phenotype needs to be taken into account to reflect the whole population.

A number of steps are involved for this type of analysis:

1.The use of the quantitative metabolism data for each phenotype and the specific variability associated with it.

2.Data on variability for EM and PM (GM, GSD) subjects will provide the specific variability for each phenotype.

3.Combining both distributions for each phenotype using the frequency of PMs (i.e 8% of PMs in Caucasian for CYP2D6 and the difference in internal dose between EMs and PMs (i.e. if 3-fold increase in internal dose GM=3 for PM).

4.Comparing simulated results to *in vivo* data from the literature.

From these analyses the uncertainty factors necessary to cover defined percentiles of poor metabolisers, can be defined and compared to the uncertainty factors derived here for the general healthy adult population. Including these two separate areas of uncertainty together could give a basis for regulators and risk assessors to build a probabilistic model or to make decisions as to which uncertainty factor to use for a given chemical.

These concepts could also be applied to chemicals undergoing polymorphic metabolism in specific human populations for example Asian EM and PM subjects given the frequency of poor metabolisers (CYP2C19, 14-21% in Asian against 2.8% in Caucasian) and the difference in internal dose between phenotypes, as well as other subgroups (neonates).

# Chapter VIII: Discussion

## Human variability in kinetics for the major metabolic pathways : Applications for chemical risk assessment

This work has analysed human variability in kinetics for the major human metabolic pathways to move away from the standard 3.16 kinetic default factor used for the risk assessment of thresholded toxicants. The 3.16 kinetic default factor resulted originally from refinements of the 100-fold default factor approach used for the last forty years by most regulatory agencies in the world (IPCS, 1994). This 100-fold uncertainty factor (or safety factor) originally allowed for interspecies differences (10-fold) and human variability (10-fold) (WHO, 1987) and each 10-fold factor were further subdivided to account for toxicokinetic and toxicodynamic aspects (Renwick, 1993). Equal values for toxicokinetic and toxicodynamic default factors of $10^{0.5}$ (3.16) for human variability have been accepted as the standard default factors for both aspects of uncertainty (IPCS, 1994; IPCS, 1999). Importantly, the subdivision of the 10-fold factors was to allow the incorporation of suitable compound-specific data for a particular aspect of uncertainty (eg. human toxicokinetics) to replace default values; the product of the chemical-specific value and the remaining defaults would give a chemical-specific adjustment factor (CSAF) (IPCS, 2001 see WHO website).

The assessment of human variability in kinetics for specific pathways resulted in the proposal of pathway-related uncertainty factors for healthy adults and subgroups of the population as an intermediate approach between CSAFs and the 3.16 kinetic default factor (Renwick and Lazarus, 1998). These uncertainty factors could replace the 3.16 default for the kinetic aspect when the metabolic fate of the chemical under assesment is known, but chemical-specific kinetic data in humans are not available or adequate to use CSAFs. Previous analyses have not considered human variability in kinetics on the basis of *in vitro* (microsomes, cell lines and primary cell cultures) and quantitative *in vivo*

(urinary and faecal excretion) biotransformation data in order to select suitable *in vivo* probe substrates, and to estimate the overall *in vivo* human kinetic variability in kinetics for a particular pathway. Importantly, the variability specific to a particular enzyme and the corresponding pathway-related uncertainty factors have been derived, when possible, from several compounds and independently of the size of the database for each compound. All suitable substrates were analysed so as to include substrates with different affinities, binding sites on the catalytic site of the enzyme and provide an "overall estimation" of the pathway *in vivo* variability.

This final discussion chapter will describe the main outcomes of the overall analysis for healthy adults and subgroups of the population (effect of ethnicity and age only) and provide insights to the value of pathway-related uncertainty factors towards the refinement of the chemical risk assessment process. Finally, further work will be suggested to try to improve science–based uncertainty factors in the future.

## I.Pathway related uncertainty factors in subgroups of the population

### I.1 Healthy adults

Human variability in kinetics for monomorphic Phase I (CYP1A2, CYP2C9, CYP2E1, ADH and hydrolyis), Phase II (Glucuronidation, Glycine and sulphate conjugation) pathways and renal excretion was relatively low (21%-31%), the only exception being CYP3A4 metabolism (46%).

The physiological/molecular basis accounting for the higher CYP3A4 variability (for the oral route) has already been discussed (chapter V) and was probably related to the expression of CYP3A4 in the intestine as well as in the liver, the existence of different allelic and protein variants revealing a polymorphism (for which the clinical relevance is still not well characterised), and competition between CYP3A4 metabolism and P-glycoprotein in the gastrointestinal tract (Wacher *et al.,* 1995; Suzuki and Sugiyama, 2000; Sata *et al.,* 2000; Eseilt *et al.,* 2001).

Pathway-related uncertainty factors for these processes were all below the 3.16 for chemicals handled by these routes with values ranging between 1.6-2.2 for all pathways and up to 2.8 for CYP3A4 metabolism to cover general healthy adults (at the 99$^{th}$ centile).

In contrast, pathway-related uncertainty factors for polymorphic Phase I (CYP2D6, CYP2C19) and Phase II (N-acetyltransferases) pathways (Table I) have demonstrated that the 3.16 kinetic default factor would be inadequate for chemicals metabolised via these enzymes. Pathway-related uncertainty factors of up to 18 (CYP2D6), 52 (CYP2C19) and 5.2 (N-acetyltransferases) would cover poor metabolisers (PMs) (CYP2D6 and CYP2C19) and slow acetylators (N-acetyltransferases) up to the 99$^{th}$ centile (assuming the parent compound was the proximate toxicant).

The large variability within extensive metabolisers (EMs) and the difference in internal dose between EMs and PMs for the CYP2D6 pathway (chapter IV) have been recognized to involve the number of copies of the CYP2D6 enzyme present in an individual, or the existence of enzymes with an altered or absent catalytic activity. Two studies have shown the presence of multiple copies in EMs and that up to 13 copies can be present in super fast oxidisers whereas "strict" poor metabolisers would not possess any copies (Dahl *et al.,* 1995; Dalen *et al.,* 1998; Dalen *et al.,* 1999). The same concepts also apply to CYP2C19 metabolism (Wedlund, 2000) and N-acetylation (NAT2* gene) for which 8 and 14 alleles have been found in Caucasian respectively (Lin et al., 1993).

The uncertainty factors derived for each polymorphic pathway have been developed for compounds handled primarily via CYP2D6, CYP2C19 or N-acetyltransferases [60-100% of an oral dose handled by this route in EMs or Fast Acetylators (FAs)] and correspond to a near worse case scenario. However, an exponential relationship has been demonstrated between the extent of CYP2D6 metabolism in EMs and the CYP2D6-related uncertainty factors. This relationship was shown to be critical for the estimation of the appropriate uncertainty factor and the 3.16 kinetic default factor would cover PMs (99$^{th}$ centile) for substrates that were metabolised up to 25% by CYP2D6 in EMs (chapter IV, Table 13). More quantitative metabolism data describing the kinetics of CYP2C19 and N-acetyltransferase "minor substrates" (Chapter IV) would be required to investigate if the same relationship holds between the extent of metabolism and the uncertainty factors for each pathway.

From these findings, particular concerns have been raised about the main polymorphic CYP isoforms (CYP2D6 and CYP2C19), N-acetylation and the CYP3A4 pathway. Applications for chemical risk assessment will be discussed in Section II.

**Table 1. Pathway-related uncertainty factors for healthy adults (oral route of exposure).**

| Pathway | Group | PK parameter | Nc | Ns | n | $CV_{LN}$ | Pathway-related uncertainty factors (Lognormal distribution) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 95th | 97.5th | 99th |
| **Phase I** | | | | | | | | | |
| Monomorphic pathways | | | | | | | | | |
| CYP1A2 | Healthy | CL, CL*, AUC | 4 | 30 | 379 | 30 | 1.6 | 1.8 | 2.0 |
| CYP2C9 | Healthy | CL, CL*, AUC | 2 | 14 | 159 | 32 | 1.7 | 1.9 | 2.2 |
| CYP2E1 | Healthy | CL, AUC | 2 | 20 | 263 | 26 | 1.5 | 1.7 | 1.8 |
| CYP3A4 | Healthy | CL, CL*, AUC | 10 | 76 | 1040 | 46 | 2.1 | 2.4 | 2.8 |
| ADH | Healthy | CL, CL*, AUC | 1 | 15 | 281 | 24 | 1.5 | 1.6 | 1.8 |
| Hydrolysis | Healthy | CL, AUC | 4 | 22 | 166 | 28 | 1.6 | 1.7 | 1.9 |
| Polymorphic pathways | | | | | | | | | |
| CYP2C19 | NP | CL, CL*, AUC | 2 | 7 | 223 | 44 | 2.0 | 2.3 | 2.7 |
| CYP2C19 | EM | CL, CL*, AUC | 2 | 7 | 56 | 60 | 2.5 | 3.1 | 3.8 |
| CYP2C19 | PM | CL, CL*, AUC | 2 | 4 | 21 | 20 | 45 | 48 | 52 |
| CYP2D6 | NP | CL, CL*, AUC | 8 | 41 | 520 | 63 | 3.0 | 3.7 | 4.7 |
| CYP2D6 | EM | CL, CL*, AUC | 9 | 24 | 192 | 66 | 3.5 | 4.4 | 5.8 |
| CYP2D6 | PM | CL, CL*, AUC | 7 | 13 | 74 | 29 | 15 | 16 | 18 |
| **Phase II** | | | | | | | | | |
| Monomorphic pathways | | | | | | | | | |
| Glucuronidation | Healthy | CL, CL*, AUC | 15 | 87 | 906 | 29 | 1.6 | 1.8 | 2.0 |
| Glycine conjugation | Healthy | CL, CL*, AUC | 2 | 21 | 205 | 21 | 1.4 | 1.5 | 1.6 |
| Sulphation | Healthy | CL, CL*, AUC | 3 | 13 | 91 | 26 | 1.5 | 1.7 | 1.8 |
| Polymorphic pathways | | | | | | | | | |
| NAT | FA | CL, CL*, AUC | 2 | 15 | 191 | 32 | 1.7 | 1.8 | 2.1 |
| NAT | SA | CL, CL*, AUC | 2 | 16 | 472 | 22 | 4.4 | 4.8 | 5.2 |
| **Renal Excretion** | | | | | | | | | |
| Renal | Healthy | CL, CL*, CL**, AUC | 10 | 48 | 444 | 21 | 1.4 | 1.5 | 1.6 |

**NP** Non-phenotyped healthy adults; **EM** Extensive metabolisers; **PM** Poor metabolisers; **FA** Fast acetylators; **SA** Slow acetylators; **Nc** Number of compounds; **Ns** Number of studies; **n** Number of subjects; **Mean CV** Coefficient of variation; **CL** Clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL*** Clearance not adjusted to body weight ($mlmin^{-1}$); **CL**** Clearance adjusted to body surface ($mlmin^{-1}1.73m^{-2}$); **AUC** Area-under-the-plasma-concentration-curve ($ngmlh^{-1}$) corrected for dose expressed per mean body weight ($mgkg^{-1}$).

## I.2 Subgroups of the population

### I.2.1 Interethnic differences

The pathway-related uncertainty factors derived for ethnic minorities (mainly African and Asian healthy adults) are summarised in Table 2; for monomorphic pathways most factors were below the 3.16 kinetic default which is consistent with the data for general healthy adults. However, factors just above the 3.16 with values of 5.0 and about 4.0 were found for metabolism via hydrolysis in Asian (based only on 12 subjects and 1 compound) and for CYP3A4 metabolism in Black African (3.8) and Asian (3.9) to cover each subgroup to the 99th centile.

Data for polymorphic pathways raised the same concerns as for the general healthy adults, since most of the subgroups would not be covered by the 3.16 for compounds handled primarily via the CYP2D6, CYP2C19, or N-acetylation. Asian healthy adult

EMs and PMs were an exception to this conclusion because of an overall increase in clearance in Asian EMs compared with general adult EMs and virtually no difference in clearance between Asian PM and general healthy adult. The frequency of PMs in Asian populations (2% against 8% in Caucasian) would play a critical part in these differences (Chapter IV). The same consideration can be raised for the observed differences between general healthy adult FA and Asian FAs and SAs since the frequency of SAs in Caucasian populations is high (40-70%) and much lower in Japanese and Chinese populations (10-20%). However because acetylation has been shown to be generally slower in Asian healthy adults than in Caucasian populations, pathway-related uncertainty factors were above the 3.16 for both FAs and SAs among healthy adult Japanese (Meyer,1994; Johnson, 2000).

In contrast to the CYP2D6 metabolism, both the variability in CYP2C19 metabolism in Asian EMs and the frequency of PMs in Asian are much higher than in Caucasian populations (14-21.3% against 2.8% respectively)(Wedlund, 2000). However, CYP2C19-related uncertainty factors for healthy adults were higher than those for Asian, due to the larger difference in internal dose between healthy adult EMs and PMs and compared with Asian PMs (although the data only included 21 subjects).

**Table 2. Pathway-related default uncertainty factors for ethnic minorities.**

| Pathway | Group | PK parameter | Nc | Ns | n | $CV_{LN}$ | Ratio Mean | Pathway-related uncertainty factors (Lognormal distribution) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $95^{th}$ | $97.5^{th}$ | $99^{th}$ |
| **African** | | | | | | | | | | |
| CYP1A2 | Black African | CL (IV) | 1 | 1 | 16 | 27 | 1.6 | 2.5 | 2.7 | 3.0 |
| CYP2D6 | Healthy NP | CL* (PO) | 1 | 1 | 10 | 64 | 1.1 | 2.9 | 3.5 | 4.3 |
| CYP2D6 | Healthy EM | CL* (PO) | 1 | 1 | 18 | 120 | 1.8 | 8.2 | 11 | 15 |
| CYP3A4 | North African | AUC (PO) | 1 | 1 | 10 | 30 | 1.3 | 2.1 | 2.3 | 2.6 |
| CYP3A4 | Black African | AUC (PO) | 2 | 2 | 21 | 42 | 1.5 | 2.9 | 3.3 | 3.8 |
| **Asian** | | | | | | | | | | |
| CYP2C19 | EM | CL, CL*, AUC (PO) | 2 | 6 | 40 | 63 | 1.7 | 4.4 | 5.3 | 6.6 |
| CYP2C19 | PM | CL*, AUC (PO) | 2 | 6 | 34 | 27 | 15 | 24 | 26 | 28 |
| CYP2D6 | NP | CL , AUC (PO) | 3 | 4 | 70 | 69 | 0.80 | 2.1 | 2.6 | 3.2 |
| CYP2D6 | EM | CL*, AUC (PO) | 4 | 6 | 60 | 36 | 0.27 | <1 | <1 | <1 |
| CYP2D6 | PM | CL , AUC (PO) | 2 | 2 | 16 | 41 | 1.2 | 2.1 | 2.4 | 2.7 |
| CYP3A4 | Healthy | CL*, AUC (PO) | 5 | 13 | 134 | 39 | 1.5 | 2.9 | 3.3 | 3.9 |
| ADH | Healthy | ER (PO) | 1 | 5 | 154 | 21 | 0.87 | 1.2 | 1.3 | 1.4 |
| Hydrolysis | Healthy | CL (PO) | 1 | 1 | 12 | 43 | 2.0 | 3.8 | 4.3 | 5.0 |
| NAT | Japanese FA | CL* (PO) | 1 | 1 | 33 | 34 | 1.8 | 3.1 | 3.4 | 3.9 |
| NAT | Japanase SA | CL* (PO) | 1 | 1 | 5 | 39 | 2.8 | 5.2 | 5.9 | 6.7 |
| Renal | Healthy | CL*, AUC (PO) | 3 | 30 | 22 | 80 | 30 | 1.2 | 1.3 | 1.4 |

**NP** Non-phenotyped healthy adults; **EM** Extensive metabolisers; **PM** Poor metabolisers; **FA** Fast acetylators; **SA** Slow acetylators **Nc** Number of compounds; **Ns** Number of studies; **n** Number of subjects; **Mean CV** Coefficient of variation; **CL** Clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL*** Clearance not adjusted to body weight ($mlmin^{-1}$); **AUC** Area-under-the-plasma-concentration-curve ($ngmlh^{-1}$) corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### I.2.2 Neonates and Children

Data describing kinetic variability in neonates (Table 3) compared to healthy adults were only available for 4 pathways: CYP1A2, glucuronidation, glycine conjugation and renal excretion); all pathway-related default uncertainty factors were above 3.16 with values of 14, 12, 28 and 3.7 ($99^{th}$ centile) respectively. The increase in internal dose observed in neonates compared to healthy relates mostly to the immaturity of these enzymes (Aranda *et al.*, 1980; Pons *et al.*, 1988; Kraus *et al.*, 1993; Cazeneuve *et al.*, 1994; Cresteil, 1998; Sonnier and Cresteil, 1998; Leeder *et al.,* 2000).

The ontogenesis of the CYP1A2 isoform in the human liver has been investigated; the immunodetectable protein and enzyme activity were absent in foetal and neonatal livers, increased in infant tissues between 1-3 months, and reached 50% of the adult level after a year. Neonates have been shown to eliminate caffeine and theophylline mainly via renal clearance, with some limited metabolism via CYP3A7 (a CYP3A isoform specific to foetal liver tissue) and CYP1A2 (Aranda *et al.*, 1980; Pons *et al.*, 1988; Kraus *et al.*, 1993; Cazeneuve *et al.*, 1994; Cresteil, 1998). In contrast, other CYP isoforms (CYP3A7, CYP2C, CYP2D6 and CYP2E1) are expressed to a much greater extent immediately post-natally (Sonnier and Cresteil, 1998; Leeder *et al.,* 2000).

Quantitative age-related differences in glucuronidation *in vitro* have been reported previously, and hepatic glucuronidation in the human neonate has been shown to be relatively immature at birth in contrast with considerably more mature neonatal hepatic sulfation activity. These findings are in agreement with the *in vivo* neonate data for this pathway (Miners and Mackenzie, 1991; de Wildt *et al.,* 1999; Gow *et al.,* 2001).

The capacity of the immature liver or kidney for detoxification through glycine conjugation to form hippuric acid from benzoate has been studied in premature newborns for the intravenous route (n= 10) (Le Bel *et al.,* 1986). However, data on oral kinetics would be required in term neonates because glycine conjugation has been recognised to be matured in neonates and to be a highly saturable metabolic pathway (Gow *et al.,* 2001).

Finally, glomerular filtration and tubular secretion has been shown to increase as a function of post-conceptional age until adult values are achieved by approximately 2.5-5

months of age and 7 months respectively (Besunder *et al.,* 1988). This would explain the lower clearances observed in neonates compared to healthy adults for xenobiotics excreted via the kidney.

Data describing the variability in kinetics for polymorphic pathways in neonates were only available for CYP2D6 and showed a dramatic increase in internal dose (19- and 33-fold) although the number of subjects (n= 2) and their ethnic origin (Japanese) did not allow a reliable conclusion (Ito *et al.,* 1998). However, these data indicate concerns for CYP2D6 metabolism and the neonatal population. Taken together with the data for children (high variability and 4-fold increase in internal dose-see below) and the data for healthy adults, one could speculate that neonates would be the most susceptible subgroup when exposed to compounds handled by CYP2D6 metabolism.

The data for children (Table 3) were similar to those for healthy adults for all the metabolic pathways and pathway-related factors were below 3.16 (including N-acetylation) except for the polymorphic CYP2D6 and CYP2C19 isoforms.

Data for CYP2D6 and CYP2C19 pathways were available only for non-phenotyped individuals and the large database for CYP2D6 (but only for one compound) showed that variability for CYP2D6 metabolism was very high in children (requiring a default of 45 to cover the $99^{th}$ centile).

**Table 3. Pathway-related default uncertainty factors for children and neonates.**

| Pathway | PK parameter | Nc | Ns | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Pathway-related uncertainty factors (Lognormal distribution) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | $95^{th}$ | $97.5^{th}$ | $99^{th}$ |
| **Neonates** | | | | | | | | | |
| CYP1A2 | CL (IV) | 2 | 7 | 251 | 35 | 6.2 | 11 | 12 | 14 |
| Glucuronidation | CL (IV) | 4 | 14 | 94 | 50 | 3.9 | 8.6 | 10 | 12 |
| Glycine Conjugation | AUC (IV) | 2 | 1 | 10 | 16 | 19 | 25 | 26 | 28 |
| Renal excretion | CL, CL* (IV) | 6 | 23 | 488 | 33 | 1.8 | 3.0 | 3.2 | 3.7 |
| **Children** | | | | | | | | | |
| CYP1A2 | CL, CL*, AUC (PO) | 1 | 12 | 195 | 34 | 0.82 | 1.4 | 1.6 | 1.8 |
| CYP2C19 | CL* (PO) | 1 | 1 | 25 | 86 | 1.6 | 5.4 | 6.9 | 9.0 |
| CYP2D6 | CL (PO) | 1 | 2 | 173 | 140 | 4.0 | 22 | 31 | 45 |
| CYP3A4 | CL, AUC (PO) | 3 | 3 | 16 | 45 | 0.70 | 1.4 | 1.6 | 1.8 |
| Hydrolysis | CL, AUC (PO) | 3 | 3 | 43 | 40 | 0.80 | 1.5 | 1.7 | 2.0 |
| Glucuronidation | CL, AUC (PO) | 5 | 13 | 131 | 23 | 0.86 | 1.3 | 1.4 | 1.5 |
| Glycine Conjugation | CL (PO) | 1 | 1 | 20 | 27 | 0.98 | 1.5 | 1.6 | 1.8 |
| NAT | CL (PO) | 1 | 1 | 25 | 37 | 1.1 | 2.0 | 2.2 | 2.5 |
| NAT | CL (PO) | 1 | 1 | 25 | 13 | 1.8 | 2.2 | 2.3 | 2.4 |
| Renal Excretion | CL, CL*, CL** (IV) | 4 | 8 | 118 | 31 | 0.80 | 1.2 | 1.4 | 1.5 |

**Nc** Number of compounds; **Ns** Number of studies; **n** Number of subjects; **Mean CV** Coefficient of variation; **CL** Clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL*** Clearance not adjusted to body weight ($mlmin^{-1}$); **AUC** Area-under-the-plasma-concentration-curve ($ngmlh^{-1}$) corrected for dose expressed per mean body weight ($mgkg^{-1}$).

### I.2.3 The elderly

The pathway-related uncertainty factors derived for the elderly are summarised in Table 4 and were mostly similar to those derived for healthy adults. Most uncertainty factors for monomorphic pathways were found to be below the 3.16 kinetic default factor with two exceptions for renal excretion and CYP3A4 metabolism for which factors of 4.3 and 4.6 would cover the elderly to the $99^{th}$ centile.

The physiological basis for these differences has been well characterised and old age has been recognised to affect both hepatic and the renal function (Durnas *et al.*, 1990; Le Couteur and McLean, 1999). The age-related differences for the elimination of CYP3A4 substrates would be due to secondary changes in liver blood flow, drug binding and distribution (Hunt *et al.*, 1992). However major differences have not been observed for other monomorphic CYP substrates (CYP1A2, CYP2C9, CYP2E1), and this is probably due to the fact that CYP3A4 constitutes at least half of the total hepatic CYP activity (de Wildt *et al.*, 1999) whereas other isoforms would only represent between 5 to 15% of this activity.

The differences demonstrated for the polymorphic pathways between the elderly and healthy adults were also consistent with altered hepatic function in old age (Durnas *et al.*,

1990; Le Couteur and McLean, 1999). Pathway–related uncertainty factors for CYP2D6 metabolism, CYP2C19 metabolism and N-acetylation (slow acetylators) were all above the 3.16 kinetic default with respective values of 8.4, 4.3 and 7.6 (99$^{th}$ centile). The data for the elderly related to CYP2D6 and CYP2C19 metabolism were mostly available for non-phenotyped healthy adults and no data were available for elderly PMs. However, one would expect that elderly PMs would have even lower clearances than healthy adult PMs, as found with the data describing the differences in N-acetylation between healthy adult FA and elderly.

**Table 4. Pathway-related default uncertainty factors for the elderly.**

| Pathway | PK parameter | Nc | Ns | n | $CV_{LN}$ | Ratio $H/S_{LN}$ | Pathway-related uncertainty factors (Lognormal distribution) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 95$^{th}$ | 97.5$^{th}$ | 99$^{th}$ |
| **Phase I** | | | | | | | | | |
| CYP1A2 | CL (PO) | 2 | 3 | 27 | 37 | 1.1 | 1.4 | 1.6 | 1.8 |
| CYP2C9 | CL (PO) | 1 | 1 | 12 | 30 | 0.74 | 1.2 | 1.3 | 1.5 |
| CYP2C19 | CL (PO) | 1 | 1 | 10 | 39 | 1.8 | 3.4 | 3.8 | 4.3 |
| CYP2D6 (NP) | CL, CL*, AUC (PO) | 5 | 7 | 69 | 88 | 1.4 | 5.0 | 6.3 | 8.4 |
| CYP2D6 (EM) | AUC (PO) | 1 | 1 | 6 | 74 | 0.50 | 1.5 | 1.8 | 2.3 |
| CYP2E1 | CL (PO) | 1 | 2 | 22 | 26 | 1.3 | 1.9 | 2.1 | 2.3 |
| CYP3A4 | CL, CL*, AUC (PO) | 8 | 13 | 143 | 46 | 1.7 | 3.4 | 3.9 | 4.6 |
| ADH | CL, CL*, AUC (PO) | 1 | 2 | 29 | 43 | 1.2 | 2.4 | 2.8 | 3.2 |
| Hydrolysis | CL, AUC (PO) | 2 | 4 | 31 | 35 | 0.66 | 1.2 | 1.3 | 1.5 |
| **Phase II** | | | | | | | | | |
| Glucuronidation | CL, CL*, AUC (PO) | 10 | 14 | 140 | 28 | 1.4 | 2.3 | 2.5 | 2.7 |
| Glycine conjugation | AUC (PO) | 1 | 3 | 19 | 26 | 1.0 | 1.6 | 1.8 | 2.0 |
| Sulphation | CLm (IV) | 3 | 3 | 24 | 23 | 1.1 | 1.6 | 1.7 | 1.9 |
| NAT | CL (PO) | 2 | 4 | 56 | 37 | 1.3 | 2.3 | 2.5 | 2.9 |
| NAT | CL (PO) | 2 | 4 | 105 | 29 | 3.9 | 6.3 | 6.9 | 7.6 |
| **Renal excretion** | | | | | | | | | |
| Renal | CL, CL* (PO) | 3 | 6 | 84 | 34 | 2.0 | 3.5 | 3.8 | 4.3 |

**Nc** Number of compounds; **Ns** Number of studies; **n** Number of subjects; **Mean CV** Coefficient of variation; **CL** Clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL*** Clearance not adjusted to body weight ($mlmin^{-1}$); **AUC** Area-under-the-plasma-concentration-curve ($ngmlh^{-1}$) corrected for dose expressed per mean body weight ($mgkg^{-1}$).

## II.Application to quantitative risk assessment of thresholded chemicals

The main application of these analyses is to provide regulators and risk managers with sets of pathway-related uncertainty factors (95$^{th}$, 97.5$^{th}$ or 99$^{th}$ centile) relevant to the particular fate of the chemical under assessment in order to replace the default kinetic uncertainty factor. The main advantages of this approach are that regulators and risk managers can now choose from the different percentiles, based on real in vivo data as opposed to the single 3.16 default value (Table 1-4). However, this would require a major change in the philosophy behind calculating ADI values, because the value, by definition

would not cover every member of the exposed population (see below for PMs and subgroups).

For all monomorphic pathways the 3.16 would be too conservative to cover healthy adults up to the 99$^{th}$ centile and this default could be replaced by the relevant pathway-related values (Table 1). In contrast polymorphic pathways (CYP2D6, CYP2C19 and NATs) are of most concern since the 3.16 kinetic default factor is not adequate to cover the general healthy adult population, let alone subgroups of the population. Applying these conclusions, PMs and SAs would be at risk if the parent compound were the proximate toxicant. On the other hand, EMs and FAs (92% of Caucasian for CYP2D6, 97% for CYP2C19 and 30-60% for N-acetylation) would be more at risk if the metabolite were the proximate toxicant. From these observations it would be important to incorporate into the regulatory perspective, data describing *in vitro* metabolism of the particular contaminant under assessment using readily available *in vitro* techniques. This would allow the identification of the CYP isoform(s), as well as the consequences of metabolism (because either EMs/FAs or PMs/SAs could be the potentially susceptible subgroup) (Chapter IV).

A simple scenario would illustrate the latter point. A particular pesticide is metabolised primarily by the CYP2D6 isoform and PMs constitute the potentially susceptible subgroup in the healthy adult population. In this case, pathway-related uncertainty factors developed from our database could be applied in two possible ways:

-The percentage of an oral dose handled by CYP2D6 is unknown in EMs (only *in vitro* data are available). Regulators could apply the CYP2D6-related uncertainty factors developed for the PMs (Chapter IV) with values of 15, 16 and 18 to cover the latter group to the 95$^{th}$, 97.5$^{th}$ or 99$^{th}$ centiles.

-The percentage of an oral dose handled by CYP2D6 is known in EMs (using *in vitro-in vivo* extrapolations or *in vivo* data (unlikely for ethical reasons)). Regulators could then use the relationship between the extent of CYP2D6 metabolism and the uncertainty factors for PMs (Chapter IV) and derive a CYP2D6-related uncertainty factor for the particular chemical. For example, if 25% of an oral dose of the chemical were handled by

CYP2D6 metabolism, an uncertainty factor of 3.14 would be required to cover PMs to the 99$^{th}$ centile.

Another crucial issue in chemical risk assessment is the incorporation of subgroups of the population. Some of the pathway-related uncertainty factors derived from our database for particular subgroups could also be used in the future by regulatory agencies.

An important issue that would require resolution is, "Should regulators apply the pathway-related uncertainty factors developed for healthy adults or values derived from the most potentially susceptible individuals?" All groups of the population have been shown to be potentially susceptible to compounds handled by polymorphic pathways and particular concerns have been raised for CYP2C19, CYP3A4 metabolism in Asian (15-20% CYP2C19 PMs in Asian populations), CYP2D6, CYP2C19, NAT and CYP3A4 in the elderly and CYP2D6, CYP2C19 in children. Neonates would be the most susceptible subgroup for all of these pathways from the point of view that metabolism would be immature after birth (Renwick *et al.,* 2000; Cresteil, 1998; Gow *et al.,* 2001), however reliable data were not available the polymorphic routes. Previous authors have suggested that neonates would need an extra uncertainty factor compared to healthy adults (Renwick, 1998; Renwick *et al.,* 2000). Our database has been able to define more precisely the magnitude of the difference between healthy adults and neonates for only those metabolic pathways: CYP1A2, glucuronidation and renal excretion.

Taking the example of CYP2D6 metabolism discussed previously, the most susceptible individuals (with available data) for this pathway would be children (chapter IV), and an uncertainty factor of 45 would be required to cover this subgroup to the 99$^{th}$ centile. This value has been derived for desipramine and constitutes a near worst-case scenario for CYP2D6 metabolism (70% of CYP2D6 metabolism). One would expect neonates to be even more susceptible than children for this pathway but the small database (n=2) prevents the calculation of reliable quantitative differences. However, this data gap could now be incorporated in chemical risk assessment by regulators who may now be aware that neonates would need an extra uncertainty factor higher than that in children for CYP2D6 metabolism.

Regulators could integrate these data gaps in the risk assessment for chemicals for which metabolism is likely to be a source of variability and health concern (CYP2D6, CYP2C19, NAT, CYP3A4). This conclusion would particularly apply to neonates for polymorphic pathways (CYP2D6, CYP2C19, NAT) and CYP3A4 metabolism. A possibility would be to use the data available for healthy adults and children and the data available in neonates (both *in vitro* and *in vivo*) for all other pathways to predict the magnitude of the difference between neonates and healthy adults. Finally, an analysis of uncertainty for these assumptions could provide a basis for a probabilistic model.

Finally, pathway-related uncertainty factors have been derived for compounds handled by a single major route of elimination (>60%). However, this scenario is unusual and many environmental contaminants are eliminated by several pathways.

A preliminary study (chapter VII) focusing on compounds metabolised by multiple pathways (including polymorphic enzymes) was undertaken to test the validity of a Monte Carlo model, combining the variability for different pathways, to predict the overall variability in kinetics for different compounds. The coefficients of variation in propranolol and diazepam kinetics (eliminated by CYP1A2, CYP2D6, glucuronidation and CYP2C19, CYP3A4 respectively) were calculated by pooling data from individual *in vivo* kinetic studies. The Monte Carlo model output was compared with *in vivo* estimates for both propranolol and diazepam and no major differences in variability were found between the Monte Carlo model and the *in vivo* data. This model, for which further work is required (see next section), shows the potential use of pathway-related variability derived from our database to predict kinetic variability (and therefore uncertainty factors) for compounds handled by multiple pathways.

Such models could be potentially useful tools for regulators especially for environmental contaminants such as pesticides since their metabolism in humans can involve CYP2D6 and CYP3A4 (Sams *et al.*, 2000) resulting in potentially high variability *in vivo* with several potential susceptible subgroups (EMs, PMs, elderly, children, neonates for CYP2D6 metabolism and elderly, neonates and Asian healthy adults for CYP3A4, Chapter IV and V).

## III.Future refinements to pathway-related uncertainty factors

Further work is required to move forward from the default factor approach used for thresholded toxicants and refine the approach developed here. First of all, the analysis of human metabolic pathways was not complete because no probe substrates were found for glutathione-S-tranferases and methyltransferases and further investigation would be required in the future for these two pathways.

The next step would be to include an analysis of human variability in toxicodynamics in order to develop categorical uncertainty factors related to mechanisms of toxicity. Renwick and Lazarus (1998) have developed a limited database largely for therapeutic effects showing that the overall variability for this aspect was 51% resulting in overall defaults of 2.2, 2.6 and 3.1 to cover $95^{th}$, $97.5^{th}$ and $99^{th}$ centile of the general healthy adult population.

The validation of the Monte Carlo model developed in Chapter VII to estimate kinetic variability for compounds metabolised by multiple pathways would constitute another important aspect of this work. First, it would require the identification of probe substrates handled by several pathways for which the metabolism has been well characterized (based on urinary excretion data and in vitro data with identifying the specific isoforms involved in metabolism). The kinetic data for all these probe substrates in healthy adults and subgroups of the population (differences between phenotypes (polymorphic pathways), interethnic differences, effects of age (neonates, infants, children and the elderly)) could be analysed and compared to the Monte Carlo model for each compound. In addition, compounds with low clearances and compounds with high clearances (variability which depends on liver blood flow rather than enzyme activity) could also be looked at separately to quantify the effect of liver blood flow on human variability for single and multiple metabolic pathways.

Finally, regulators throughout the world have recognized the potential advantage of moving away from the default factors (point estimation) to probabilistic models (Slob and Pieters., 1998, Swartout *et al.,* 1998). The main advantages of such an analysis is that it will allow regulators to move away from default uncertainty factors without the need for *in vivo* toxicokinetic studies in humans. Probabilistic multiplication of the distributions of the pathway-related defaults available in our database with the distribution of the dynamic default derived from Renwick and Lazarus (1998) can be carried out to derive

combined probability distributions to replace the 10-fold uncertainty factors. These analyses should be undertaken for compounds handled by a single pathway and for compounds eliminated by multiple pathways.

# Conclusion

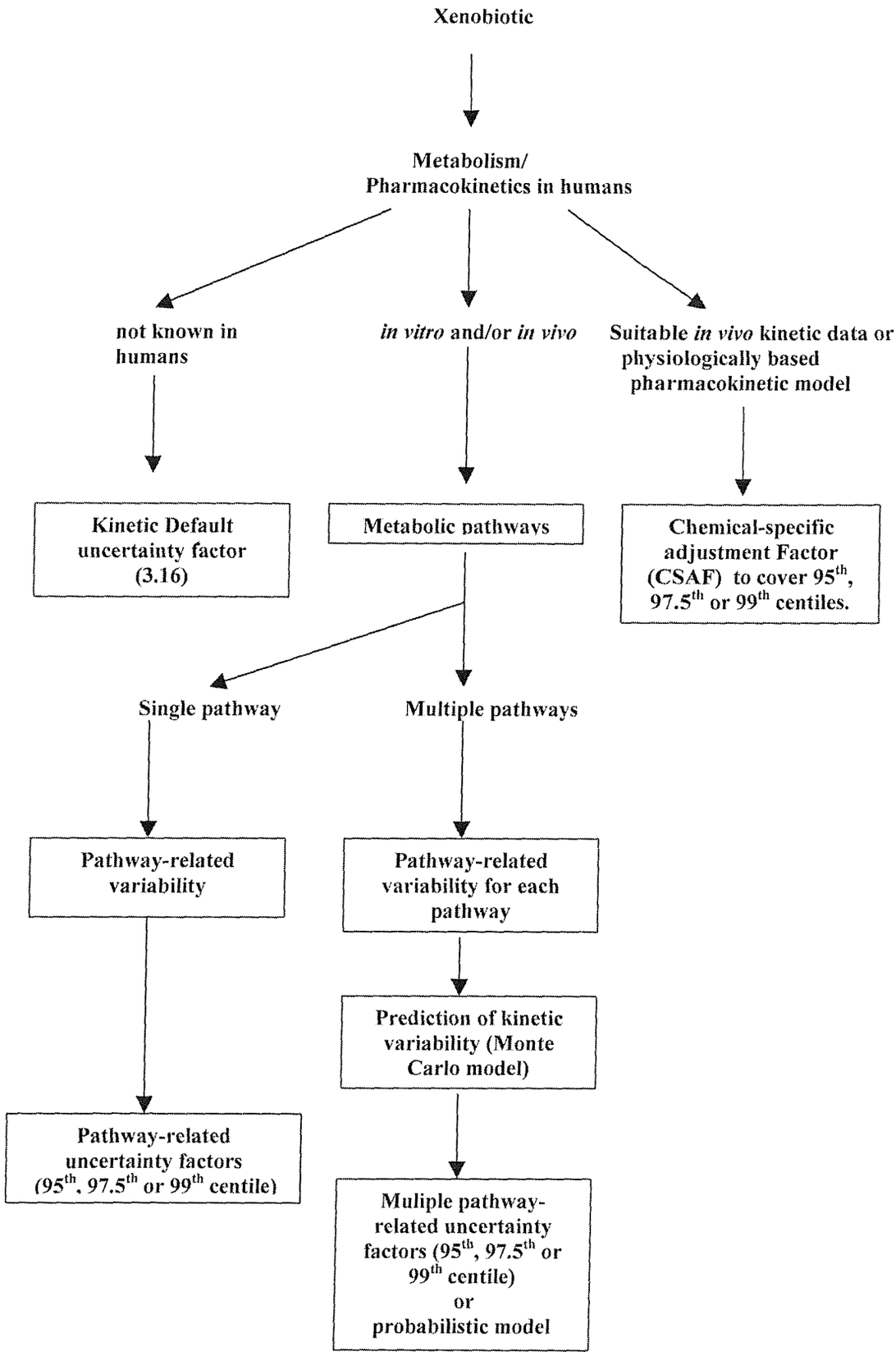
These analyses of human variability in kinetics for the main metabolic pathways have enabled the derivation of pathway-related uncertainty factors for healthy adults and subgroups of the population to move away from the kinetic default factor (3.16).

Figure 1 summarises the approach developed in this work and its applications for chemical risk assessment. The levels of refinement of the uncertainty factor would depend on the data available for the chemical (knowledge-based). The worse case scenario would be that no data describing the metabolism /kinetics of the compound under assessment were available, and the use of the standard kinetic default (3.16) would be appropriate. However, many *in vitro* techniques are available to investigate the metabolism of xenobiotics, and therefore the kinetic default could already be replaced by pathway-related uncertainty factors depending on which particular enzyme(s) was/were responsible for the metabolism of the compound. For compounds handled by multiple pathways, the validation of a Monte Carlo model (Chapter VII), aiming to predict the overall variability in kinetics using pathway-related variability, would provide (multiple) pathway-related (chemical-related) uncertainty factors as percentile values. In the furture, this model could also be refined to a probabilistic model incorporating the uncertainty in metabolism for polymorphic pathways in phenotyped individuals.

Ideally, databases describing the metabolism and/or toxicokinetics of a particular chemical in humans would be used to derive the internal body burden, or to build a physiologically-based pharmacokinetic model. The incorporation of such data would enable to derive chemical-specific adjustment factors.

Finally, the concepts of this flexible framework could also be applied to the analysis of human variability in toxicodynamics.

**Figure 1 Knowledge-based framework to derive uncertainty factors accounting for human variability in kinetics**



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## Chapter III: Human variability in glucuronidation in relation to uncertainty factors for risk assessment

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## Chapter IV: Human variability in polymorphic CYP2D6 metabolism: is the 3.16 kinetic default factor still relevant ?

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## Chapter V: Human variability in CYP3A4 metabolism and CYP3A4-related default uncertainty factors

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## Chapter VI: Human variability in Phase I, Phase II metabolic pathways and renal excretion

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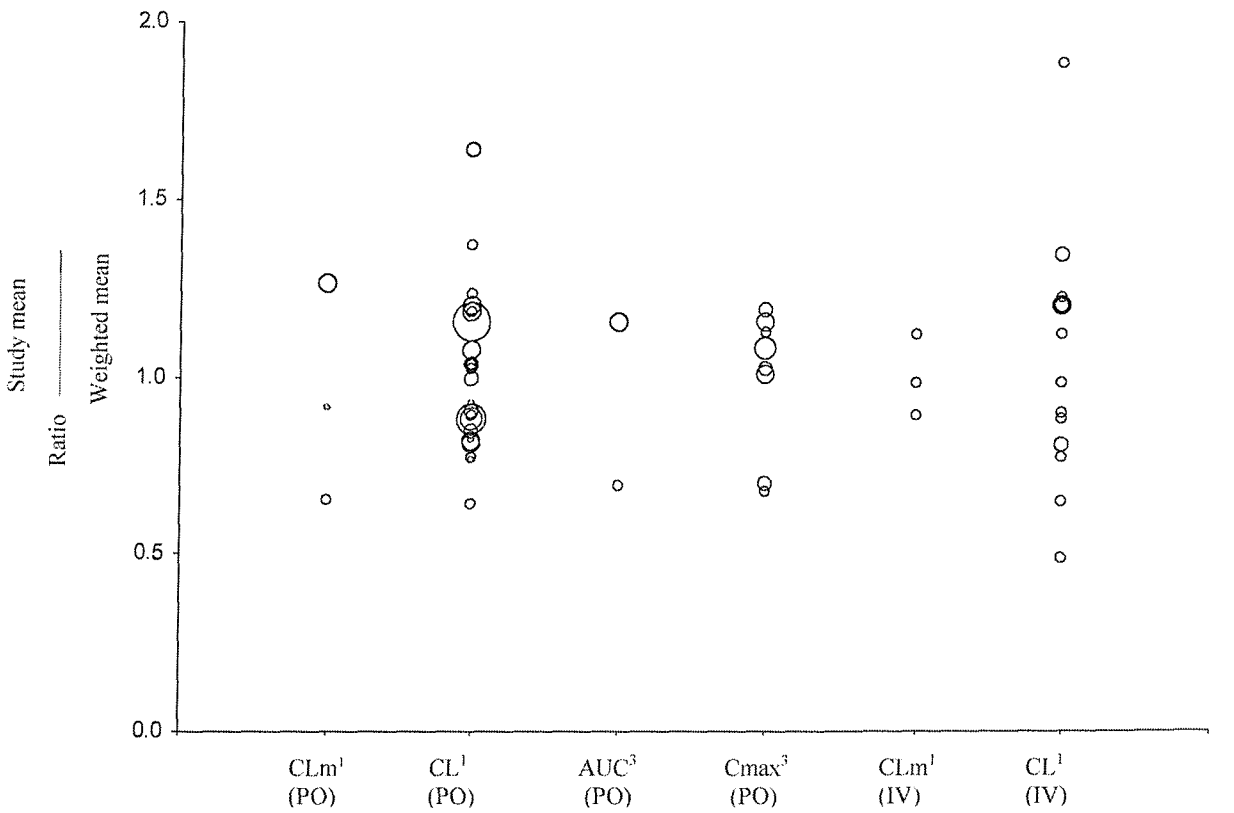
# Appendix

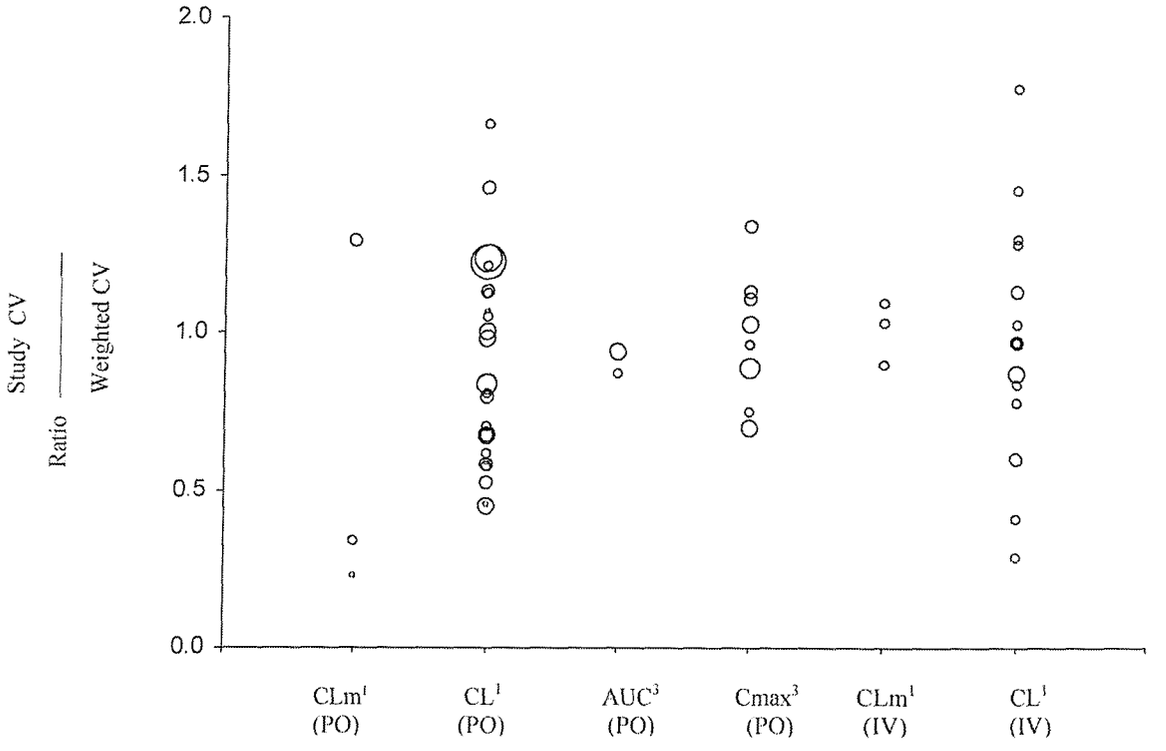
## Human variability in Phase I, Phase II and renal excretion: Inter-study variation in healthy adults

**Figure 1. Inter-study variation in kinetic parameters for CYP1A2 probe substrates after oral administration and intravenous in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



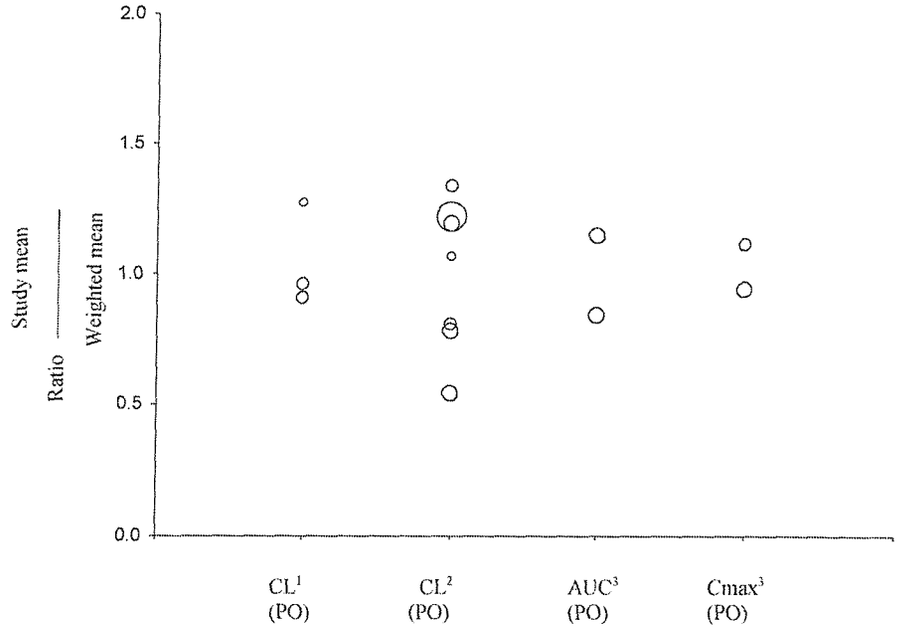

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; CLm: Metabolic clearance; CL: total Clearance; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [3]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CLm^1$ (PO)-data for theobromine (3 studies); $CL^1$ (PO)-data for caffeine ( 12 studies), theophylline (6 studies) and theobromine (6 studies); $AUC^2$ -data for theophylline (2 studies); $Cmax^3$-data for Caffeine (3 studies) and theophylline (2 studies); $CLm^1$(IV) -data for theophylline (3 studies), $CL^1$(IV) -data for Caffeine (2 studies) and theophylline (12 studies).

**Figure 2. Inter-study variation in kinetic parameters for CYP1A2 probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



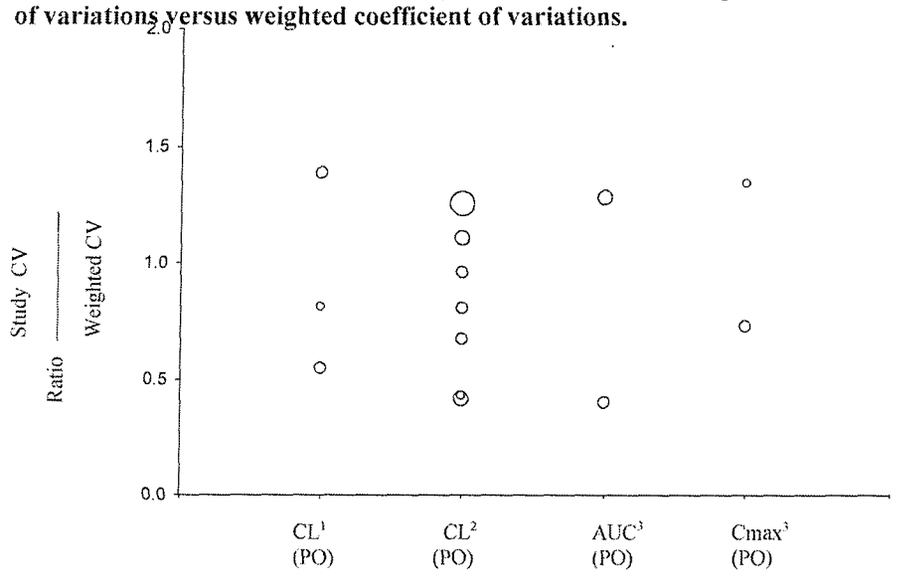

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; CLm: Metabolic clearance; CL: total Clearance; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [3]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CLm^1$ (PO)-data for theobromine (3 studies); $CL^1$ (PO)-data for caffeine ( 12 studies), theophylline (6 studies) and theobromine (6 studies); $AUC^2$ -data for theophylline (2 studies); $Cmax^3$-data for Caffeine (3 studies) and theophylline (2 studies); $CLm^1$(IV) -data for theophylline (3 studies), $CL^1$(IV) -data for Caffeine (2 studies) and theophylline (12 studies).

**Figure 3. Inter-study variation in kinetic parameters for CYP2C9 probe substrates after oral administration and intravenous in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



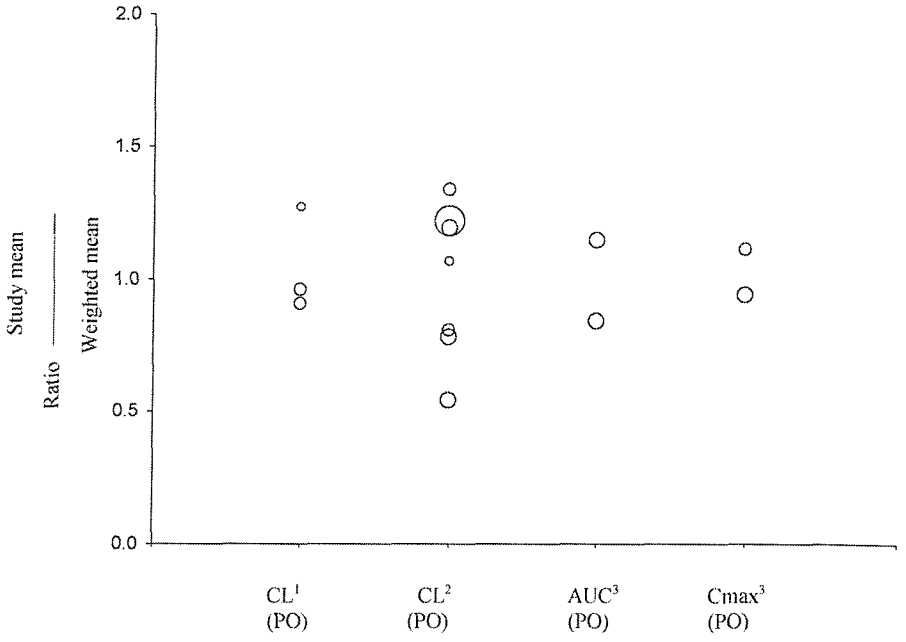

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for tolbutamide (3 studies); $CL^2$ (PO)-data for S-warfarin (7 studies); $AUC^3$ -data for tolbutamide (2 studies); $Cmax^4$-data for tolbutamide (3 studies).

**Figure 4. Inter-study variation in kinetic parameters for CYP2C9 probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



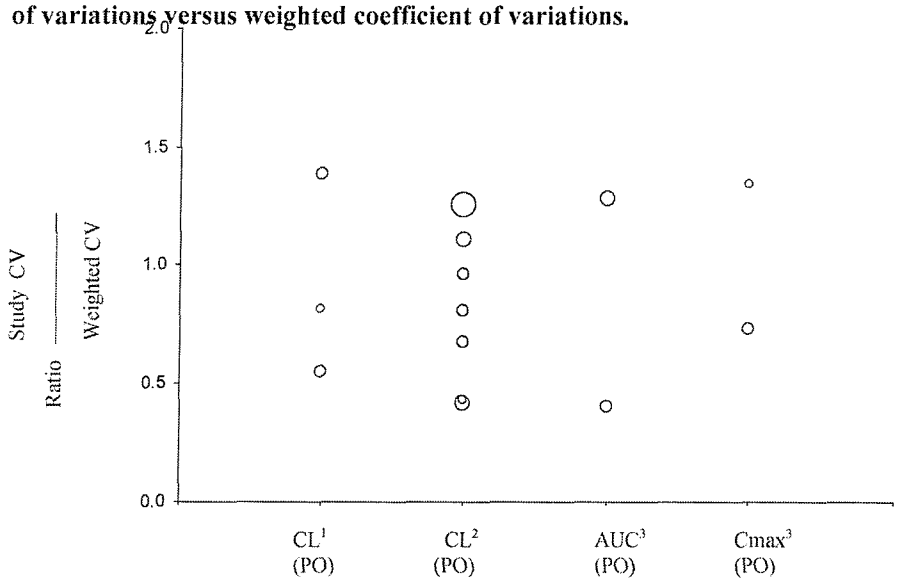

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for tolbutamide (3 studies); $CL^2$ (PO)-data for S-warfarin (7 studies); $AUC^3$ -data for tolbutamide (2 studies); $Cmax^4$-data for tolbutamide (3 studies).

**Figure 3. Inter-study variation in kinetic parameters for CYP2C9 probe substrates after oral administration and intravenous in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



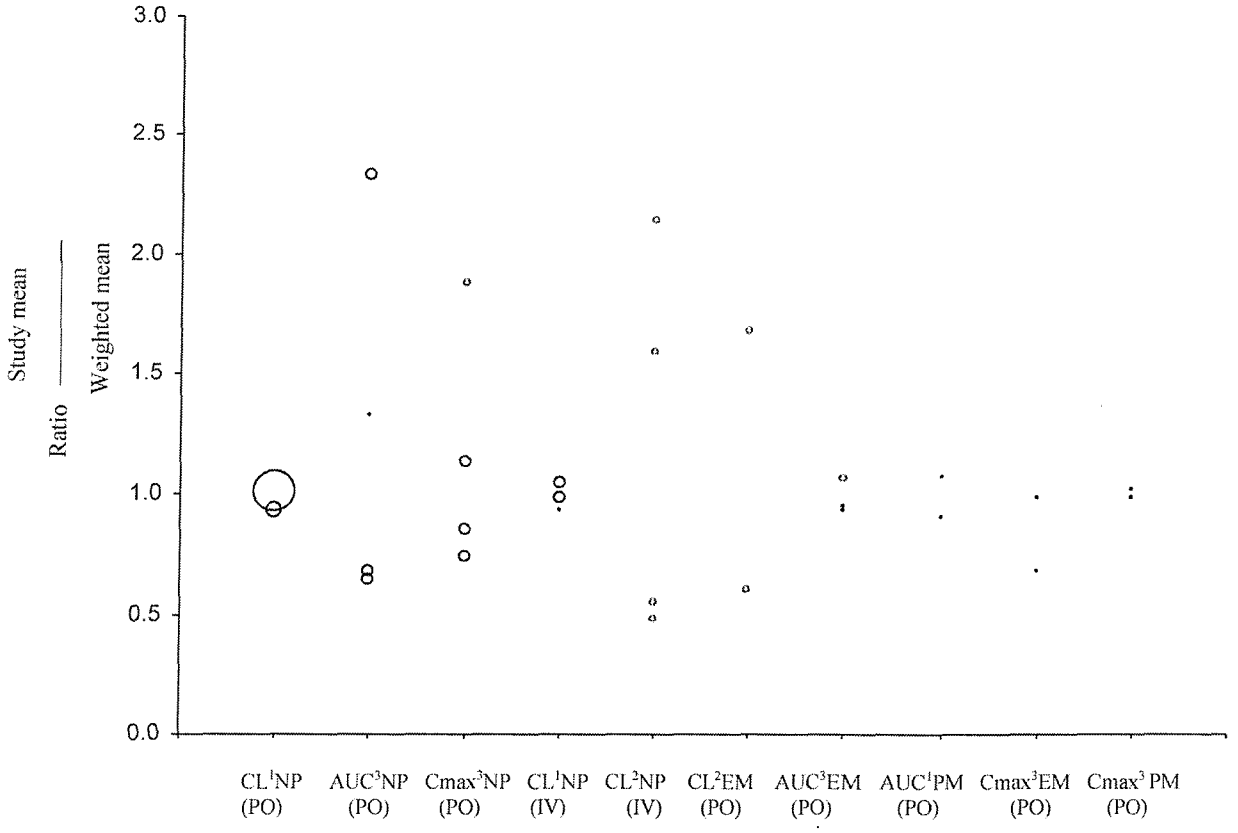

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for tolbutamide (3 studies); $CL^2$ (PO)-data for S-warfarin (7 studies); $AUC^3$ -data for tolbutamide (2 studies); $Cmax^4$-data for tolbutamide (3 studies).

**Figure 4. Inter-study variation in kinetic parameters for CYP2C9 probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



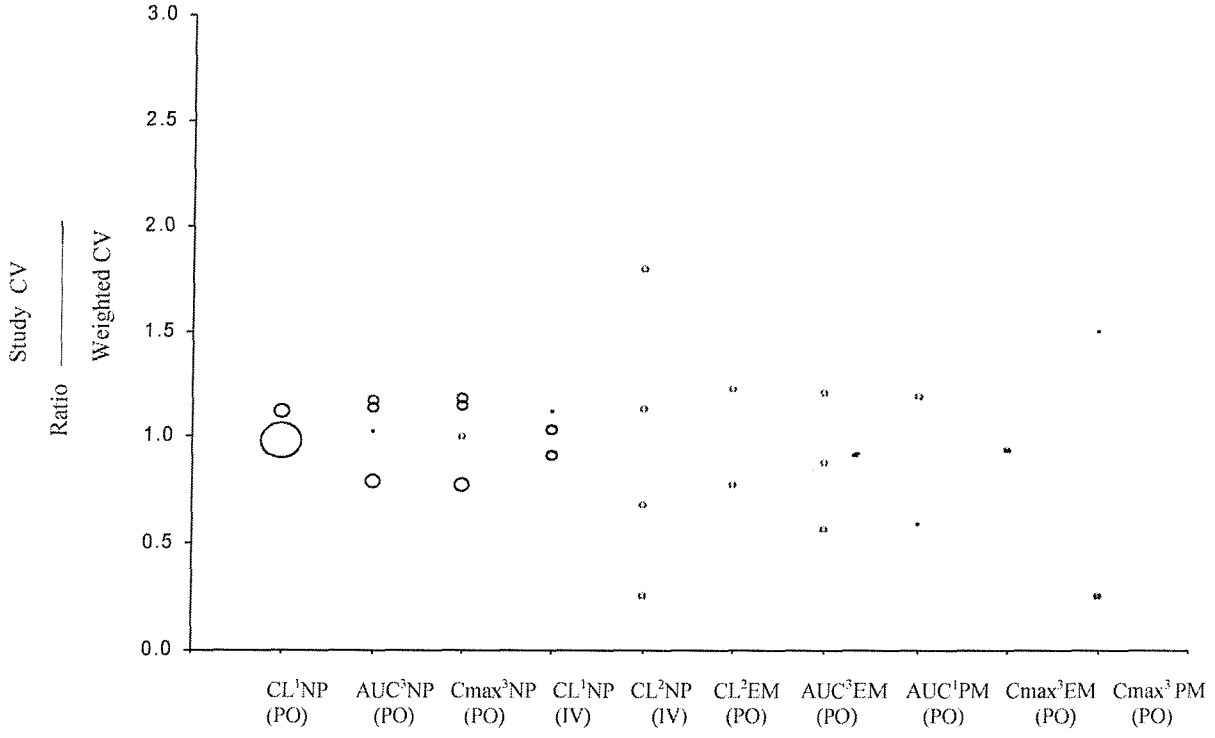

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for tolbutamide (3 studies); $CL^2$ (PO)-data for S-warfarin (7 studies); $AUC^3$ -data for tolbutamide (2 studies); $Cmax^4$-data for tolbutamide (3 studies).

**Figure 5. Inter-study variation in kinetic parameters for CYP2C19 probe substrates after oral administration and intravenous in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



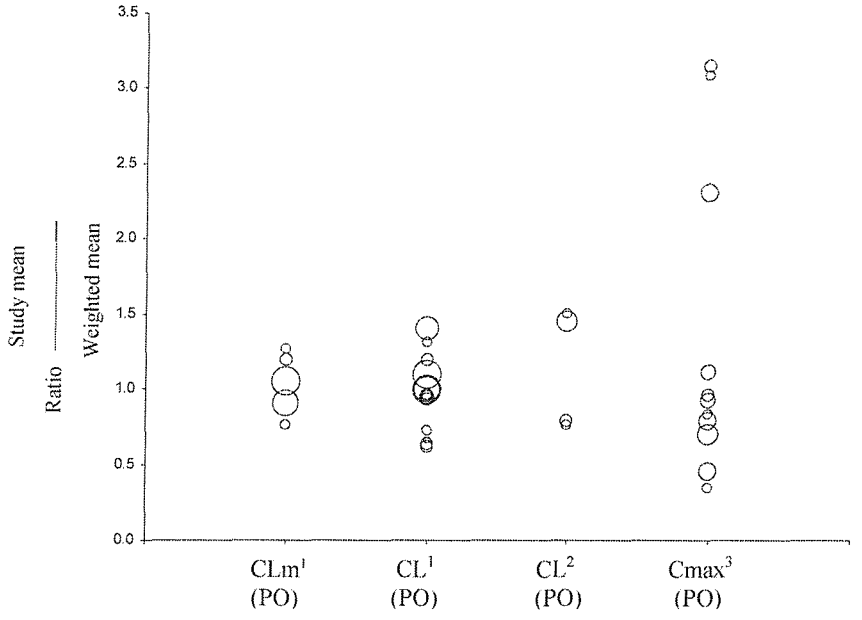

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; NP non-phenotyped individuals; EM Extensive metabolisers of S-mephenytoin; PM Poor metabolisers of S-mephenytoin; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^{1}$ (PO)-data for hexobarbital (2 studies); $AUC^{3}NP$ (PO)-data for omeprazole (4 studies); $Cmax^{3}NP$ (PO)-data for omeprazole (4 studies); $CL^{1}NP$ (IV)-data for hexobarbital (3 studies); $CL^{2}NP$ (IV)-data for omeprazole (4 studies); $CL^{2}EM$ -data for S-mephenytoin (2 studies); $AUC^{3}EM$ (PO) -data for omeprazole (3 studies); $AUC^{3}PM$ (PO)-data for omeprazole (2 studies); $Cmax^{4}EM$ (PO)-data for omeprazole (2 studies); $Cmax^{4}PM$ (PO) -data for omeprazole (2 studies).

**Figure 6. Inter-study variation in kinetic parameters for CYP2C19 probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



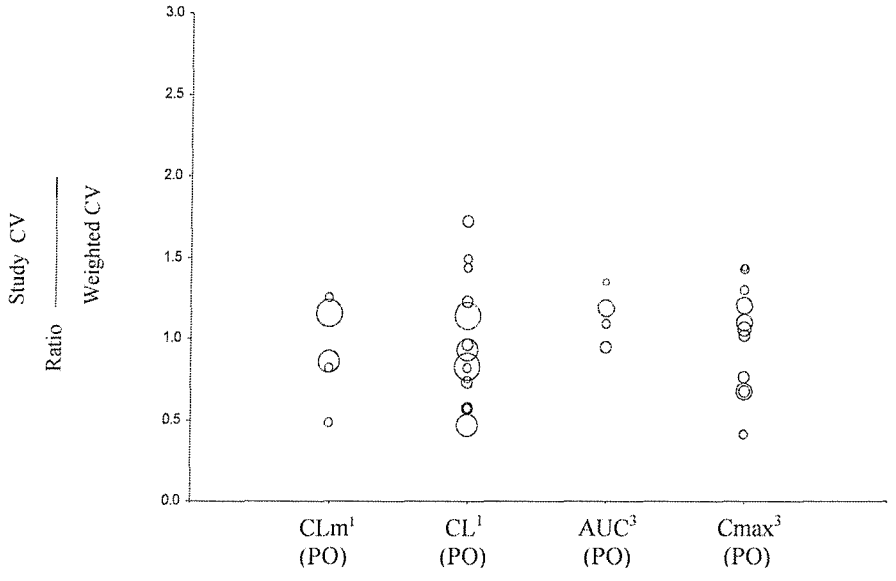

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; NP non-phenotyped individuals; EM Extensive metabolisers of S-mephenytoin; PM Poor metabolisers of S-mephenytoin; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^{1}$ (PO)-data for hexobarbital (2 studies); $AUC^{3}NP$ (PO)-data for omeprazole (4 studies); $Cmax^{3}NP$ (PO)-data for omeprazole (4 studies); $CL^{1}NP$ (IV)-data for hexobarbital (3 studies); $CL^{2}NP$ (IV)-data for omeprazole (4 studies); $CL^{2}EM$ -data for S-mephenytoin (2 studies); $AUC^{3}EM$ (PO) -data for omeprazole (3 studies); $AUC^{3}PM$ (PO)-data for omeprazole (2 studies); $Cmax^{4}EM$ (PO)-data for omeprazole (2 studies); $Cmax^{4}PM$ (PO) -data for omeprazole (2 studies).

**Figure 7. Inter-study variation in kinetic parameters for CYP2E1 probe substrates after oral administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



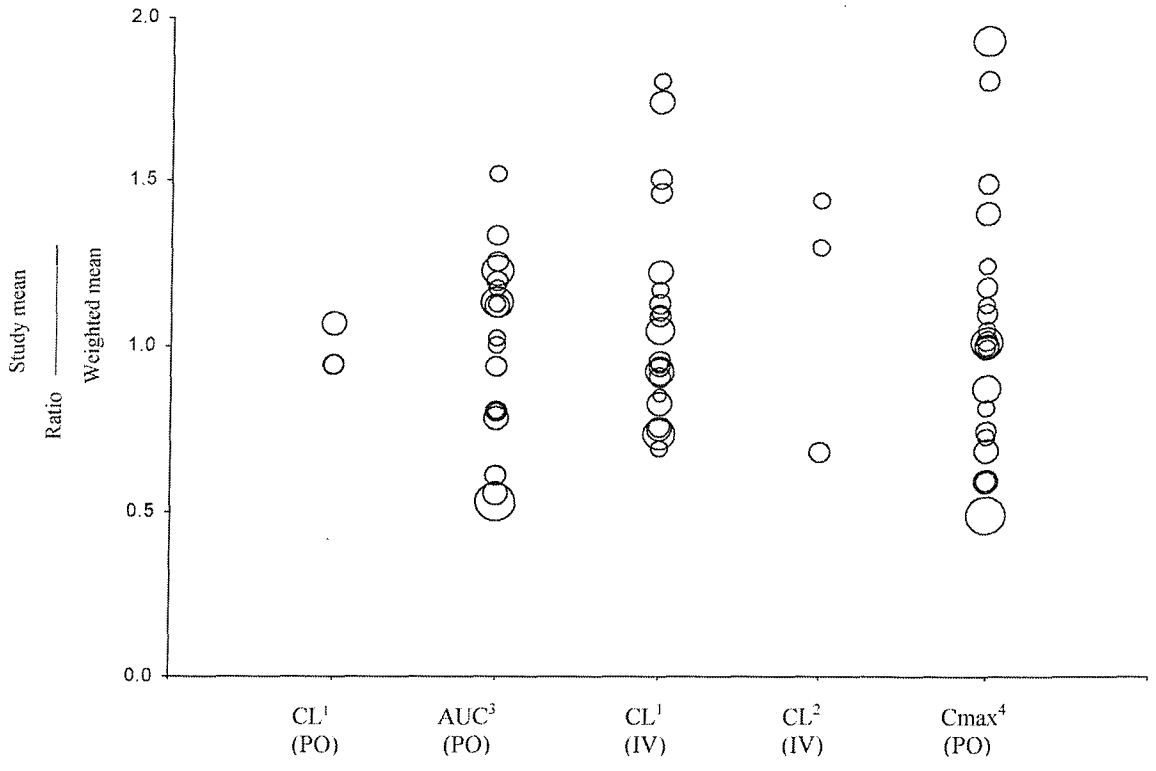

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; CLm[1] Metabolic clearance ($ml.min^{-1}kg^{-1}$); CL[1] Total Clearance ($ml.min^{-1}kg^{-1}$); CL[2] Total Clearance $(ml.min^{-1})^2$AUC/dose ($ngml^{-1}h$); [3]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); CLm[1] (PO)-data for chlorozoxazone (5 studies); CL[1] (PO)-data for chlorozoxazone (6 studies) and trimethadione (8 studies); AUC[2] -data for chlorozoxazone (2 studies) and trimethadione (2 studies); Cmax[3](PO) -data for chlorozoxazone (8 studies) and trimethadione (3 studies).

**Figure 8. Inter-study variation in kinetic parameters for CYP2E1 probe substrates after oral in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



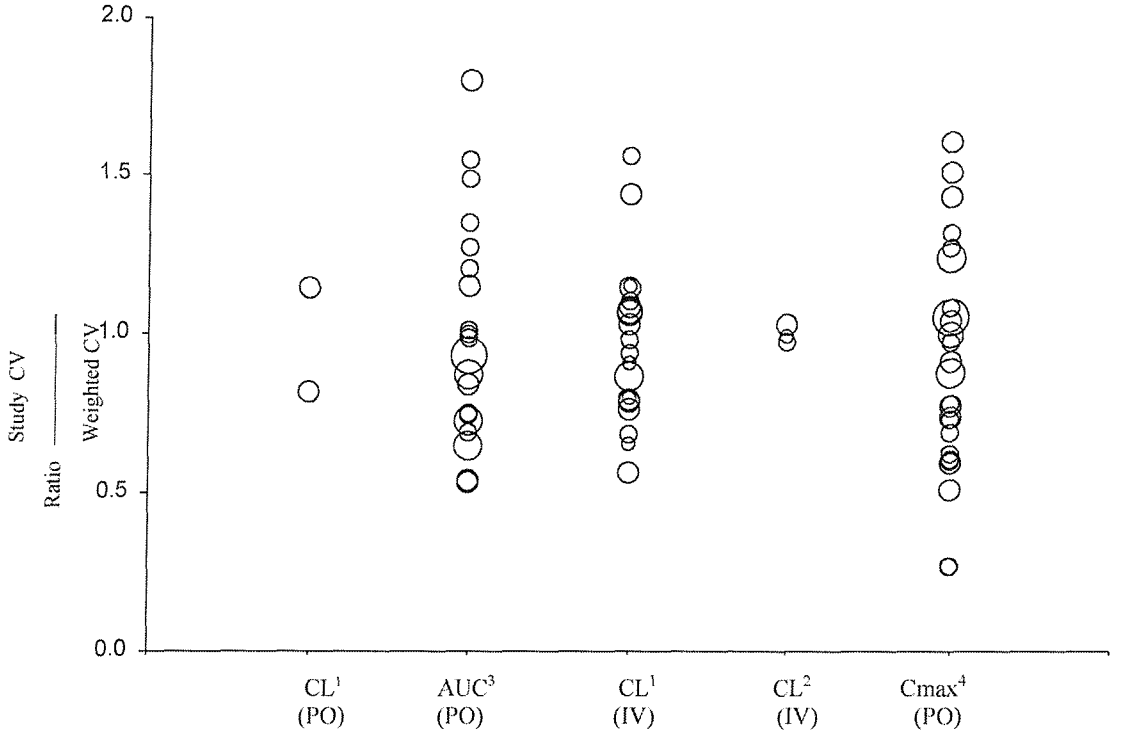

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; CLm[1] Metabolic clearance ($ml.min^{-1}kg^{-1}$); CL[1] Total Clearance ($ml.min^{-1}kg^{-1}$); CL[2] Total Clearance $(ml.min^{-1})^2$AUC/dose ($ngml^{-1}h$); [3]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); CLm[1] (PO)-data for chlorozoxazone (5 studies); CL[1] (PO)-data for chlorozoxazone (6 studies) and trimethadione (8 studies); AUC[2] -data for chlorozoxazone (2 studies) and trimethadione (2 studies); Cmax[3](PO) -data for chlorozoxazone (8 studies) and trimethadione (3 studies).

**Figure 9. Inter-study variation in kinetic parameters for metabolism via hydrolysis after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



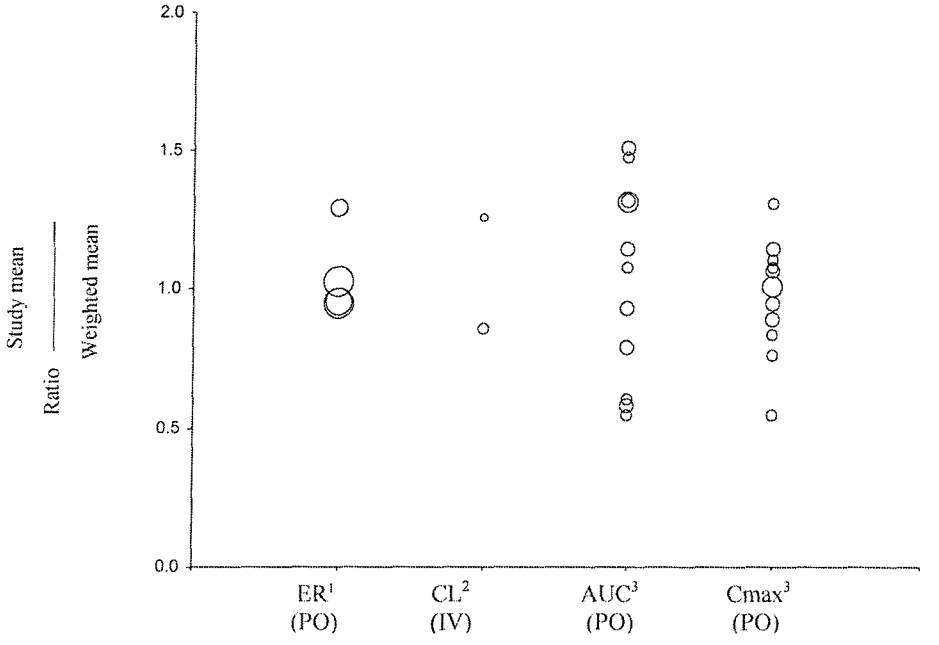

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for aspirin (2 studies); $AUC^3$ (PO)-data for aspirin (9 studies), fosinopril (9 studies) and flumazenil (2 studies); $CL^1$ (IV) -data for cocaine (3 studies), esmolol (3 studies), etodimate (7 studies), flestolol (2 studies), fosinopril (3 studies), flumazenil (3 studies); $CL^2$ (IV) -data for cocaine (3 studies); $Cmax^3$-data for aspirin (13 studies), fosinopril (9 studies) and flumazenil (2 studies).

**Figure 10. Inter-study variation in kinetic parameters for metabolism via hydrolysis after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



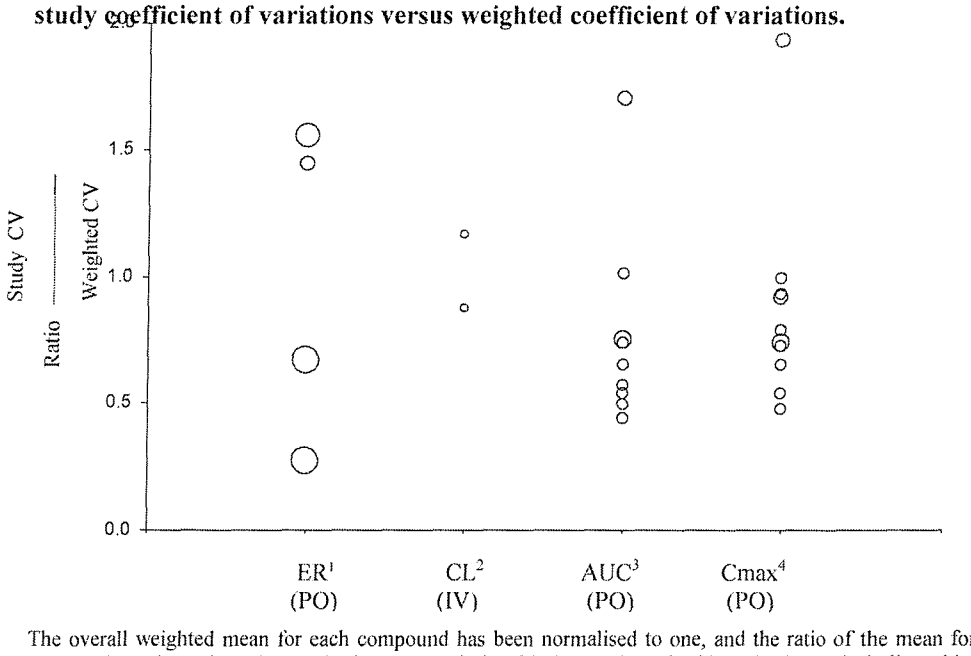

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; CL: total Clearance; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for aspirin (2 studies); $AUC^3$ (PO)-data for aspirin (9 studies), fosinopril (9 studies) and flumazenil (2 studies); $CL^1$ (IV) -data for cocaine (3 studies), esmolol (3 studies), etodimate (7 studies), flestolol (2 studies), fosinopril (3 studies), flumazenil (3 studies); $CL^2$ (IV) -data for cocaine (3 studies); $Cmax^3$-data for aspirin (13 studies), fosinopril (9 studies) and flumazenil (2 studies).

**Figure 11. Inter-study variation in kinetic parameters for metabolism via Alcohol dehydrogenase after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



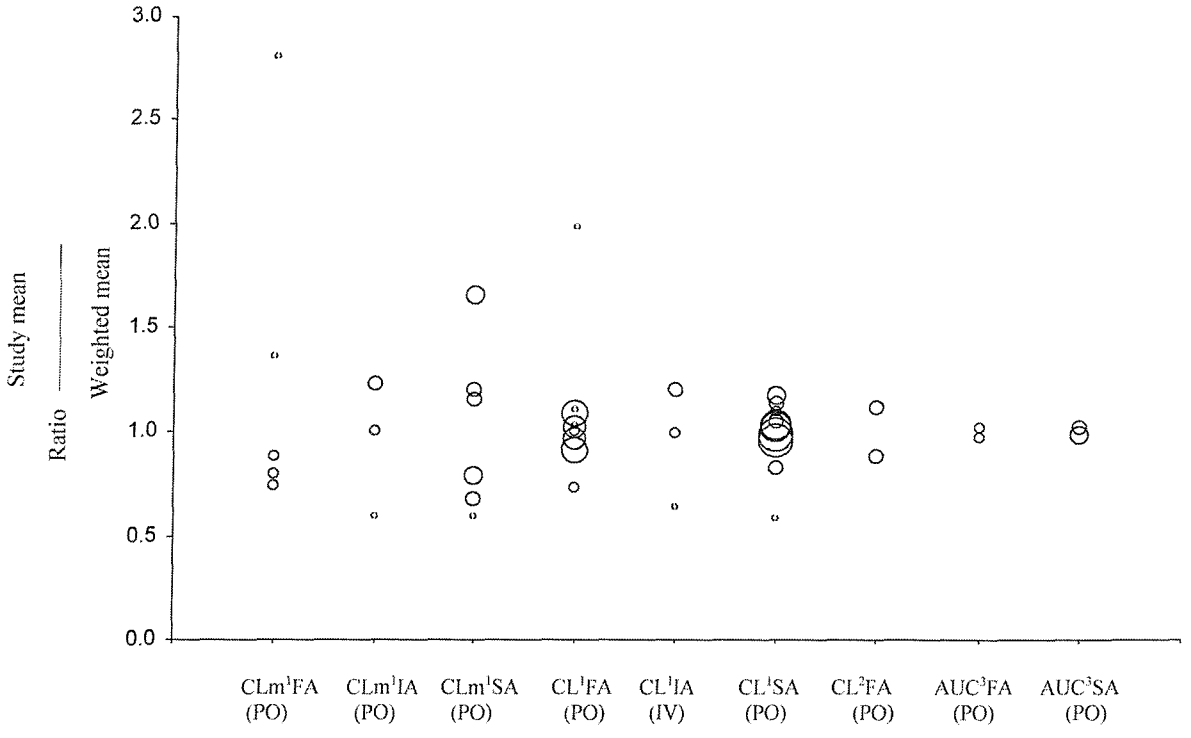

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; ER[1] Elimination Rate ($g.min^{-1}kg^{-1}$); CL[2] total Clearance ($ml.min^{-1}kg^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); ER[1] (PO)-data for Ethanol (3 studies); CL[1] (IV)-data for Ethanol (2 studies); AUC[2] -data Ethanol (11 studies); Cmax[4](PO)- data for Ethanol (9 studies).

**Figure 12. Inter-study variation in kinetic parameters for metabolism via Alcohol dehydrogenase after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



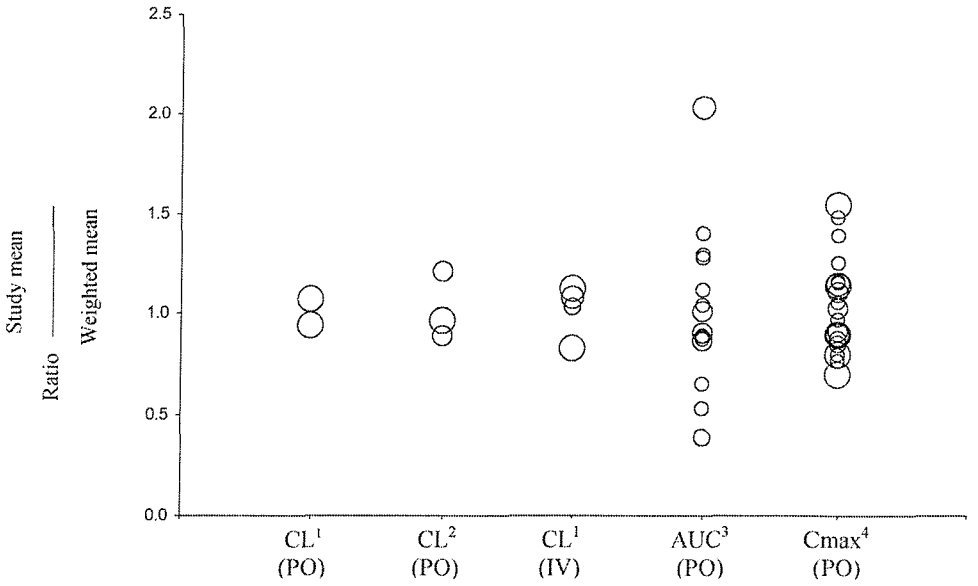

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; ER[1] Elimination Rate ($g.min^{-1}kg^{-1}$); CL[2] total Clearance ($ml.min^{-1}kg^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); ER[1] (PO)-data for Ethanol (3 studies); CL[1] (IV)-data for Ethanol (2 studies); AUC[2] -data Ethanol (11 studies); Cmax[4](PO)- data for Ethanol (9 studies).

**Figure 13. Inter-study variation in kinetic parameters for N-acetyltransferase probe substrates after oral administration in phenotyped healthy adult volunteers (Fast, Intermediate and Slow acetylators). Comparisons of individual study means versus weighted geometric means.**



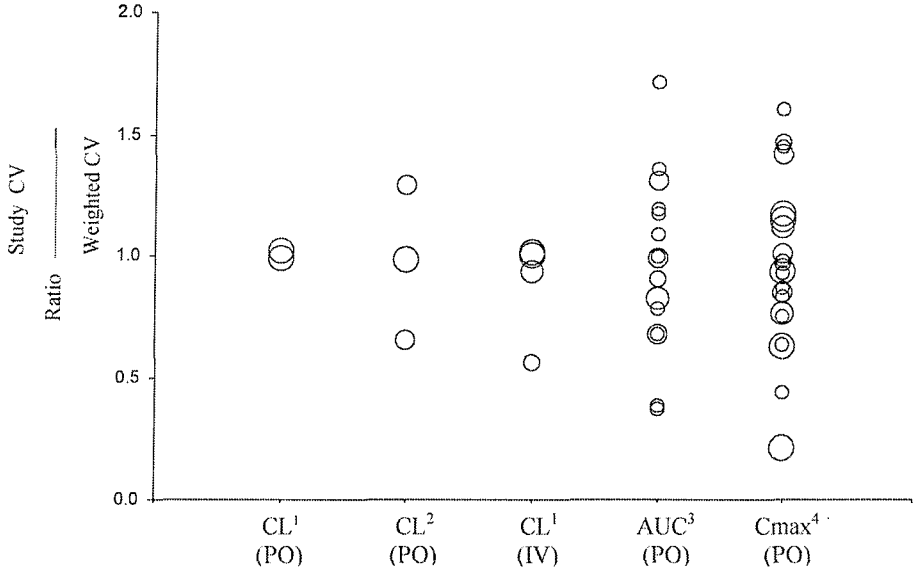

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; CLm Metabolic Clearance; CL Total Clearance; FA Fast acetylators; IA Intermediate acetylators; SA Slow acetylators; [1]Clearance ($ml.min^{-1}kg^{-1}$); [2]Clearance ($ml.min^{-1}$); [3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); $CLm^1$ FA (PO)- data for Sulphametazine (5 studies); $CLm^1$ IA (PO)- data for Sulphametazine (3 studies); $CLm^1$ SA (PO)- data for Sulphametazine (6 studies); $CL^1$ FA (PO)- data for isoniazid (6 studies), Sulphametazine (3 studies); $CL^1$ IA (PO)- data for Sulphametazine (3 studies); $CL^1$ FA (PO)- data for isoniazid (6 studies), Sulphametazine (4 studies); $CL^2$ FA (PO)- data for isoniazid (2 studies); $AUC^3$ FA (PO)- data for Sulphametazine (2 studies); $AUC^3$ SA (PO)- data for Sulphametazine (2 studies.

**Figure 15. Inter-study variation in kinetic parameters for Glycine conjugation probe substrates after oral administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



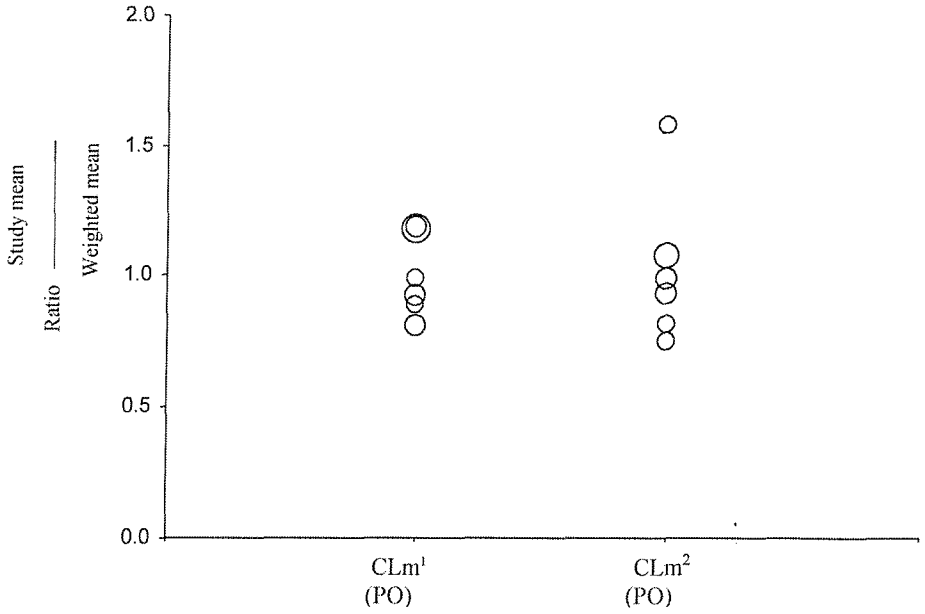

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle;; CL: total Clearance; [1]Clearance ($ml.min^{-1}kg^{-1}$) [2]Clearance ($ml.min^{-1}$);[3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for Salicylate (2 studies); $CL^2$ (PO)-data for Salicylate (2 studies); $CL^1$ (IV)-data for Salicylate (4 studies); $AUC^3$ -data for Salicylate (15 studies); $Cmax^3$-data for Salicylate (21 studies).

**Figure 16. Inter-study variation in kinetic parameters for salicylate probe substrates after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



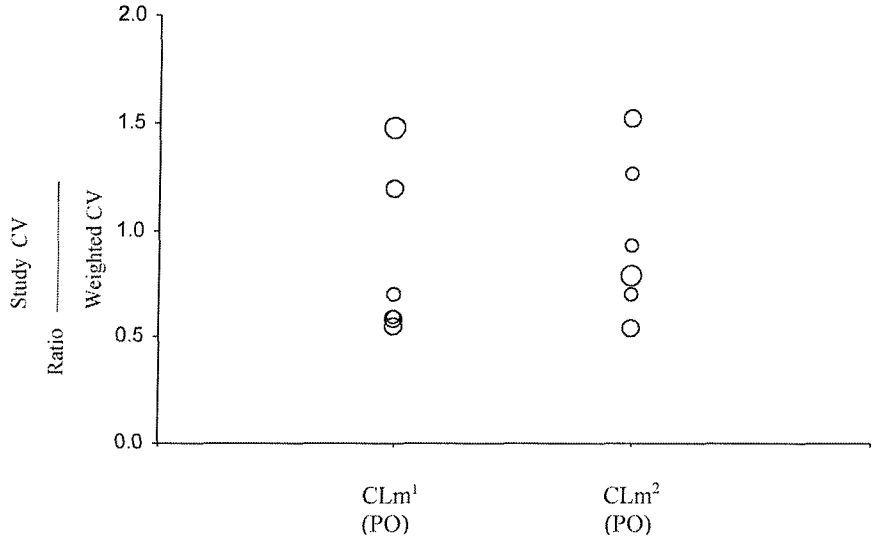

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle;; CL: total Clearance; [1]Clearance ($ml.min^{-1}kg^{-1}$) [2]Clearance ($ml.min^{-1}$);[3]AUC/dose ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [4]Cmax/dose ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CL^1$ (PO)-data for Salicylate (2 studies); $CL^2$ (PO)-data for Salicylate (2 studies); $CL^1$ (IV)-data for Salicylate (4 studies); $AUC^3$ -data for Salicylate (15 studies); $Cmax^3$-data for Salicylate (21 studies).

**Figure 17. Inter-study variation in metabolic clearances for Sulphate conjugation after oral administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**



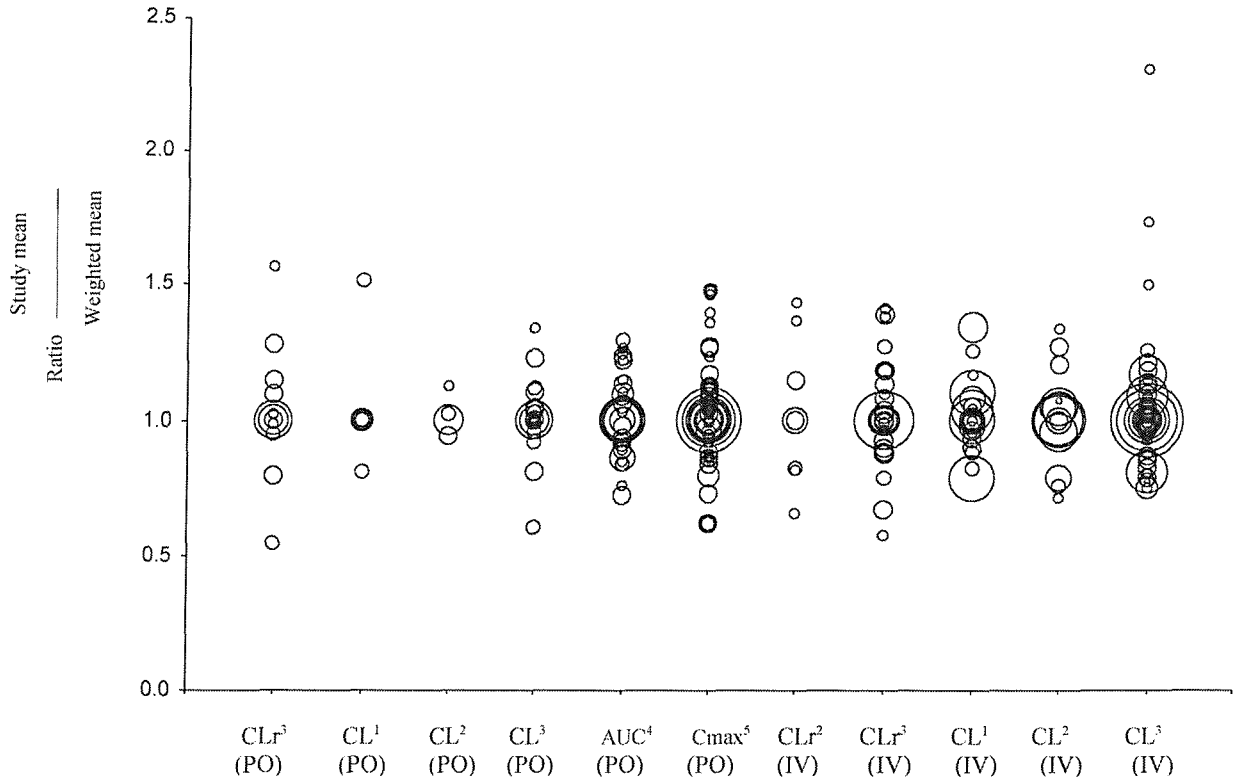

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; $CLm^1$ Metabolic Clearance ($ml.min^{-1}kg^{-1}$) $CLm^2$ Metabolic Clearance ($ml.min^{-1}$) ; $CLm^1$ (PO)-data for paracetamol (6 studies); $CLm^2$ (PO)-data for diflunisal (3 studies) and paracetamol (3 studies).

**Figure 18. Inter-study variation in metabolic clearances for Sulphate conjugation after oral administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**



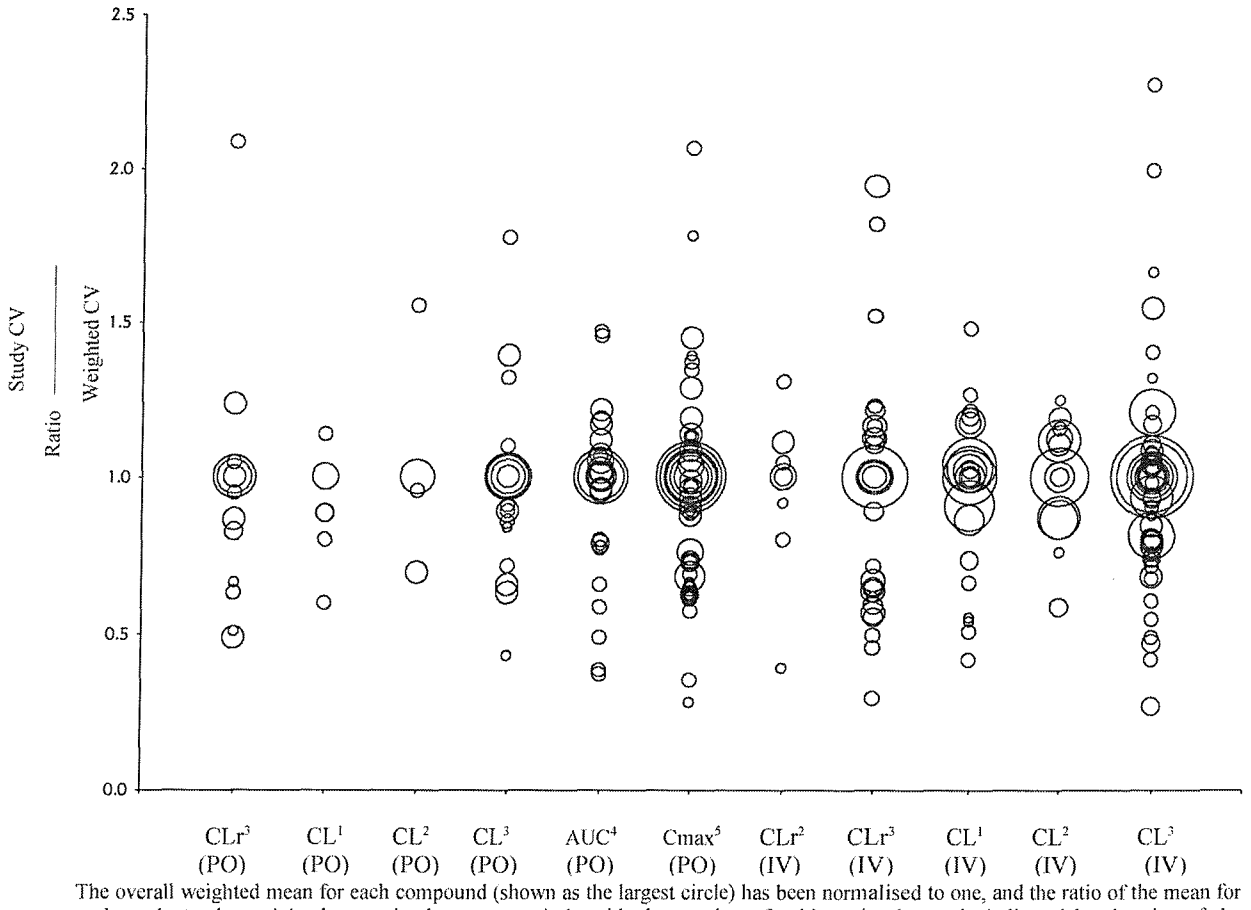

The overall weighted mean for each compound has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle; $CLm^1$ Metabolic Clearance ($ml.min^{-1}kg^{-1}$) $CLm^2$ Metabolic Clearance ($ml.min^{-1}$) ; $CLm^1$ (PO)-data for paracetamol (6 studies); $CLm^2$ (PO)-data for diflunisal (3 studies) and paracetamol (3 studies).

**Figure 19. Inter-study variation in kinetic parameters for compounds handled by renal excretion after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study means versus weighted geometric means.**




The overall weighted mean for each compound (shown as the largest circle) has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle.[1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}.1.73m^{-2}$; [3]Clearance expressed in $ml.min^{-1}$; [4]AUC/dose expressed as $(ngml^{-1}h)$ corrected for dose and body weight $(mgkg^{-1})$; [5]Cmax/dose expressed as $(ngml^{-1})$ corrected for dose and body weight $(mgkg^{-1})$; $CLr^3$ (PO)–data for ciprofloxacin (4 studies), fluconazole (3 studies) and ofloxacin (6 studies); $CL^1$(PO)–data for lomefloxacin (3 studies), and ofloxacin (3 studies); $CL^2$(PO)–data for lomefloxacin (3 studies); $CL^3$(PO)–data for ciprofloxacin (4 studies), fluconazole (3 studies) , lomefloxacin (6 studies) and ofloxacin (6 studies); $AUC^4$(PO)–data for amoxicillin (7 studies), ampicillin (3 studies), ciprofloxacin (3 studies), fluconazole (6 studies) and lomefloxacin (8 studies); $Cmax^5$(PO)–data for amoxicillin (5 studies), ampicillin (4 studies), ciprofloxacin (7 studies), fluconazole (6 studies) , lomefloxacin (18 studies) and ofloxacin (2 studies); $CLr^2$ (IV)–data for ciprofloxacin (3 studies), gentaimicin (3 studies) and piperacillin (3 studies); $CLr^3$(IV)–data for ampicillin (4 studies), cefazolin (3 studies), cefpirome (4 studies), ciprofloxacin (10 studies), piperacillin (3 studies) and trobamycin (4 studies); $CL^1$(IV)–data for ampicillin (3 studies), cefazolin (3 studies), cefpirome (4 studies), ciprofloxacin (10 studies), genatmicin (7 studies), ofloxacin (3 studies), piperacillin (3 studies) and trobamycin (5 studies); $CL^2$(IV)–data for acyclovir (5 studies), ampicillin (3 studies), cefazolin (3 studies), gentamicin (3 studies), and piperacillin (3 studies); $CL^3$(IV)–data for ampicillin (4 studies), cefazolin (4 studies),cefpirome (10 studies), ciprofloxacin (12 studies) gentamicin (4 studies), ofloxacin (3 studies), piperacillin (5 studies) and trobamycin (6 studies).

**Figure 20. Inter-study variation in kinetic parameters for compounds handled by renal excretion after oral and intravenous administration in healthy adult volunteers. Comparisons of individual study coefficient of variations versus weighted coefficient of variations.**




The overall weighted mean for each compound (shown as the largest circle) has been normalised to one, and the ratio of the mean for each study to the weighted mean is shown as a circle with the number of subjects in the study indicated by the size of the circle. [1]Clearance expressed in $ml.min^{-1}kg^{-1}$; [2]Clearance expressed in $ml.min^{-1}.1.73m^{-2}$; [3]Clearance expressed in $ml.min^{-1}$; [4]AUC/dose expressed as ($ngml^{-1}h$) corrected for dose and body weight ($mgkg^{-1}$); [5]Cmax/dose expressed as ($ngml^{-1}$) corrected for dose and body weight ($mgkg^{-1}$); $CLr^3$ (PO)–data for ciprofloxacin (4 studies), fluconazole (3 studies) and ofloxacin (6 studies); $CL^1$(PO)–data for lomefloxacin (3 studies), and ofloxacin (3 studies); $CL^2$(PO)–data for lomefloxacin (3 studies); $CL^3$(PO)–data for ciprofloxacin (4 studies), fluconazole (3 studies) , lomefloxacin (6 studies) and ofloxacin (6 studies); $AUC^4$(PO)–data for amoxicillin (7 studies), ampicillin (3 studies), ciprofloxacin (3 studies), fluconazole (6 studies) and lomefloxacin (8 studies); $Cmax^5$(PO)–data for amoxicillin (5 studies), ampicillin (4 studies), ciprofloxacin (7 studies), fluconazole (6 studies) , lomefloxacin (18 studies) and ofloxacin (2 studies); $CLr^2$ (IV)–data for ciprofloxacin (3 studies), gentaimicin (3 studies) and piperacillin (3 studies); $CLr^3$(IV)–data for ampicillin (4 studies), cefazolin (3 studies), cefpirome (4 studies), ciprofloxacin (10 studies), piperacillin (3 studies) and trobamycin (4 studies); $CL^1$(IV)–data for ampicillin (3 studies), cefazolin (3 studies), cefpirome (4 studies), ciprofloxacin (10 studies), genatmicin (7 studies), ofloxacin (3 studies), piperacillin (3 studies) and trobamycin (5 studies); $CL^2$(IV)–data for acyclovir (5 studies), ampicillin (3 studies), cefazolin (3 studies), gentamicin (3 studies), and piperacillin (3 studies); $CL^3$(IV)–data for ampicillin (4 studies), cefazolin (4 studies),cefpirome (10 studies), ciprofloxacin (12 studies) gentamicin (4 studies), ofloxacin (3 studies), piperacillin (5 studies) and trobamycin (6 studies).

# Human variability in Phase I, Phase II and renal excretion: Individual data

## I.PHASE I Pathways

## I.1.CYP1A2

### I.1.1 Metabolic Clearances

**Table 1. Metabolic clearances for the CYP1A2 pathway of elimination in healthy adult volunteers [a].**

| Drug (Clearance unit) | Reaction | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| *Oral Administration* | | | | | | | | | | |
| Caffeine ($ml min^{-1} kg^{-1}$) | 1-N-demethylation | 1 | 1[1] | 5 | 0.24 | 0.07 | 29 | 0.23 | 1.3 | 29 |
| Caffeine ($ml min^{-1} kg^{-1}$) | 3-N-demethylation | 1 | 1[1] | 5 | 1.8 | 1.08 | 59 | 1.54 | 1.7 | 59 |
| Caffeine ($ml min^{-1} kg^{-1}$) | 7-N-demethylation | 1 | 1[1] | 5 | 0.08 | 0.02 | 25 | 0.08 | 1.3 | 25 |
| Theophylline ($ml min^{-1} kg^{-1}$) | 1-N-demethylation | 1 | 1[2] | 13 | 0.21 | 0.11 | 52 | 0.19 | 1.6 | 52 |
| Theophylline ($ml min^{-1} kg^{-1}$) | 3-N-demethylation | 1 | 1[2] | 13 | 0.16 | 0.10 | 62 | 0.14 | 1.8 | 63 |
| Theobromine ($ml min^{-1} kg^{-1}$) | 1-N-demethylation | 3 | 3[3] | 23 | 0.20 | 0.09 | 42 | 0.18 | 1.4 | 38 |
| Paraxanthine ($ml min^{-1} kg^{-1}$) | 7-N-demethylation | 1 | 1[4] | 6 | 0.89 | 0.26 | 29 | 0.62 | 1.3 | 29 |
| *Intravenous Administration* | | | | | | | | | | |
| Theophylline ($ml min^{-1} kg^{-1}$) | 1-N-demethylation | 3 | 2[5] | 22 | 0.16 | 0.06 | 37 | 0.15 | 1.3 | 26 |
| Theophylline ($ml min^{-1} kg^{-1}$) | 3-N-demethylation | 1 | 1[6] | 6 | 0.19 | 0.06 | 31 | 0.18 | 1.4 | 31 |
| R-Warfarin ($ml min^{-1}$) | 8-Hydroxylation | 1 | 1[7] | 6 | 0.26 | 0.15 | 59 | 0.23 | 1.7 | 59 |

[a]**Ns** number of studies; **Np** number of publications; **n** number of subjects; $\mathbf{X_w}$ weighted mean; $\mathbf{SD_w}$ weighted standard deviation; $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Lelo *et al.*, 1986a. [2]Birkett *et al.*, 1985. [3]Birkett *et al.*, 1985; Miners *et al.*, 1982; Tarka *et al.*, 1983. [4]Lelo *et al.*, 1989. [5]Loi *et al.*, 1993; Loi *et al.*, 1997 (2). [6]Loi *et al.*, 1993. [7]Abernethy *et al.*, 1991.

## 1.1.2 Healthy adults

**Table 2. Pharmacokinetics of CYP1A2 probe substrates in healthy adults [a].**

| Parameter | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | | |
| $CL^a$ | Caffeine | 12 | 12[1] | 163 | 1.2 | 0.43 | 36 | 1.1 | 1.4 | 36 |
| $CL^a$ | Paraxanthine | 1 | 1[2] | 6 | 1.7 | 0.30 | 18 | 1.7 | 1.2 | 18 |
| $CL^a$ | Theobromine | 6 | 6[3] | 45 | 1.0 | 0.33 | 32 | 0.96 | 1.3 | 28 |
| $CL^a$ | Theophylline | 6 | 6[4] | 106 | 0.90 | 0.38 | 41 | 0.83 | 1.4 | 36 |
| $CL^b$ | Caffeine | 1 | 1[5] | 10 | 140 | 79 | 56 | 120 | 1.6 | 52 |
| $AUC^c$ | Caffeine | 1 | 1[6] | 15 | 17000 | 9500 | 55 | 15000 | 1.6 | 53 |
| $AUC^c$ | Theophylline | 2 | 2[7] | 22 | 24000 | 5800 | 24 | 23000 | 1.2 | 22 |
| $AUC^c$ | Theobromine | 1 | 1[8] | 6 | 13000 | 5500 | 43 | 12000 | 1.5 | 39 |
| $Cmax^d$ | Caffeine | 5 | 5[9] | 67 | 1800 | 440 | 24 | 1700 | 1.3 | 23 |
| $Cmax^d$ | Theophylline | 3 | 3[10] | 32 | 4600 | 840 | 18 | 4400 | 1.2 | 18 |
| ***Intravenous Administration*** | | | | | | | | | | |
| $CL^a$ | Caffeine | 2 | 2[11], | 20 | 2.0 | 0.92 | 47 | 1.8 | 1.50 | 43 |
| $CL^a$ | Theophylline | 12 | 11[12] | 92 | 1.00 | 0.29 | 29 | 0.93 | 1.3 | 25 |
| $AUC^c$ | Caffeine | 1 | 1[13] | 8 | 14000 | 5800 | 41.0 | 13000 | 1.5 | 39 |
| $AUC^c$ | Theophylline | 2 | 1[14] | 14 | 52000 | 10000 | 19 | 50000 | 1.2 | 19 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); $\mathbf{CL^a}$: Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) $\mathbf{CL^b}$ Total clearance not adjusted to body weight ($mlmin^{-1}$); $\mathbf{AUC^c}$: AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); $\mathbf{Cmax^d}$ Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Desmond *et al.*, 1980, Newton *et al.*, 1981, May *et al.*, 1982, Tang-liu *et al.*, 1983, Lelo *et al.*, 1986a, Joeres *et al.*, 1988, Denaro *et al.*, 1990, Tang *et al.*, 1994, Kamimori *et al.*, 1995,Wittayalertpayana *et al.*, 1996, Kaplan *et al.*, 1997; [2]Lelo *et al.*, 1989; [3] Miners *et al.*, 1982, Tarka *et al.*, 1983, Birkett *et al.*, 1985, Miners *et al.*, 1985, Shively *et al.*, 1985, Lelo *et al.*, 1986b; [4] Gal *et al.*, 1978, Blouin *et al.*, 1982, Fox *et al.*, 1983, Gardner *et al.*, 1983, Jonkman *et al.*, 1984, Colli *et al.*, 1988; [5]Beach *et al.*, 1986, [6]Amchin *et al.*, 1999, [7]Ishizaki *et al.*, 1983, Rizzo *et al.*, 1990; [8]Rodopoulos *et al.*, 1996; [9]Blanchard and Savers,1983a, Beach *et al.*, 1986, Wittayalertpayana *et al.*, 1996, Kaplan *et al.*, 1997, Amchin *et al.*, 1999; [10]Fox *et al.*, 1983, Jonkman *et al.*, 1984, Rizzo *et al.*, 1990; [11] Blanchard and Savers, 1983a, Denaro *et al.*, 1996; [12]Chrzanowski *et al.*, 1977, Cusack *et al.*, 1980, Staib *et al.*, 1980, Bauer *et al.*, 1982, Kraan *et al.*, 1988, Shin *et al.*, 1988, Amodio *et al.*, 1991, Dal-Negro *et al.*, 1993, Loi *et al.*, 1993, Loi *et al.*, 1997; [13]Blanchard and Savers, 1983a; [14]Jennings *et al.*, 1993(2).

## I.1.3 Healthy subgroups of the population

**Table 3. Pharmacokinetics of CYP1A2 probe substrates: Comparison between healthy adults and healthy subgroups of the population after oral and intravenous administration [a]**

| Parameter (Route) | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Smokers* | | | | | | | | | | | | |
| CL[a] (PO) | Caffeine | 4 | 3[1] | 38 | 2.6 | 0.93 | 36 | 2.3 | 1.4 | 33 | 0.49 | 0.91 |
| CL[a] (PO) | Theophylline | 1 | 1[2] | 15 | 1.2 | 0.30 | 26 | 1.1 | 1.3 | 26 | 0.77 | 0.72 |
| AUC[c] (PO) | Theophylline | 1 | 1[3] | 6 | 12000 | 4849 | 40 | 11000 | 1.5 | 40 | 0.49 | 1.6 |
| Cmax[a] (PO) | Caffeine | 1 | 1[4] | 6 | 1800 | 610.0 | 35 | 1700 | 1.4 | 35 | 0.97 | 1.5 |
| CL[a] (IV) | Theophylline | 1 | 1[5] | 8 | 0.72 | 0.17 | 24 | 0.70 | 1.3 | 26 | 1.3 | 1.04 |
| AUC[c] (IV) | Theophylline | 2 | 1[6] | 14 | 33000 | 10300 | 31 | 31000 | 1.4 | 31 | 0.62 | 1.6 |
| *Black Zimbabwean* | | | | | | | | | | | | |
| CL[a] (IV) | Theophylline | 1 | 1[7] | 16 | 0.62 | 0.17 | 27 | 0.60 | 1.31 | 27 | 1.6 | 1.1 |
| *Pregnant Women* | | | | | | | | | | | | |
| CL[a](PO) | Caffeine | 2 | 2[8] | 14 | 0.58 | 0.32 | 55 | 0.49 | 1.6 | 47 | 2.3 | 1.3 |
| CL[a](IV) | Theophylline | 3 | 3[9] | 14 | 0.83 | 0.22 | 26 | 0.81 | 1.3 | 23 | 1.2 | 0.92 |
| Cmax[c](PO) | Caffeine | 1 | 1[10] | 8 | 2020 | 1500 | 72 | 1900 | 1.9 | 72 | 1.1 | 3.1 |
| ***Elderly Smokers*** | | | | | | | | | | | | |
| CL[a](PO) | Theophylline | 1 | 1[11] | 11 | 0.75 | 0.11 | 15 | 0.74 | 1.2 | 15 | 1.1 | 0.40 |
| Cmax[c](PO) | Theophylline | 1 | 1[11] | 11 | 2478 | 352 | 14 | 2455 | 1.15 | 14 | 0.56 | 0.78 |
| ***Elderly non Smokers*** | | | | | | | | | | | | |
| CL[a](PO) | Theophylline | 1 | 1[12] | 19 | 0.73 | 0.11 | 15 | 0.72 | 1.2 | 15 | 1.2 | 0.42 |
| AUC[c](PO) | Caffeine | 1 | 1[13] | 8 | 12000 | 6000 | 48 | 11000 | 1.6 | 48 | 0.74 | 0.90 |
| CL[a] (IV) | Caffeine | 2 | 2[14] | 18 | 1.4 | 0.50 | 35 | 1.3 | 1.4 | 36 | 1.3 | 1.1 |
| CL[a] (IV) | Theophylline | 5 | 4[15] | 41 | 0.72 | 0.32 | 45 | 0.64 | 1.5 | 44 | 1.5 | 1.8 |
| Cmax[a] (PO) | Caffeine | 1 | 1[13] | 8 | 370 | 64.54 | 17 | 360 | 1.2 | 17 | 0.20 | 1.6 |
| Cmax[a] (PO) | Theophylline | 1 | 1[12] | 19 | 2700 | 408 | 15 | 2700 | 1.2 | 15 | 0.60 | 0.82 |
| ***Neonates*** | | | | | | | | | | | | |
| CL[a](PO) | Caffeine | 1 | 1[16] | 5 | 0.13 | 0.02 | 18 | 0.12 | 1.2 | 18 | 9.0 | 0.502 |
| CL[a](IV) | Caffeine | 2 | 2[17] | 31 | 0.14 | 0.06 | 42 | 0.13 | 1.5 | 40 | 13 | 1.1 |
| CL[a] (IV) | Theophylline | 5 | 4[18] | 220 | 0.35 | 0.17 | 36 | 0.32 | 1.3 | 30 | 2.9 | 1.2 |
| Cmax[a] (PO) | Caffeine | 2 | 2[19] | 16 | 1280 | 100 | 7.8 | 1300 | 1.1 | 7 | 0.75 | 0.27 |
| ***Infants*** | | | | | | | | | | | | |
| CL[a](PO) | Caffeine | 1 | 1[16] | 4 | 1.0 | 1.0 | 104 | 0.69 | 2.4 | 104 | 1.6 | 0.86 |
| CL[a](PO) | Theophylline | 2 | 2[20] | 33 | 1.0 | 0.58 | 58 | 0.76 | 1.9 | 71 | 1.1 | 0.64 |
| CL[a](IV) | Theophylline | 3 | 2[21] | 43 | 0.46 | 0.17 | 36 | 0.43 | 1.4 | 33 | 2.2 | 1.3 |
| Cmax (PO)[d] | Theophylline | 1 | 1[22] | 20 | 2600 | 990 | 38 | 2440 | 1.4 | 38 | 0.55 | 2.1 |
| *Children* | | | | | | | | | | | | |
| CL[1](PO)[a] | Caffeine | 1 | 1[16] | 3 | 1.8 | 0.57 | 32 | 1.7 | 1.4 | 32 | 0.66 | 0.83 |
| CL[1](IV)[a] | Theophylline | 12 | 7[23] | 195 | 1.2 | 0.44 | 36 | 1.1 | 1.4 | 34 | 0.82 | 1.4 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_w$** Weighted standard deviation (normal distribution); **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** Coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$** Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Total clearance adjusted to body weight ($ml min^{-1} kg^{-1}$); [b]Total clearance not adjusted to body weight ($ml min^{-1}$); [c]AUC/dose ($ng ml^{-1} h$) and Cmax/dose ($ng ml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$).

[1]May *et al.*, 1982, Joeres *et al.*, 1988 (2), Murphy *et al.*, 1988; [2]Gardner *et al.*, 1983; [3]Ishizaki *et al.*, 1983; [4]May *et al.*, 1982; [5]Cusack *et al.*, 1980; [6]Jennings *et al.*, 1993(2); [7]Jameson and Munyika, 1980; [8]Aldridge *et al.*, 1981, Brazier *et al.*, 1983; [9]Sutton *et al.*, 1978, Romero *et al.*, 1983, Frederiksen *et al.*, 1986; [10]Brazier *et al.*, 1983; [11]Fox *et al.*, 1983; [12]Blouin *et al.*, 1982; [13]Blanchard and Sawers, 1983b; [14]Trang *et al.*, 1982, Blanchard and Sawers, 1983a; [15]Cusack *et al.*, 1980 (2), Fox *et al.*, 1983, Au *et al.*, 1985, Shin *et al.*, 1988; [16]Pons *et al.*, 1988; [17]Aranda *et al.*, 1977, Gorodischer, 1977, Gorodischer and Karplus, 1982; [18] Hilligoss *et al.*, 1980, Gilman *et al.*, 1986 (2), Stile *et al.*, 1986, Kraus *et al.*, 1993; [19]Giacoia *et al.*, 1989 (2); [20]Rosen *et al.*, 1979, Peskine *et al.*, 1983; [21]Giaicoia *et al.*, 1976; Kraus *et al.*, 1993(2); [22]Peskine *et al.*, 1983; [23]Ellis *et al.*, 1976, Loughnan *et al.*, 1976, Arnold *et al.*, 1981, Bellon *et al.*, 1981, Kraus *et al.*, 1993,Yamazaki *et al.*, 1995 (6), El-Desoky *et al.*, 1997.

## 1.1.4 Patients with liver disease and patients with renal disease

**Table 4. Pharmacokinetics of CYP1A2 probe substrates: Comparison between healthy adults and patients with liver and renal disease after oral and intravenous administration [a]**

| Parameter (Route) | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Patients with liver disease* | | | | | | | | | | | | |
| CL[a] (PO) | Caffeine | 7 | 4[1] | 81 | 0.62 | 0.61 | 99 | 0.39 | 2.1 | 87 | 2.9 | 2.4 |
| CL[a] (PO) | Theophylline | 2 | 2[2] | 35 | 0.38 | 0.16 | 43 | 0.35 | 1.5 | 42 | 2.4 | 1.2 |
| CL[a] (IV) | Caffeine | 3 | 3[3] | 45 | 1.00 | 0.48 | 48 | 0.83 | 1.6 | 53 | 2.0 | 1.2 |
| CL[a] (IV) | Theophylline | 8 | 4[4] | 68 | 0.52 | 0.40 | 78 | 0.41 | 1.6 | 53 | 2.3 | 2.1 |
| Cmax[b] (PO) | Caffeine | 3 | 1[5] | 27 | 1700 | 280 | 17 | 1600 | 1.2 | 16 | 0.97 | 0.68 |
| *Patients with renal disease* | | | | | | | | | | | | |
| CL[a](IV) | Caffeine | 1 | 1[6] | 5 | 0.78 | 0.35 | 44 | 0.72 | 1.5 | 42 | 2.4 | 1.0 |
| CL[a](IV) | Theophylline | 4 | 3[7] | 31 | 0.97 | 0.33 | 34 | 0.91 | 1.4 | 36 | 1.0 | 1.4 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given afte(r a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); [b]Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Desmond *et al.*, 1980, Joeres *et al.*, 1988, Scott *et al.*, 1988 (2), Wittayalertpayana *et al.*, 1996 (3); [2]Mangione *et al.*, 1978 Colli *et al.*, 1988; [3]Sanchez *et al.*, 1991, Ferre *et al.*, 1994, Denaro *et al.*, 1996; [4]Piafsky *et al.*, 1977, Staib *et al.*, 1980(5), Kraan *et al.*, 1988, Amodio *et al.*, 1991; [5]Wittayalertpayana *et al.*, 1996 (3); [6]Kraan *et al.*, 1988; [7]Bauer *et al.*, 1982(2), Kradjan *et al.*, 1982, Kraan *et al.*, 1988.

# I.2.CYP2C9

## I.2.1 All subgroups of the population

**Table 5. Pharmacokinetics of CYP2C9 probe substrates: comparison between healthy adults, elderly, liver disease and renal disease patients after oral administration [a].**

| Parameter | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | | | | |
| *Healthy* | | | | | | | | | | | | |
| $CL^a$ | S-warfarin | 1 | 1[1] | 5 | 0.19 | 0.04 | 22 | 2.57 | 1.3 | 25 | | |
| $CL^a$ | Tolbutamide | 2 | 2[2] | 16 | 0.21 | 0.05 | 25 | 0.20 | 1.3 | 26 | | |
| $CL^b$ | S-warfarin | 7 | 5[3] | 93 | 4.5 | 1.9 | 43 | 4.02 | 1.4 | 38 | | |
| $CL^b$ | Tolbutamide | 1 | 1[4] | 7 | 10.5 | 3.9 | 37 | 9.84 | 1.4 | 37 | | |
| $AUC^c$ | S-Warfarin | 1 | 1[5] | 12 | 140000 | 16000 | 12 | 140000 | 1.1 | 12 | | |
| $AUC^c$ | Tolbutamide | 2 | 2[6] | 26 | 95000 | 28000 | 29 | 90000 | 1.3 | 26 | | |
| $Cmax^c$ | S-warfarin | 1 | 1[7] | 12 | 1200 | 420 | 38 | 1050 | 1.4 | 38 | | |
| $Cmax^c$ | Tolbutamide | 2 | 2[8] | 18 | 6400 | 1300 | 20 | 6300 | 1.2 | 18 | | |
| ***Intravenous Administration*** | | | | | | | | | | | | |
| $CLm^a$ | Tolbutamide | 1 | 1[9] | 7 | 0.18 | 0.06 | 33 | 0.17 | 1.4 | 34 | | |
| $CLm^a$ | Tolbutamide | 1 | 1[9] | 7 | 0.21 | 0.07 | 34 | 0.20 | 1.4 | 34 | | |
| $CL^a$ | Tolbutamide | 1 | 1[9] | 7 | 0.26 | 0.10 | 39 | 0.24 | 1.4 | 38 | | |
| $CL^b$ | S-warfarin | 1 | 1[10] | 4 | 4.24 | 1.11 | 26 | 4.10 | 1.3 | 26 | | |
| $CL^b$ | Tolbutamide | 1 | 1[11] | 12 | 21.00 | 5.40 | 26 | 20.34 | 1.3 | 26 | | |
| Chinese | | | | | | | | | | | | |
| $CL^a$ (PO) | Tolbutamide | 1 | 1[12] | 10 | 0.17 | 0.02 | 12 | 0.17 | 1.1 | 12 | 1.2 | 0.46 |
| *Elderly* | | | | | | | | | | | | |
| AUC $(PO)^c$ | Tolbutamide | 1 | 1[13] | 12 | 70000 | 21000 | 30 | 67000 | 1.3 | 29 | 0.74 | 1.1 |
| Cmax $(PO)^d$ | Tolbutamide | 1 | 1[13] | 12 | 5600 | 2100 | 38 | 5194 | 1.4 | 38 | 0.83 | 2.2 |
| *Patients with liver disease* | | | | | | | | | | | | |
| $CL^i(PO)^a$ | Tolbutamide | 1 | 1[14] | 5 | 0.43 | 0.09 | 21 | 0.42 | 1.2 | 21 | 0.44 | 0.96 |
| $CL^i(IV)^b$ | Tolbutamide | 1 | 1[14] | 5 | 0.41 | 0.09 | 22 | 0.40 | 1.2 | 22 | 0.61 | 0.57 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; $\mathbf{CLm^a}$ Metabolic clearance (carboxy group) adjusted to body weight ($mlmin^{-1}kg^{-1}$); $\mathbf{Clm^a}$ Metabolic clearance (hydroxy group) adjusted to body weight ($mlmin^{-1}kg^{-1}$); $\mathbf{CL^a}$: Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) $\mathbf{CL^b}$ Total clearance not adjusted to body weight ($mlmin^{-1}$); $\mathbf{AUC^c}$: AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); $\mathbf{Cmax^d}$ Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Heinmark *et al.*, 1992; [2] Whiting *et al.*, 1981, Robson *et al.*, 1987, Gross *et al.*, 1999; [3] Chan *et al.*, 1984, Toon *et al.*, 1986 (2), Awni *et al.*, 1995 (2), Priskorn *et al.*, 1997, Tiseo *et al.*, 1998; [4]Day *et al.*, 1995; [5]Tiseo *et al.*, 1998; [6]Awni *et al.*, 1995(2), Priskorn *et al.*, 1997, Tiseo *et al.*, 1998; [7]Priskorn *et al.*, 1997; [8]Sartor *et al.*, 1980, Antal *et al.*, 1982; [9]Bach *et al.*, 1988; [10]Abernethy *et al.*, 1991; [11]Tremaine *et al.*, 1997; [12]Gross *et al.*, 1999; [13]Sartor *et al.*, 1980; [14]Williams *et al.*, 1977.

## I.3 CYP2C19

### I.3.1 Non-phenotyped Healthy adults

**Table 6. Interindividual differences in the pharmacokinetics of CYP2C19 probe substrates: comparison between non–phenotyped healthy adults after oral and intravenous administration [a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | |
| Hexobarbital | 2 | 2[1] | 187 | 4.8 | 1.4 | 30 | 4.6 | 1.3 | 30 |
| Omeprazole | 1 | 1[2] | 6 | 0.26 | 0.10 | 39 | 0.24 | 1.4 | 38 |
| R-Hexobarbital | 1 | 1[3] | 10 | 17 | 12 | 70 | 14 | 2.0 | 76 |
| CL ($mlmin^{-1}$) | | | | | | | | | |
| Hexobarbital | 1 | 1[4] | 8 | 380 | 108 | 28 | 370 | 1.3 | 28 |
| Omeprazole | 1 | 1[5] | 8 | 805 | 300 | 37 | 750 | 1.4 | 37 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | |
| Omeprazole | 4 | 4[6] | 61 | 1400 | 1100 | 77 | 1300 | 1.8 | 68 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | |
| Hexobarbital | 1 | 1[7] | 10 | 206 | 80 | 39 | 190 | 1.5 | 39 |
| Omeprazole | 4 | 4[8] | 66 | 1020 | 600 | 59 | 850 | 1.6 | 52 |
| *Intravenous administration* | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | |
| Hexobarbital | 3 | 3[9] | 40 | 3.4 | 0.88 | 26 | 3.3 | 1.3 | 25 |
| CL ($mlmin^{-1}$) | | | | | | | | | |
| Omeprazole | 4 | 4[10] | 35 | 420 | 250 | 60 | 300 | 2.0 | 76 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | |
| Omeprazole | 1 | 1[11] | 10 | 3100 | 1800 | 58 | 2700 | 1.7 | 58 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric means between healthy adults and subgroup (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); ); [a]Ratios between non-phenotyped healthy adults and healthy asian (non-phenotyped, extensive or por metabolisers); [b]Ratios between healthy adult extensive metbolisers and healthy asian (non-phenotyped, extensive or por metabolisers); [a] Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Zilly *et al.*, 1992 (2); [2]Howden and Reid., 1988; [3]Chandler *et al.*,1988; [4]Van der Graaf *et al.*,1986; [7]Bertilsson *et al.*,1997; Duchauvelle *et al.*,1998; Pillai *et al.*,1998; Thoring *et al.*, 1999; [8]Andersson *et al.*,1990b, Duchauvelle *et al.*,1998, Pillai et al., 1998, Thoring et al., 1999; [9]Breimer et al., 1975, Richter et al., 1980, Zilly et al., 1975; [10]Andersson *et al.*,1990b, Regardh *et al.*,1990, Vinayek *et al.*,1991, Ching *et al.*,1991; [10]Jansen *et al.*,1988.

## I.3.2 Phenotyped Healthy adults

**Table 7. Interindividual differences in the pharmacokinetics of CYP2C19 probe substrates: comparison between extensive metabolisers and poor metabolisers after oral and intravenous administration [a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $EM/PM_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | | |
| CLm ($mlmin^{-1}$) | | | | | | | | | | | |
| R-Hexobarbital (EM) | 1 | 1[1] | 13 | 35 | 27 | 78 | 27 | 2.00 | 78 | | |
| R-Hexobarbital (PM) | 1 | 1[1] | 6 | 0.67 | 0.33 | 50 | 0.60 | 1.60 | 50 | 46 | 0.64 |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Omeprazole (EM) | 1 | 1[2] | 5 | 21 | 7.3 | 35 | 20 | 1.4 | 35 | | |
| Omeprazole (SEM) | 1 | 1[2] | 4 | 5.2 | 0.7 | 13 | 5.1 | 1.1 | 13 | 3.8 | 0.36 |
| Omeprazole (PM) | 1 | 1[2] | 5 | 1.0 | 0.2 | 17 | 1.0 | 1.2 | 17 | 20 | 0.47 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| R-Hexobarbital (EM) | 1 | 1[1] | 8 | 2300 | 1900 | 83 | 1700 | 2.1 | 83 | | |
| R-Hexobarbital (PM) | 1 | 1[1] | 2 | 73 | 130 | 183 | 35 | 3.4 | 183 | 50 | 2.2 |
| S-mephenytoin (EM) | 2 | 2[3] | 16 | 3300 | 2400 | 71 | 2400 | 2.0 | 78 | | |
| S-mephenytoin (PM) | 1 | 1[4] | 6 | 29 | 7.0 | 24 | 28 | 1.3 | 24 | 86 | 0.31 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Omeprazole (EM) | 3 | 3[5] | 24 | 1200 | 550 | 45 | 1100 | 1.5 | 43 | | |
| Omeprazole (PM) | 2 | 2[6] | 10 | 3600 | 730 | 21 | 3500 | 1.2 | 20 | 3.1 | 0.46 |
| Cmax ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Omeprazole (EM) | 3 | 3[7] | 23 | 730 | 370 | 51 | 640 | 1.6 | 49 | | |
| Omeprazole (SEM) | 1 | 1[8] | 4 | 1200 | 160 | 14 | 1200 | 1.1 | 14 | 1.9 | 0.28 |
| Omeprazole (PM) | 2 | 2[9] | 11 | 3400 | 870 | 25 | 3300 | 1.3 | 24 | 5.3 | 0.49 |
| S-mephenytoin (EM) | 1 | 1[10] | 8 | 220 | 120 | 53 | 560 | 1.7 | 59 | | |

**EM** Extensive metabolisers; **SEM** Slow extesnive metabolisers; **PM** Poor metabolisers; **Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{EM/PM_{LN}}$ Ratio of geometric means between extensive metabolisers and poor metabolisers (SEMs and PMs) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of extensive metabolisers and poor metabolisers (SEMs and PMs) (Lognormal distribution).

[1]Adedoyin *et al.*,1994; [2]Chang *et al.*, 1995a; [3]Wedlund *et al.*,1985, Adedoyin *et al.*,1998; [4]Wedlund *et al.*,1985; [5]Andersson *et al.*,1990a. Andersson *et al.*,1992, Andersson *et al.*,1998; [6]Andersson *et al.*,1990a, Andersson *et al.*,1992; [7]Andersson *et al.*,1990a, Chang *et al.*, 1995b, Andersson *et al.*,1998; [8]Chang *et al.*, 1995; [9]Andersson *et al.*,1990a , Chang *et al.*, 1995b; [10]Adedoyin *et al.*,1998.

## I.3.3 Interethnic differences

**Table 8. Effect of ethnicity on the pharmacokinetics of CYP2C19 probe substrates after oral administration[a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Asian | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Omeprazole (EM) J | 1 | 1[1] | 9 | 18 | 18 | 95 | 13 | 2.2 | 96 | 1.5 | 2.7 |
| Omeprazole (PM) J | 1 | 1[1] | 6 | 1.2 | 0.47 | 38 | 1.2 | 1.4 | 38 | 17 | 1.1 |
| Omeprazole (EM) K | 1 | 1[2] | 8 | 7.9 | 2.6 | 33 | 7.5 | 1.4 | 31 | 2.6 | 0.87 |
| Omeprazole (PM) K | 1 | 1[2] | 8 | 1.0 | 0.1 | 15 | 1.0 | 1.2 | 15 | 20 | 0.42 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| R-Hexobarbital (EM) C | 1 | 1[3] | 4 | 1800 | 980 | 58 | 1500 | 1.7 | 58 | 1.2 | 0.69 |
| R-Hexobarbital (PM) C | 1 | 1[3] | 4 | 105 | 17 | 16 | 104 | 1.2 | 16 | 17 | 0.19 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Omeprazole (EM) C | 1 | 1[4] | 8 | 2900 | 2000 | 68 | 2400 | 1.9 | 68 | 2.2 | 1.6 |
| Omeprazole (PM) C | 1 | 1[4] | 4 | 15000 | 6200 | 42 | 14000 | 1.5 | 42 | 12. | 0.98 |
| Omeprazole (EM) J | 2 | 2[5] | 11 | 1500 | 900 | 60 | 1200 | 1.7 | 59 | 1.1 | 1.4 |
| Omeprazole (SEM) J | 2 | 2[5] | 10 | 3500 | 1700 | 48 | 3100 | 1.6 | 51 | 2.8 | 1.2 |
| Omeprazole (PM) J | 2 | 2[5] | 12 | 14000 | 3900 | 27 | 13600 | 1.3 | 28 | 12 | 0.65 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Omeprazole (EM) J | 2 | 2[6] | 15 | 1200 | 860 | 74 | 970 | 1.8 | 64 | 1.5 | 1.3 |
| Omeprazole (SEM) J | 1 | 1[7] | 6 | 1900 | 1090 | 59 | 1600 | 1.7 | 59 | 2.5 | 1.2 |
| Omeprazole (PM) J | 2 | 2[6] | 12 | 4000 | 1200 | 31 | 3700 | 1.4 | 34 | 5.8 | 0.69 |
| Omeprazole (EM) K | 1 | 1[2] | 8 | 1200 | 460 | 40 | 1070 | 1.4 | 38 | 1.7 | 0.77 |
| Omeprazole (PM) K | 1 | 1[2] | 8 | 3400 | 670 | 20 | 3400 | 1.2 | 20 | 5.3 | 0.40 |

[a]**EM** Extensive metabolisers; **PM** Poor metabolisers; **Ns** Number of studies; **J** Japanese; **C** Chinese; **K** Korean; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric means between healthy adult extensive metabolisers and healthy asian subgroup (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); ); [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Yasuda *et al.*,1995; [2]Sohn *et al.*, 1992; [3]Adedoyin et al., 1994; [4]Andersson *et al.*. 1992; [5]Furuta *et al.*,1999; Sakai *et al.*, 2001; [6]Yasuda *et al.*,1995; Sakai *et al.*, 2001,[7]Sakai *et al.*, 2001.

## I.3.4 Effect of age and disease

**Table 9. Effect of age and disease on the pharmacokinetics of CYP2C19 probe substrates after oral administration.**

| Drug/Phenotype/Route | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Children* | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) (PO) | | | | | | | | | | | |
| Omeprazole (NP) (IV) | 1 | 1[1] | 13 | 4.5 | 2.5 | 56 | 3.9 | 1.7 | 56 | 1.1 | 0.73 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Omeprazole (NP) (PO) | 1 | 1[2] | 25 | 2734 | 2341 | 86 | 2077 | 2.1 | 86 | 1.6 | 1.27 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Omeprazole (NP) (PO) | 1 | 1[2] | 25 | 995 | 630 | 63 | 840 | 1.8 | 63 | 0.6 | 0.94 |
| *Elderly* | | | | | | | | | | | |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| R-Hexobarbital (NP)(PO) | 1 | 1[3] | 10 | 8.20 | 3.20 | 39 | 7.64 | 1.5 | 39 | 1.81 | 0.52 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| R-Hexobarbital (NP)(PO) | 1 | 1[3] | 10 | 288 | 103 | 36 | 271 | 1.4 | 36 | 0.71 | 0.92 |
| Liver disease | | | | | | | | | | | |
| CL ($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | |
| Hexobarbital (NP) (IV) | 3 | 3[4] | 31 | 3.04 | 1.55 | 51 | 2.59 | 1.6 | 47 | 1.29 | 1.92 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| Omeprazole (NP) (PO) | 1 | 1[5] | 8 | 98 | 43 | 44 | 89 | 1.5 | 44 | 8.5 | 1.2 |
| S-mephenytoin (EM) (PO) | 1 | 1[6] | 18 | 410 | 980 | 240 | 160 | 4.0 | 240 | 15 | 3.1 |
| Omeprazole (NP) (IV) | 1 | 1[7] | 10 | 69 | 19 | 28 | 190 | 1.4 | 31 | 1.6 | 0.41 |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | |
| Omeprazole (NP) (PO) | 1 | 1[8] | 8 | 17650 | 3761 | 21 | 17262 | 1.2 | 21 | 13.3 | 0.32 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Omeprazole (NP) (PO) | 3 | 3[9] | 26 | 4708 | 1821 | 39 | 3353 | 1.4 | 38 | 2.6 | 0.56 |
| S-mephenytoin (EM) (PO) | 1 | 1[6] | 18 | 685 | 406 | 59 | 590 | 1.7 | 59 | 3.0 | 1.1 |
| Renal disease | | | | | | | | | | | |
| CL ($mlmin^{-1}$) | | | | | | | | | | | |
| Omeprazole (NP) (IV) | 1 | 1[10] | 12 | 562 | 217 | 39 | 524 | 1.5 | 39 | 0.6 | 0.51 |
| C max/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Omeprazole (NP) (PO) | 1 | 1[10] | 12 | 2006 | 956 | 48 | 1810 | 1.6 | 48 | 1.4 | 0.71 |

[a]**NP** Non phenotyped; **EM** Extensive metabolisers; **Ns** Number of studies; **J** Japanese; **C** Chinese; **K** Korean; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{H/S_{LN}}$ Ratio of geometric means between healthy adult extensive metabolisers and healthy asian subgroup (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of healthy adults and subgroup (Lognormal distribution); ); [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Jacqz Agrain *et al.*, 1994; [2]Andersson *et al.*, 2000; [3]Chandler *et al.*, 1988; [4] Breimer et al., 1975, Richter et al., 1980 (2); [5]Rinetti *et al.*, 1991; [6]Adedoyin et al., 1998; [7]McKee et al., 1988; [8]Andersson et al,1993; [9]McKee *et al.*, 1988, Rinetti *et al.*, 1991, Andersson *et al*, 1993; [10]Naesdal *et al.*, 1986.

# I.4.CYP2E1

## I.4.1 All subgroups of the population

**Table 10. Inter-individual differences in the pharmacokinetics of CYP2E1 probe substrates: Comparison between healthy adults, elderly, patients with liver disease and patients with renal disease after oral administration [a].**

| Parameter | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | | | | |
| *Healthy* | | | | | | | | | | | | |
| $CLm^a$ | Chlorozoxazone | 5 | 3 | 91 | 3.0 | 0.98 | 33 | 2.8 | 1.4 | 32 | | |
| $CL^a$ | Chlorozoxazone | 6 | 4 | 101 | 4.4 | 1.7 | 29 | 4.2 | 1.3 | 29 | | |
| | Trimethadione | 8 | 6 | 81 | 0.75 | 0.13 | 17 | 0.72 | 1.2 | 19 | | |
| $CL^b$ | Chlorozoxazone | 4 | 4 | 65 | 300 | 110 | 37 | 260 | 1.4 | 33 | | |
| | Trimethadione | 2 | 2 | 16 | 68 | 19 | 28 | 63 | 1.3 | 25 | | |
| $Cmax^c$ | Chlorozoxazone | 6 | 5 | 73 | 940 | 390 | 41 | 690 | 1.4 | 32 | | |
| | Trimethadione | 3 | 1 | 14 | 1300 | 115 | 9 | 1300 | 1.1 | 8 | | |
| *Elderly* | | | | | | | | | | | | |
| $CL^a$ | Trimethadione | 2 | 2 | 22 | 0.58 | 0.15 | 25 | 0.56 | 1.3 | 26 | 1.3 | 1.4 |
| *Patients with liver disease* | | | | | | | | | | | | |
| $CL^a$ | Trimethadione | 6 | 3 | 71 | 0.63 | 0.16 | 26 | 0.54 | 1.4 | 37 | 1.3 | 2.0 |
| $CL^b$ | Trimethadione | 1 | 1 | 10 | 11.8 | 6.8 | 58 | 10.2 | 1.7 | 58 | 6.1 | 2.3 |
| *Patients with Renal disease* | | | | | | | | | | | | |
| $CL^b$ | Trimethadione | 1 | 1 | 13 | 0.26 | 0.10 | 39 | 0.25 | 1.4 | 39 | 2.9 | 2.1 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; **Clm**[a]: Metabolic clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **Cl**[a]: Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) **Cl**[b]: Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC**[c]: AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax**[d]: Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

Kharasch *et al.*,1993, Kim *et al.*,1995 (2), O'Shea *et al.*,1997 (2); [2]Kharasch *et al.*,1993, Kim *et al.*,1995 (2),O'Shea *et al.*,1997 (2), Leclercq *et al.*,1998; [3]Kobayashi *et al.*,1984 (3), Tanaka *et al.*,1987a, Tanaka *et al.*,1987b, Tanaka *et al.*,1993, Abei *et al.*,1995, Tanaka *et al.*,1999; [4]Desiraju *et al.*,1983, De Vries *et al.*,1994, Girre *et al.*,1994, Eap *et al.*,1999; [5]Tanaka *et al.*,1989, Ohashi *et al.*,1991; [6]Kharasch *et al.*,1993, De Vries *et al.*,1994, Girre *et al.*,1994 (2), Leclercq *et al.*,1998, Eap *et al.*,1998; [7]Kobayashi *et al.*,1984 (3); [8]Tanaka *et al.*,1987, Tanaka *et al.*,1994; [9]Tanaka *et al.*,1987, Tanaka *et al.*,1994, Abei *et al.*,1995 (4); [10]Tanaka *et al.*,1989;[11]Abei *et al.*,1995.

## I.5.Hydrolysis

### I.5.1 Healthy adults

**Table 11. Interindividual differences for compounds handled via esterase hydrolysis in healthy adults after oral and intravenous administration [a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | |
| Aspirin | 2 | 1[1] | 15 | 19 | 3.6 | 19 | 18 | 1.2 | 19 |
| AUC/dose ($ng ml^{-1} h$)[a] | | | | | | | | | |
| Aspirin | 9 | 8[2] | 89 | 920 | 201 | 22 | 770 | 1.2 | 22 |
| Flumazenil | 2 | 2[3] | 12 | 210 | 82 | 39 | 190 | 1.4 | 38 |
| Fozinopril | 9 | 1[4] | 50 | 6500 | 2000 | 31 | 6100 | 1.3 | 30 |
| C max/dose ($ng ml^{-1}$)[a] | | | | | | | | | |
| Aspirin | 13 | 11[5] | 115 | 1200 | 430 | 34 | 1000 | 1.4 | 31 |
| Flumazenil | 2 | 2[6] | 14 | 180 | 60 | 34 | 170 | 1.4 | 33 |
| Fozinopril | 9 | 1[4] | 50 | 860 | 240 | 28 | 830 | 1.3 | 27 |
| *Intravenous administration* | | | | | | | | | |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | |
| Fozinopril | 1 | 1[7] | 1 | 9 | 0.26 | 0.09 | 0.33 | 0.25 | 1.38 |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | |
| Aspirin | 1 | 1[8] | 6 | 9.3 | 1.2 | 13 | 9.3 | 1.1 | 13 |
| Cocaine | 3 | 3[9] | 12 | 28 | 5.4 | 20 | 27 | 1.2 | 19 |
| Esmolol | 3 | 3[10] | 27 | 193 | 84 | 43 | 170 | 1.4 | 37 |
| Etodimate | 7 | 7[11] | 44 | 17 | 6.5 | 38 | 15 | 1.3 | 31 |
| Flestolol | 2 | 2[12] | 13 | 190 | 69 | 36 | 180 | 1.4 | 36 |
| Flumazenil | 1 | 1[13] | 12 | 15 | 3.3 | 22 | 15 | 1.2 | 22 |
| Fozinopril | 1 | 1[7] | 9 | 0.50 | 0.11 | 21 | 0.49 | 1.2 | 21 |
| CL ($ml min^{-1}$) | | | | | | | | | |
| Cocaine | 3 | 3[14] | 16 | 1800 | 494 | 27 | 1600 | 1.3 | 24 |
| Flumazenil | 4 | 4[15] | 30 | 1000 | 196 | 20 | 980 | 1.2 | 19 |
| Fozinopril | 3 | 2[16] | 25 | 25 | 9.7 | 40 | 23 | 1.4 | 37 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); [a]AUC/dose ($ng ml^{-1} h$) and Cmax ($(ng ml^{-1})$) with mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$).

[1]Siegmund *et al.*, 1994(2); [2]Brantmark *et al.*, 1982, Ho *et al.*, 1985 (2), Hsyu *et al.*, 1989, Mason and Winer., 1981, Moolenaar *et al.*, 1979, Roberts *et al.*, 1983, Shrurer *et al.*, 1996, Vigano *et al.*, 1991.[3]Roncari *et al.*, 1986, Roncari *et al.*, 1993; [4]Duchin *et al.*, 1991; [5]Benedek *et al.*, 1995, Bochner *et al.*, 1988, Brantmark *et al.*, 1982, Ho etal,1985 (2), Hsyu *et al.*, 1989, Mason and Winer., 1981, Montgomery *et al.*, 1986, Moolenaar *et al.*, 1979, Roberts *et al.*, 1983, Siegmund *et al.*, 1994(2), Vigano *et al.*, 1991; [6]Janseen *et al.*, 1989, Roncari *et al.*, 1993; [13]Short *et al.*, 1984; [8]Bochner *et al.*, 1988; [9]Barnett *et al.*, 1981, Chow *et al.*, 1985, Jeffcoat *et al.*, 1989; [10]De Bruijn *et al.*, 1983, Flaherty *et al.*, 1989, Sum et al.., 1983; [11]Bonnardot *et al.*, 1991, De Ruiter et al.., 1981, Hebron *et al.*, 1983, Schuttler *et al.*, 1980, Sfez *et al.*, 1990, Van Beem *et al.*, 1983, Van Hamme *et al.*, 1978; [12]Achari *et al.*, 1985, Achari *et al.*, 1987; [13]Hu *et al.*, 1997; [14]Cone *et al.*,1988, Javaid *et al.*,1983, Kumor *et al.*,1988; [15]Breimer *et al.*, 1991, Debruyne *et al.*, 1991, Janseen *et al.*, 1989, Klotz *et al.*, 1985. [16]Hui et al., 1991, Kostis et al., 1995 (2).

## I.5.2 Subgroups of the population

**Table 12. Interindividual differences for compounds handled via esterase hydrolysis: Compariion between healthy adults, healthy Chinese, children, elderly, patients with liver disease and patients with renal disease after oral and intravenous administration [a].**

| Parameter (Route) | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chinese healthy adults | | | | | | | | | | | | |
| CLm[a](IV) | Fozinopril | 1 | 1[1] | 12 | 0.27 | 0.12 | 43 | 0.25 | 1.5 | 43 | 1.9 | 2.0 |
| CL[a](IV) | Fozinopril | 1 | 1[1] | 12 | 0.16 | 0.08 | 54 | 0.14 | 1.7 | 54 | 1.8 | 1.3 |
| *Children* | | | | | | | | | | | | |
| CL[a](IV) | Esmolol | 1 | 1[2] | 19 | 320 | 240 | 74 | 260 | 1.9 | 72 | 0.65 | 1.9 |
| | Etodimate | 1 | 1[3] | 12 | 17 | 4.6 | 27 | 17 | 1.3 | 27 | 0.91 | 0.88 |
| | Flumazenil | 1 | 1[4] | 12 | 21 | 6.9 | 34 | 20 | 1.4 | 34 | 0.85 | 1.3 |
| *Elderly* | | | | | | | | | | | | |
| AUC[c] (PO) | Aspirin | 3 | 2[5] | 19 | 730 | 380 | 52 | 640 | 1.5 | 39 | 0.83 | 1.8 |
| | Flumazenil | 1 | 1[6] | 12 | 360 | 110 | 32 | 340 | 1.4 | 32 | 0.53 | 0.80 |
| Cmax[d] (PO) | Aspirin | 3 | 2[5] | 19 | 1200 | 470 | 40 | 1040 | 1.5 | 40 | 1.04 | 1.27 |
| | Flumazenil | 1 | 1[6] | 12 | 204 | 82 | 34 | 190 | 1.5 | 40 | 0.18 | 1.02 |
| *Patients with liver disease* | | | | | | | | | | | | |
| AUC[c](PO) CL[a](IV) | Aspirin | 1 | 1[7] | 4 | 955 | 403 | 0.42 | 880 | 1.50 | 42 | 1.14 | 1.94 |
| | Etodimate | 1 | 1[8] | 12 | 12 | 3.6 | 0.31 | 11 | 1.4 | 31 | 1.36 | 1.01 |
| | Esmolol | 1 | 1[9] | 9 | 151 | 44.0 | 0.29 | 145 | 1.33 | 29 | 1.28 | 0.67 |
| CL[b](IV) | Flumazenil | 2 | 2[10] | 11 | 561 | 313 | 56 | 435 | 1.6 | 0.48 | 2.24 | 2.6 |
| Cmax[d] (PO) | Aspirin | 1 | 1[7] | 4 | 1044 | 630 | 0.60 | 894 | 1.7 | 0.60 | 0.89 | 1.93 |
| | Esmolol | 1 | 1[10] | 9 | 588 | 180 | 0.31 | 562 | 1.3 | 0.31 | 0.64 | 0.72 |
| *Patients with Renal disease* | | | | | | | | | | | | |
| CL[b](IV) | Fozinopril | 3 | 1[11] | 13 | 14 | 4.2 | 0.30 | 13 | 1.4 | 0.30 | 1.7 | 0.82 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $X_W$ Arithmetic weighted mean (normal distribution); $SD_w$ Weighted standard deviation (normal distribution); $CV_N$ coefficient of variation (normal distribution); $GM_W$ Geometric weighted mean (lognormal distribution); $GSD_w$ Weighted geometric standard deviation (lognormal distribution); $CV_{LN}$ coefficent of variation; (lognormal distribution); **Ratio** $S/H_{LN}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $CV_{LN}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation.; **Clm**[a] Metabolic clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CLm**[a] Metabolic clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL**[a] Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) **CL**[b] Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC**[c] AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax**[d] Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Hu *et al.*, 1997; [2]Wiest *et al.*, 1991; [3]Sfez *et al.*, 1990; [4]Jones *et al.*, 1993; [5]Roberts *et al.*, 1983, Ho *et al.*, 1985 (2); [6]Roncari *et al.*, 1993; [7]Roberts *et al.*, 1983; [8]Bonnardot *et al.*, 1991; [9]Buch *et al.*, 1987; [10]Janseen *et al.*,1989, Van der Rijt *et al.*, 1991; [10]Janseen et al.,1989; [11]Hui *et al.*, 1991(3).

## I.6. Alcohol dehydogenase

## I.6. 1 All subgroups of the population

**Table 13. Interindividual differences for compounds handled via alcohol dehydrogenase: Comparison between healthy adults, healthy orientals and elderly after oral and intravenous administration [a].**

| Parameter (Route) | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Healthy adults* | | | | | | | | | | | |
| *Oral administration* | | | | | | | | | | | |
| ER[a] | 4 | 4[1] | 145 | 1.9 | 0.37 | 20 | 1.8 | 1.2 | 18 | | |
| AUC[c] | 11 | 8[2] | 136 | 3.6 | 1.0 | 29 | 3.2 | 1.3 | 30 | | |
| AUC[c] (Sigma ADH) | 1 | 1[3] | 10 | 0.96 | 0.22 | 22.4 | 0.9 | 1.3 | 23 | | |
| Cmax[d] | 9 | 7[4] | 112 | 1.4 | 0.32 | 23 | 1.3 | 1.2 | 21 | | |
| *Intravenous administration* | | | | | | | | | | | |
| CL[b] | 2 | 1[5] | 12 | 290 | 89 | 31 | 273 | 1.3 | 29 | | |
| AUC[c] | 1 | 1[6] | 24 | 4.9 | 1.2 | 25 | 4.8 | 1.3 | 25 | | |
| *Orientals (Oral administration)* | | | | | | | | | | | |
| ER[a] | 5 | 2[7] | 154 | 2.1 | 0.46 | 21 | 2.1 | 1.2 | 21 | 0.87 | 1.2 |
| ER[a] (ADH+) | 4 | 1[8] | 114 | 1.7 | 0.20 | 11 | 1.5 | 1.1 | 14 | 1.18 | 0.74 |
| ER[a] (ADH-) | 4 | 1[8] | 166 | 1.6 | 0.21 | 14 | 1.7 | 1.1 | 11 | 1.21 | 0.62 |
| AUC[c] (Sigma ADH) | 1 | 1[3] | 10 | 0.88 | 0.10 | 12 | 0.9 | 1.1 | 11 | 1.07 | 0.50 |
| *Elderly (Oral administration)* | | | | | | | | | | | |
| AUC[c] | 2 | 1[9] | 29 | 3.3 | 2.5 | 75 | 2.7 | 1.9 | 73 | 0.82 | 2.4 |
| Cmax[d] | 2 | 1[9] | 29 | 1.7 | 0.74 | 43 | 1.5 | 1.5 | 46 | 0.88 | 2.1 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_w$** Weighted standard deviation (normal distribution); **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$** Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; **Sigma ADH** Sigma phenotype for ADH (slow metabolism); **ADH** + Fast phenotype for ADH; **ADH** + Slow otype for ADH; **ER[a]** Elimination rate in $mgmin^{-1}kg^{-1}$; **CL[a]** Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) **CL[b]** Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC[c]** AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax[d]** Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Fenna *et al.*, 1971, Farris *et al.*, 1978, Hanna *et al.*, 1978, Nuutinen *et al.*, 1985; [2]Marshall *et al.*, 1983 (2), Jones and Jonsson, 1994, Kamali *et al.*, 1994, Minocha *et al.*, 1995, Ammon *et al.*, 1996(2), Jones *et al.*,1997, Lucey *et al.*, 1999(2), Mumenthaler *et al.*, 1999, [3]Dohmen *et al.*, 1996; [4]Marshall *et al.*, 1983 (2), Jones and Jonsson, 1994, Kamali *et al.*, 1994, Minocha *et al.*, 1995, Jones *et al.*, 1997, Lucey *et al.*, 1999(2), Mumenthaler *et al.*, 1999; [5]Hahn *et al.*, 1994; [6]Jones *et al.*, 1992; [7]Hanna *et al.*, 1978(2); Mizoi *et al.*, 1985; [8]Mizoi *et al.*, 1987; [9]Lucey *et al.*, 1999.

# II.PHASE II Pathways

## II.1. N-acetyltransferases

### II.1.1 Phenotyped Healthy adults

**Table 1. Interindividual variation in pharmacokinetic parameters of N-acetyltransferase probe substrates in phenotyped healthy adult volunteers (FA, IA and SA) after oral administration[a].**

| Drug/ Phenotype | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $FA/SA_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *CLm ($ml min^{-1} kg^{-1}$)* | | | | | | | | | | | |
| Sulphametazine (FA) | 5 | 4[1] | 33 | 1.1 | 0.33 | 29 | 0.98 | 1.4 | 35 | | |
| Sulphametazine (IA) | 3 | 2[2] | 21 | 1.4 | 0.50 | 35 | 1.25 | 1.4 | 34 | 0.78 | 0.97 |
| Sulphametazine (SA) | 6 | 4[3] | 73 | 0.29 | 0.17 | 60 | 0.25 | 1.5 | 41 | 3.9 | 1.2 |
| *CLm ($ml min^{-1}$)* | | | | | | | | | | | |
| Isoniazid (FA) acetyl | 1 | 1[4] | 7 | 270 | 57 | 21 | 270 | 1.2 | 21 | | |
| Isoniazid (SA) acetyl | 1 | 1[4] | 7 | 160 | 24 | 15 | 160 | 1.2 | 15 | 1.6 | 0.70 |
| Isoniazid (FA) MAH | 1 | 1[4] | 7 | 1300 | 300 | 23 | 1300 | 1.3 | 23 | | |
| Isoniazid (SA) MAH | 1 | 1[4] | 7 | 810 | 45 | 6 | 810 | 1.1 | 6 | 1.6 | 0.24 |
| *CL ($ml min^{-1} kg^{-1}$)* | | | | | | | | | | | |
| Isoniazid (FA) | 6 | 3[5] | 125 | 7.3 | 2.6 | 35 | 6.9 | 1.4 | 35 | | |
| Isoniazid (SA) | 6 | 3[5] | 202 | 3.1 | 0.9 | 29 | 3.0 | 1.3 | 28 | 2.3 | 0.81 |
| Sulphametazine (FA) | 3 | 3[6] | 17 | 1.6 | 0.44 | 28 | 1.4 | 1.3 | 23 | | |
| Sulphametazine (IA) | 3 | 3[2] | 21 | 1.4 | 0.50 | 35 | 1.3 | 1.4 | 32 | 1.0 | 1.4 |
| Sulphametazine (SA) | 4 | 3[8] | 41 | 0.41 | 0.13 | 32 | 0.38 | 1.4 | 31 | 3.6 | 1.4 |
| *CL ($ml min^{-1}$)* | | | | | | | | | | | |
| Isoniazid (FA) | 1 | 1[4] | 7 | 498 | 180 | 36 | 470 | 1.4 | 36 | | |
| Isoniazid (SA) | 1 | 1[4] | 7 | 154 | 6.6 | 4.3 | 150 | 1.1 | 4.3 | 3.1 | 0.13 |
| Sulphametazine (FA) | 3 | 2[8] | 26 | 152 | 61.23 | 40 | 140 | 1.5 | 41 | | |
| Sulphametazine (SA) | 3 | 2[8] | 27 | 43 | 10.84 | 25 | 41 | 1.3 | 25 | 3.4 | 0.62 |
| *AUC/dose ($ng ml^{-1} h$)[a]* | | | | | | | | | | | |
| Sulphametazine (FA) | 2 | 1[9] | 16 | 14000 | 3700 | 26 | 14000 | 1.3 | 26 | | |
| Sulphametazine (SA) | 2 | 1[9] | 32 | 53000 | 18000 | 33 | 50000 | 1.4 | 33 | 3.6 | 1.3 |
| *Cmax/dose ($ng ml^{-1} h$)[a]* | | | | | | | | | | | |
| Isoniazid (FA) | 1 | 1[4] | 7 | 1400 | 510 | 37 | 1300 | 1.4 | 37 | | |
| Isoniazid (SA) | 1 | 1[4] | 7 | 1300 | 230 | 17 | 1300 | 1.2 | 17 | 1.0 | 0.47 |

[a]**FA** Fast acetylators ; **IA** Intermediate acetylators; **SA** Slow acetylators; **Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $SD_w$,Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation (lognormal distribution); **Ratio** $\mathbf{FA/SA_{LN}}$ Ratio of geometric means between FAs and SAs (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of SAs and FAs (Lognormal distribution); **(n)**, in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$).

[1]Chapron et al., 1979, Siegmund et al., 1989 (2), Siegmund et al., 1991, Suhardjono et al., 1986; [2]Chapron et al., 1979, Suhardjono et al., 1986(2); [3]Chapron et al., 1979, Siegmund et al., 1989 (2), Siegmund et al., 1991, Suhardjono et al., 1986 (2); [4]Peloquin et al., 1994; [5]Advenier et al., 1980, Kergueris et al,1983, Kergueris et al,1986 (4); [6]Chapron et al., 1979,Suhardjono et al., 1986, Siegmund et al., 1991; [7]Chapron et al., 1979, Suhardjono et al., 1986 (2), Siegmund et al., 1991; [8]Olson et al,1978,(2); [9]Siegmund et al., 1989 (2).

## II.1.2 Effect of ethnicity and age

**Table 2. Effect of ethnicity and age on the pharmacokinetics of probe substrates handlded by N-acetyltransferases after oral administration[a].**

| Drug/ Phenotype/ Route | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Asian Healthy adults*** | | | | | | | | | | | |
| CLm ($ml min^{-1}$) | | | | | | | | | | | |
| Sulphametazine (FA) C | 1 | 1[1] | 5 | 130 | 15 | 11 | 130 | 1.1 | 11 | 0.54 | 0.31 |
| Sulphametazine (IA) C | 1 | 1[1] | 4 | 82 | 5.6 | 6.8 | 82 | 1.1 | 6.8 | 0.84 | 0.20 |
| Sulphametazine (SA) C | 1 | 1[1] | 1 | 40 | | | 40 | | | 1.7 | |
| CL ($ml min^{-1}$) | | | | | | | | | | | |
| Sulphametazine (FA) C | 1 | 1[1] | 5 | 140 | 17 | 12 | 136 | 1.1 | 12 | 1.0 | 0.30 |
| Sulphametazine (IA) C | 1 | 1[1] | 4 | 89 | 9.1 | 10 | 88 | 1.1 | 10 | 1.6 | 0.25 |
| Sulphametazine (SA) C | 1 | 1[1] | 1 | 49 | | | 49 | | | 2.8 | |
| Isoniazid (FA) J | 2 | 1[2] | 33 | 280 | 94 | 34 | 262 | 1.4 | 34 | 1.8 | 0.94 |
| Isoniazid (FA) J | 1 | 1[3] | 5 | 180 | 62 | 35 | 166 | 1.5 | 39 | 2.8 | 1.1 |
| ***Children*** | | | | | | | | | | | |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Isoniazid (FA) | 1 | 2[4] | 46 | 11 | 2.1 | 20 | 9.4 | 1.3 | 0.28 | 0.74 | 0.80 |
| Isoniazid (FA) | 1 | 2[4] | 44 | 4.5 | 0.5 | 10 | 4.4 | 1.1 | 0.11 | 1.6 | 0.32 |
| ***Elderly*** | | | | | | | | | | | |
| CLm ($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Sulphametazine (FA) | 1 | 1[5] | 8 | 0.93 | 0.31 | 33 | 0.88 | 1.4 | 33 | 1.1 | 0.94 |
| Sulphametazine (SA) | 1 | 1[5] | 9 | 0.19 | 0.06 | 32 | 0.18 | 1.4 | 32 | 5.4 | 0.89 |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Isoniazid (FA) | 3 | 2[6] | 48 | 6.4 | 2.8 | 44 | 5.9 | 1.5 | 43 | 1.2 | 1.2 |
| Isoniazid (FA) | 3 | 2[6] | 96 | 2.5 | 0.7 | 27 | 2.4 | 1.3 | 26 | 2.9 | 0.76 |
| Sulphametazine (FA) | 1 | 1[5] | 8 | 1.11 | 0.36 | 32 | 1.1 | 1.4 | 32 | 1.3 | 1.4 |
| Sulphametazine (SA) | 1 | 1[5] | 9 | 0.27 | 0.09 | 33 | 0.26 | 1.4 | 33 | 5.4 | 1.4 |

[a]**FA** Fast acetylators; **IA** Intermediate acetylators; **SA** Slow acetylators; **C** Chinese; **J** Japanese; **Ns** Number of studies; **Np** Number of publications; n, Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Wighted standard deviation (normal distribution); $\mathbf{CV_N}$ Cefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation (lognormal distribution); **Ratio** $\mathbf{FA/SA_{LN}}$ Ratio of geometric means between FAs and SAs (lognormal distribution) (for the AUC and Cmax 1/ ratio was calculated); **Ratio** $\mathbf{CV_{LN}}$ Ratio between the variability of SAs and FAs (Lognormal distribution); **(n)**, in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation

[1]Lee and Lee, 1982; [2]Horai *et al.*, 1982 (2); [3]Horai *et al.*, 1982 (2); [4]Kergueris *et al.*, 1986; [5]Siegmund et al., 1991; [6]Advenier et al., 1980, Kergueris *et al.*, 1986 (2).

## II.2. Glycine Conjugation

### II.2.1 All Subgroups of the Population

**Table 3. Interindividual differences for compounds handled via glycine conjugation: Comparison between healthy adults, healthy orientals and elderly after oral and intravenous administration [a].**

| Parameter | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Healthy adults*** | | | | | | | | | | | | |
| CL[a] (PO) | Salicylate | 2 | 1[1] | 44 | 0.37 | 0.08 | 21 | 0.36 | 1.2 | 21 | | |
| CL[b] (PO) | Salicylate | 3 | 2[2] | 24 | 30 | 6.8 | 23 | 29 | 1.2 | 21 | | |
| AUC[c] (PO) | Benzoate | 1 | 1[3] | 6 | 5100 | 790 | 16 | 5040 | 1.2 | 16 | | |
| AUC[c] (PO) | Salicylate | 15 | 13[4] | 131 | 42000 | 13000 | 31 | 37000 | 1.3 | 28 | | |
| Cmax[d] (PO) | Benzoate | 1 | 1[3] | 6 | 2400 | 400 | 17 | 2400 | 1.2 | 17 | | |
| Cmax[d] (PO) | Salicylate | 21 | 15[5] | 256 | 5500 | 916 | 17 | 5300 | 1.2 | 16 | | |
| CL[a] (IV) | Salicylate | 4 | 1[6] | 25 | 0.62 | 0.15 | 25 | 0.60 | 1.3 | 24 | | |
| AUC[c] (IV) | Benzoate | 1 | 1[7] | 7 | 6100 | 940 | 15 | 6050 | 1.2 | 15 | | |
| *Neonates* | | | | | | | | | | | | |
| AUC[c](IV) | Benzoate | 2 | 1[8] | 10 | 120000 | 18000 | 16 | 11000 | 1.2 | 16 | 19 | 1.1 |
| *Children* | | | | | | | | | | | | |
| CL[a](PO) | Salicylate | 2 | 1[9] | 20 | 0.38 | 0.11 | 28 | 0.37 | 1.3 | 27 | 0.98 | 1.3 |
| Cmax[d](PO) | Salicylate | 2 | 1[9] | 20 | 7800 | 2700 | 35 | 7300 | 1.4 | 33 | 1.4 | 2.1 |
| *Elderly* | | | | | | | | | | | | |
| AUC[c](PO) | Salicylate | 3 | 2[10] | 19 | 41000 | 10500 | 26 | 37000 | 1.3 | 30 | 1.0 | 1.1 |
| Cmax[d](PO) | Salicylate | 5 | 4[11] | 40 | 4800 | 840 | 18 | 4500 | 1.2 | 19 | 0.85 | 1.2 |
| CL[a](IV) | Salicylate | 2 | 1[12] | 21 | 0.54 | 0.13 | 24 | 0.52 | 1.3 | 23 | 1.1 | 0.99 |
| *Liver Disease* | | | | | | | | | | | | |
| AUC[c](PO) | Salicylate | 1 | 1[13] | 8 | 46000 | 20000 | 43 | 42000 | 1.5 | 43 | 1.1 | 1.5 |
| Cmax[d](PO) | Salicylate | 1 | 1[13] | 8 | 5300 | 1900 | 36 | 5010 | 1.4 | 36 | 0.94 | 2.3 |
| AUC[c](IV) | Benzoate | 2 | 1[7] | 30 | 3200 | 1300 | 40 | 2900 | 1.4 | 37 | 0.48 | 2.5 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; **$X_W$** Arithmetic weighted mean (normal distribution); **$SD_w$** Weighted standard deviation (normal distribution); **$CV_N$** coefficient of variation (normal distribution); **$GM_W$** Geometric weighted mean (lognormal distribution); **$GSD_w$** Weighted geometric standard deviation (lognormal distribution); **$CV_{LN}$** coefficent of variation; (lognormal distribution); **Ratio $S/H_{LN}$** Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio $CV_{LN}$** Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; **CL[a]** Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$) **CL[b]** Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC[c]** AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax[d]** Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Montgomery *et al.*,1986 (2); [2]Trnavska *et al.*,1983 (2), Abdallah *et al.*,1991; [3]Kubota and Ishizaki,1991; [4]Jamali *et al.*,1981, Mason and Winer ,1981, Brantmark *et al.*,1982, Roberts *et al.*,1983, Borgstrom *et al.*,1984, Ho *et al.*,1985 (2), Bochner *et al.*,1988, Gatti *et al.*,1989, Ho *et al.*,1989, Vigano *et al.*,1991, Siegmund *et al.*,1994(2), Benedek *et al.*,1995, Shrurer *et al.*,1996; [5]Jamali *et al.*,1981, Mason and Winer ,1981, Brantmark *et al.*,1982, Roberts *et al.*,1983, Borgstrom *et al.*,1984, Ho *et al.*,1985 (2), Greenblatt *et al.*,1986(4), Bochner *et al.*,1988, Gatti *et al.*,1989, Ho *et al.*,1989, Abdallah *et al.*,1991, Vigano *et al.*,1991, Siegmund *et al.*,1994(2), Benedek *et al.*,1995, Shrurer *et al.*,1996; [6]Greenblatt *et al.*,1986(4); [7]Yamada *et al.*,1992; [8]Le Bel *et al.*, 1988 (2) ; [9]Wilson *et al.*, 1982(2); [10]Roberts *et al.*, 1983; Ho *et al.*, 1985(2); [11]Roberts *et al.*, 1983, Ho *et al.*, 1985(2), Greenblatt *et al.*, 1986(2);[12]Greenblatt *et al.*, 1986(2); [13]Roberts *et al.*, 1983.

## II.2. Sulphate Conjugation

### II.2.1 All Subgroups of the Population

**Table 4. Interindividual differences for compounds handled via sulphate conjugation: Comparison between healthy adults, healthy orientals and elderly after oral and intravenous administration [a].**

| Parameter | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{Ln}$ | Ratio $CV_{Ln}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral administration*** | | | | | | | | | | | | |
| ***Healthy adults*** | | | | | | | | | | | | |
| CLm[a] | Diflunisal | 3 | 3[1] | 17 | 1.03 | 0.42 | 41 | 0.90 | 1.5 | 39 | | |
| CLm[a] | Paracetamol | 6 | 4[2] | 48 | 1.6 | 0.3 | 19 | 1.5 | 1.2 | 17 | | |
| CLm[b] | Paracetamol | 3 | 3[3] | 26 | 86 | 25 | 28 | 83 | 1.3 | 27 | | |
| AUC[c] | Prenalterol | 1 | 1[4] | 6 | 2800 | 770 | 28 | 2700 | 1.3 | 28 | | |
| Cmax[d] | Prenalterol | 1 | 1[4] | 6 | 1500 | 480 | 33 | 1400 | 1.4 | 33 | | |
| ***Elderly*** | | | | | | | | | | | | |
| CLm[a] | Paracetamol | 1 | 1[5] | 8 | 1.4 | 0.23 | 16 | 1.4 | 1.2 | 16 | 1.1 | 0.96 |
| ***Intravenous administration*** | | | | | | | | | | | | |
| ***Healthy adults*** | | | | | | | | | | | | |
| CLm[a] | Paracetamol | 1 | 1[6] | 10 | 1.2 | 0.44 | 36 | 1.13 | 1.4 | 36 | | |
| CLm[b] | Salbutamol | 1 | 1[7] | 8 | 55 | 21 | 36 | 51 | 1.4 | 36 | | |
| *Elderly* | | | | | | | | | | | | |
| CLm[a] | Paracetamol | 3 | 2[8] | 24 | 1.2 | 0.28 | 23 | 1.18 | 1.3 | 23 | 1.1 | 0.62 |

**Ns** Number of studies; **Np** Number of publications; **n** number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ coefficent of variation; (lognormal distribution); **Ratio** $\mathbf{S/H_{LN}}$ Ratio of geometric means between healthy adults and subgroups (for the AUC the 1/Ratio mean was calculated) (lognormal distribution); **Ratio** $\mathbf{CV_{LN}}$ Variability ratio between healthy adults and subgroup (lognormal distribution); **(n)** given after a reference indicates the number of studies in the publication entering the weighted mean/weighted standard deviation calculation; **CLm**[a] Metabolic clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CLm**[b] Metabolic clearance not adjusted to body weight ($mlmin^{-1}$); **CL**[a] Total clearance adjusted to body weight ($mlmin^{-1}kg^{-1}$); **CL**[b] Total clearance not adjusted to body weight ($mlmin^{-1}$); **AUC**[c] AUC/dose ($ngml^{-1}h$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$); **Cmax**[d] Cmax/dose ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Loewen *et al.*, 1989, Verbeeck *et al.*,1990, Macdonald *et al.*,1992; [2]Miners *et al.*,1983 (2), Miners et *et al.*,1984 (2), Miners *et al.*,1988, Osborne *et al.*,1991; [3]Miners *et al.*, 1986, Baraka *et al.*, 1990, Rumble *et al.*, 1991; [4]Graffner *et al.*,1981; [5]Miners *et al.*, 1988; [6]Wynne *et al.*, 1990; [7]Morgan *et al.*,1986; [8]Wynne *et al.*,1990; Kamali *et al.*, 1993.

# III.Renal Excretion

## III. 1. Renal Clearances in healthy adults

**Table 1. Interindividual differences in renal clearances for compounds eliminated via renal excretion after oral and intravenous administration to healthy adult volunteers[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | |
| CLr($ml\,min^{-1}kg^{-1}$) | | | | | | | | | |
| Ciprofloxacin | 1 | 1[1] | 10 | 4.4 | 0.95 | 22 | 4.3 | 1.2 | 22 |
| Lomefloxacin | 1 | 1[2] | 8 | 2.6 | 0.33 | 13 | 2.6 | 1.1 | 13 |
| Ofloxacin | 1 | 1[3] | 8 | 2.2 | 0.90 | 41 | 2.0 | 1.5 | 41 |
| CLr($ml\,min^{-1}$) | | | | | | | | | |
| Acyclovir | 1 | 1[4] | 6 | 190 | 37 | 20 | 180 | 1.2 | 20 |
| Ciprofloxacin | 3 | 3[5] | 30 | 320 | 130 | 39 | 290 | 1.5 | 41 |
| Fluconazole | 2 | 1[6] | 12 | 13 | 2.5 | 20 | 13 | 1.2 | 20 |
| Lomefloxacin | 1 | 1[7] | 25 | 180 | 40 | 22 | 180 | 1.2 | 22 |
| Ofloxacin | 5 | 5[8] | 42 | 180 | 39 | 22 | 160 | 1.3 | 27 |
| *Intravenous Administration* | | | | | | | | | |
| CLr($ml\,min^{-1}kg^{-1}$) | | | | | | | | | |
| Amoxicillin | 1 | 1[9] | 6 | 2.6 | 0.82 | 32 | 2.5 | 1.4 | 32 |
| Ciprofloxacin | 1 | 1[10] | 9 | 4.3 | 1.1 | 25 | 4.1 | 1.3 | 25 |
| Gentamicin | 1 | 1[11] | 10 | 1.02 | 0.23 | 23 | 1.0 | 1.2 | 23 |
| CLr ($ml\,min^{-1}1.73m^{-2}$) | | | | | | | | | |
| Ampicillin | 1 | 1[12] | 12 | 280 | 109 | 39 | 260 | 1.5 | 39 |
| Ciprofloxacin | 2 | 2[13] | 20 | 380 | 91 | 24 | 320 | 1.2 | 22 |
| Gentamicin | 2 | 2[14] | 10 | 83 | 13 | 16 | 80 | 1.2 | 16 |
| Piperacillin | 2 | 1[15] | 11 | 160 | 46 | 28 | 150 | 1.2 | 22 |
| CLr($ml\,min^{-1}$) | | | | | | | | | |
| Amoxicillin | 1 | 1[16] | 20 | 170 | 48 | 28 | 170 | 1.3 | 28 |
| Ampicillin | 4 | 4[17] | 29 | 280 | 64 | 23 | 260 | 1.3 | 25 |
| Cefazolin | 2 | 2[18] | 14 | 45 | 12 | 26 | 42 | 1.3 | 27 |
| Cefpirome | 3 | 3[19] | 26 | 100 | 16 | 16 | 62 | 1.2 | 22 |
| Ciprofloxacin | 9 | 7[20] | 91 | 370 | 120 | 33 | 340 | 1.3 | 30 |
| Piperacillin | 3 | 3[21] | 25 | 150 | 34 | 23 | 140 | 1.3 | 23 |
| Trobamycin | 2 | 2[22] | 21 | 76 | 21 | 28 | 64 | 1.4 | 36 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$: Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Bayer *et al.*,1987; [2]Sudoh *et al.*,1996; [3]Orlando *et al.*,1992; [4]Bridgen *et al.*,1981; [5]Gasser *et al.*,1987, Singlas *et al.*,1987, Le Bel *et al.*,1986; [6]Ripa *et al.*,1993 (2); [7]Morrison *et al.*,1988; [8]Lode *et al.*, 1987, Farinotti *et al.*, 1988, Bandai *et al.*,1989, Flor *et al.*,1991, Silvain *et al.*,1989; [9]Horber *et al.*,1986; [10]Lungberg and Nilsson.,1988; [11]Walker *et al.*,1979; [12]Rho *et al.*,1989; [13]Ljungberg and Nilsson-Ehle, 1989; [14]Hannedouche *et al.*,1986, Regamey *et al.*,1973; [15]Welling *et al.*,1983 (2);[16]Mastrandrea *et al.*,1984; [17]Blum *et al.*,1989, Brown *et al.*,1982, Lewis *et al.*,1975, Wildefeuer *et al.*,1988 ;[18]Lavillauroix *et al.*,1975, Brisson *et al.*,1980; [19]Badian *et al.*,1988, Kavi *et al.*,1988, Malerczyk *et al.*,1987; [20]Allard *et al.*,1993, Borner *et al.*,1986(3), Davis *et al.*,1987, Lettierri *et al.*,1992, Shah *et al.*,1995, Webb *et al.*,1986, Wise *et al.*,1984; [21]Aronoff *et al.*,1983, Lode *et al.*,1984, Jonhson *et al.*,1992; [22]Davis *et al.*,1988, Pechere and Dugal., 1976.

## III. 2. Kinetics after oral administration in healthy adults

**Table 2. Interindividual differences in the pharmacokinetics of compounds eliminated via renal excretion after oral administration to healthy adult volunteers.**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL($ml min^{-1} kg^{-1}$) | | | | | | | | | |
| Amoxicillin | 1 | 1[1] | 8 | 5.2 | 1.0 | 19 | 5.1 | 1.2 | 19 |
| Lomefloxacin | 3 | 3[2] | 22 | 4.7 | 0.66 | 14 | 4.4 | 1.2 | 16 |
| Ofloxacin | 2 | 2[3] | 18 | 2.9 | 0.96 | 34 | 2.7 | 1.4 | 33 |
| CL ($ml min^{-1} 1.73m^{-2}$) | | | | | | | | | |
| Ciprofloxacin | 1 | 1[4] | 8 | 560 | 120 | 22 | 550 | 1.2 | 22 |
| Lomefloxacin | 3 | 3[5] | 27 | 230 | 50 | 22 | 220 | 1.2 | 21 |
| CL($ml min^{-1}$) | | | | | | | | | |
| Ciprofloxacin | 3 | 3[6] | 30 | 850 | 440 | 52 | 760 | 1.5 | 42 |
| Fluconazole | 2 | 1[7] | 12 | 21 | 5.3 | 25 | 20 | 1.3 | 25 |
| Lomefloxacin | 5 | 1[8] | 40 | 260 | 38 | 15 | 260 | 1.1 | 14 |
| Ofloxacin | 5 | 5[9] | 48 | 220 | 43 | 20 | 210 | 1.2 | 22 |
| AUC/dose ($nghml^{-1}$)[a] | | | | | | | | | |
| Amoxicillin | 6 | 6[10] | 55 | 3000 | 600 | 20 | 2800 | 1.2 | 22 |
| Ampicillin | 2 | 2[11] | 21 | 2200 | 770 | 36 | 2010 | 1.4 | 34 |
| Ciprofloxacin | 2 | 2[12] | 20 | 1400 | 330 | 24 | 1300 | 1.38 | 33 |
| Fluconazole | 5 | 5[13] | 66 | 68000 | 11000 | 16 | 66000 | 1.2 | 15 |
| Lomefloxacin | 7 | 3[14] | 48 | 5000 | 670 | 13 | 4900 | 1.1 | 13 |
| Ofloxacin | 1 | 1[15] | 21 | 5500 | 850 | 15 | 5400 | 1.2 | 15 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | |
| Amoxicillin | 4 | 4[16] | 42 | 880 | 290 | 32 | 820 | 1.3 | 30 |
| Ampicillin | 3 | 3[17] | 27 | 360 | 140 | 40 | 320 | 1.4 | 37 |
| Ciprofloxacin | 6 | 6[18] | 57 | 310 | 110 | 35 | 290 | 1.4 | 36 |
| Fluconazole | 5 | 5[13] | 66 | 1400 | 260 | 18 | 1410 | 1.2 | 17 |
| Lomefloxacin | 18 | 9[19] | 122 | 650 | 150 | 24 | 610 | 1.2 | 22 |
| Ofloxacin | 8 | 8[20] | 87 | 740 | 220 | 30 | 701 | 1.3 | 27 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$: Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]AUC/dose ($ngml^{-1}h$) and Cmax ($ngml^{-1}$) with mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$).

[1]Westphal *et al.*,1990; [2]Gros and Carbon., 1990, Sudoh *et al.*,1994, Sudoh *et al.*,1996; [3]Gascon *et al.*,1998, Orlando *et al.*,1992; [4]Ljungberg and Nilsson-Ehle, 1989; [5]Nilsen *et al.*,1992, Blum *et al.*,1990, Leroy *et al.*,1990; [6]Gasser *et al.*,1987, Le Bel *et al.*,1986, Singlas *et al.*,1987; [7]Ripa *et al.*,1993(2); [8]Morrison *et al.*,1988 (5); [9]Bandai *et al.*,1989, Bouquet *et al.*,1988, Flor *et al.*,1991, Molinaro *et al.*,1992, Silvain *et al.*,1989; [10]Dalhoff *et al.*,1981, Adam *et al.*,1982, Guibert *et al.*,1985, Paintaud *et al.*,1992, Molinaro *et al.*,1997, Prevot *et al.*,1987; [11]Eshelman *et al.*,1978, Kaumeier *et al.*,1980; [12]Bayer *et al.*,1987, Hoffken *et al.*,1985; [13]Pfaff *et al.*,1993, Shiba *et al.*,1990, Thorpe *et al.*,1990, Yeates *et al.*,1995, Zimmermann *et al.*,1994; [14]Morse *et al.*,1990 (5), Stone *et al.*,1988, Stuht *et al.*,1995; [15]Dudley *et al.*,1991; [16]Adam *et al.*,1982, Paintaud *et al.*,1992, Molinaro *et al.*,1997, Prevot *et al.*,1997; [17]Eshelman *et al.*,1978, Kaumeier *et al.*,1980, Triggs *et al.*,1980; [18]Bayer *et al.*,1987, Esposito *et al.*,1989, Gasser *et al.*,1987, Hoffken *et al.*,1985, Le Bel *et al.*,1986, Singlas *et al.*,1987; [19]Blum *et al.*,1990, Gros and Carbon., 1990, Leroy *et al.*,1990, Morrison *et al.*,1988 (5), Morse *et al.*,1990 (5), Nilsen *et al.*,1992, Stuht *et al.*,1995, Sudoh *et al.*,1994, Sudoh *et al.*,1996; [20]Bandai *et al.*,1989, Bouquet *et al.*,1988, Dudley *et al.*,1991, Flor *et al.*,1991, Gascon *et al.*,1998, Molinaro *et al.*,1992, Orlando *et al.*,1992, Silvain *et al.*,1989.

## III. 3. Kinetics after intravenous administration in healthy adults

**Table 3. Interindividual differences in the pharmacokinetics of compounds eliminated via renal excretion after intravenous administration to healthy adult volunteers.**

| Drug | Ns | Np | n | $X_W$ | $SD_W$ | $CV_N$ | $GM_W$ | $GSD_W$ | $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|
| CL($ml min^{-1} kg^{-1}$) | | | | | | | | | |
| Acyclovir | 1 | 1[1] | 6 | 3.8 | 1.2 | 31 | 3.6 | 1.3 | 31 |
| Amoxicillin | 1 | 1[2] | 6 | 3.7 | 1.0 | 28 | 3.5 | 1.4 | 33 |
| Ampicillin | 2 | 2[3] | 11 | 4.2 | 1.4 | 34 | 4.0 | 1.4 | 32 |
| Cefazolin | 2 | 2[4] | 13 | 1.1 | 0.25 | 23 | 1.06 | 1.3 | 24 |
| Fluconazole | 1 | 1[5] | 10 | 0.36 | 0.06 | 17 | 0.34 | 1.4 | 33 |
| Gentamycin | 6 | 5[6] | 219 | 1.3 | 0.50 | 40 | 1.2 | 1.5 | 39 |
| Ofloxacin | 2 | 1[7] | 22 | 3.4 | 0.58 | 17 | 3.2 | 1.4 | 33 |
| Piperacillin | 2 | 2[8] | 15 | 4.9 | 3.6 | 73 | 4.1 | 1.6 | 53 |
| Trobamycin | 4 | 3[9] | 65 | 1.4 | 0.41 | 30 | 1.3 | 1.3 | 31 |
| CL ($ml min^{-1} 1.73m^{-2}$) | | | | | | | | | |
| Acyclovir | 4 | 2[10] | 74 | 240 | 71 | 29 | 230 | 1.3 | 29 |
| Ampicillin | 2 | 2[11] | 23 | 290 | 65 | 22 | 270 | 1.4 | 33 |
| Gentamycin | 2 | 1[12] | 80 | 84 | 34 | 40 | 78 | 1.5 | 40 |
| Piperacillin | 2 | 1[13] | 11 | 230 | 57 | 25 | 207 | 1.4 | 33 |
| CL($ml min^{-1}$) | | | | | | | | | |
| Amoxicillin | 1 | 1[14] | 20 | 247 | 82 | 33 | 230 | 1.5 | 40 |
| Ampicillin | 3 | 3[15] | 23 | 360 | 54 | 15 | 340 | 1.2 | 16 |
| Cefazolin | 3 | 3[16] | 24 | 65 | 16 | 24 | 63 | 1.2 | 22 |
| Cefpirome | 9 | 4[17] | 62 | 130 | 29 | 23 | 120 | 1.2 | 18 |
| Ciprofloxacin | 9 | 11[18] | 176 | 630 | 140 | 23 | 608 | 1.2 | 22 |
| Gentamycin | 3 | 2[19] | 149 | 75 | 31 | 41 | 69 | 1.5 | 42 |
| Ofloxacin | 2 | 2[20] | 18 | 240 | 35 | 15 | 230 | 1.2 | 15 |
| Piperacillin | 4 | 4[21] | 30 | 250 | 76 | 30 | 220 | 1.3 | 24 |
| Trobamycin | 5 | 5[22] | 44 | 87 | 19 | 22 | 81 | 1.3 | 23 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$: Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** number of studies in the publication entering the weighted mean/weighted standard deviation calculation.

[1]Bridgen *et al.*,1981; [2]Horber *et al.*,1986; [3]Breiby *et al.*,1983, Ehrnebo *et al.*,1979; [4]Ohashi *et al.*,1986, Philipson *et al.*,1987; [5]Ruhnke *et al.*,1995; [6]Bauer *et al.*,1982(2), Lackner *et al.*,1990, Merritt and slade., 1993, Rosell-Rovira., 1994, Walker *et al.*,1979; [7]Guay *et al.*,1992 (2); [8]Fourtillan *et al.*,1986, Hary *et al.*,1991; [9]Aronoff *et al.*,1990, Bauer and Blouin., 1981(2), Winslade *et al.*,1987; [10]De Miranda and Blum., 1983 (3), Laskin *et al.*,1982a; [11]Rho *et al.*,1989, Sjovall *et al.*,1986; [12]Bianco *et al.*,1989 (2); [13]Welling *et al.*,1983 (2); [14]Mastrandera *et al.*,1984; [15]Brown *et al.*,1982, Lewis *et al.*,1975, Wildfeuer *et al.*,1988; [16]Lavillauroix *et al.*,1975, Sheld *et al.*,1980, Brisson *et al.*,1981; [17]Badian *et al.*,1988, Kavi *et al.*,1988, Malerczyk *et al.*,1987, Nakayama *et al.*,1992(6); [18]Wise *et al.*,1984, Borner *et al.*,1986(3), Webb *et al.*,1986, Bergan *et al.*,1987, Davis *et al.*,1987, Lettierri *et al.*,1992, Nix *et al.*,1992, Allard *et al.*,1993 Shah *et al.*,1995; [19]El Sayed *et al.*,1989(2), Matzke *et al.*,1987; [20]Farinotti *et al.*,1988, Lode *et al.*,1987; [21]Aronoff *et al.*,1983, Heikkila and Erkkola., 1991, Jonhson *et al.*,1992, Lode *et al.*,1984; [22]Champoux *et al.*,1996, Davis *et al.*,1988, Guglielmo *et al.*,1987, Haughey *et al.*,1980, Pechere and Dugal., 1976.

## III. 4. Interethnic differences

**Table 4. Pharmacokinetics of compounds eliminated via renal excretion: comparison between healthy adults and Asian healthy adults after oral and intravenous administration[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | | |
| CL(mlmin$^{-1}$) | | | | | | | | | | | |
| Lomefloxacin | 1 | 1[1] | 12 | 406 | 101 | 25 | 394 | 1.3 | 25 | 0.65 | 1.74 |
| Ofloxacin [I] | 1 | 1[2] | 8 | 330 | 35 | 11 | 330 | 1.1 | 11 | 0.64 | 0.50 |
| AUC/dose (ngml$^{-1}$ h)[a] | | | | | | | | | | | |
| Fluconazole | 1 | 1[3] | 12 | 69000 | 16000 | 24 | 67000 | 1.3 | 24 | 1.02 | 1.6 |
| Ofloxacin | 1 | 1[4] | 7 | 4500 | 800 | 18 | 4400 | 1.2 | 18 | 0.82 | 1.2 |
| Cmax/dose (ngml$^{-1}$)[a] | | | | | | | | | | | |
| Fluconazole | 1 | 1[3] | 12 | 1400 | 280 | 24 | 1300 | 1.2 | 19 | 0.96 | 1.1 |
| Lomefloxacin | 1 | 1[1] | 12 | 304 | 106 | 35 | 290 | 1.4 | 35 | 0.47 | 1.6 |
| Ofloxacin | 1 | 1[4] | 7 | 750 | 89 | 12 | 740 | 1.1 | 12 | 1.06 | 0.44 |
| Ofloxacin [I] | 1 | 1[2] | 8 | 430 | 72 | 17 | 420 | 1.2 | 17 | 0.60 | 0.62 |

**Ns** Number of studies; **Np,** Number of publications; **n**, number of subjects; $\mathbf{X_W}$, Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$, Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight (mgkg$^{-1}$); **I**: Indian subjects.

[1]Zhang *et al.*,1996; [2]Nataraj *et al.*,1998; [3]Yeates *et al.*,1995;[4]Hasegawa *et al.*,1994.

## III. 5. Neonates, Infants and Children

**Table 5. Pharmacokinetics of compounds eliminated via renal excretion: comparison between healthy adults, neonates, infants and children after oral and intravenous administration[a].**

| Parameter/ Group | Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Oral Administration*** | | | | | | | | | | | | |
| AUC/dose ($ngml^{-1}$ h)[a] | | | | | | | | | | | | |
| Children | Fluconazole | 1 | 1[1] | 9 | 55000 | 16000 | 29 | 53000 | 1.3 | 29 | 0.80 | 1.9 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | | |
| Neonates | Amoxicillin | 1 | 1[2] | 7 | 550 | 120 | 22 | 530 | 1.2 | 22 | 0.65 | 0.71 |
| Children | Fluconazole | 1 | 1[1] | 9 | 2800 | 1400 | 51 | 2500 | 1.6 | 51 | 1.75 | 3.0 |
| *Intravenous administration* | | | | | | | | | | | | |
| CLr($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | | |
| Neonates | Gentamycin | 2 | 1[3] | 29 | 0.41 | 0.16 | 39 | 0.38 | 1.5 | 39 | 2.6 | 1.7 |
| | Piperacillin | 1 | 1[4] | 12 | 2.6 | 0.90 | 35 | 2.5 | 1.4 | 35 | 0.81 | 1.5 |
| Infants | Gentamicin | 1 | 1[3] | 7 | 1.2 | 0.39 | 32 | 1.1 | 1.4 | 32 | 0.9 | 1.4 |
| | Piperacillin | 1 | 1[5] | 12 | 2.0 | 0.60 | 30 | 1.9 | 1.3 | 30 | 1.04 | 1.3 |
| Children | Piperacillin | 2 | 1[6] | 18 | 3.5 | 0.92 | 26 | 3.4 | 1.3 | 25 | 0.59 | 1.09 |
| CL($mlmin^{-1}kg^{-1}$) | | | | | | | | | | | | |
| Neonates | Amoxicillin | 2 | 2[7] | 24 | 1.5 | 1.0 | 65 | 1.3 | 1.4 | 38 | 2.6 | 1.2 |
| | Cefazolin | 1 | 1[8] | 11 | 0.80 | 0.19 | 24 | 0.78 | 1.3 | 24 | 1.4 | 1.0 |
| | Gentamycin | 7 | 4[9] | 315 | 0.67 | 0.26 | 38 | 0.72 | 1.4 | 33 | 1.6 | 0.85 |
| | Piperacillin | 4 | 2[10] | 32 | 2.4 | 0.62 | 26 | 2.3 | 1.3 | 25 | 1.8 | 0.47 |
| | Trobamycin | 7 | 3[11] | 69 | 1.1 | 0.57 | 52 | 0.98 | 1.6 | 53 | 1.3 | 1.7 |
| | Trobamycin [J] | 2 | 2[12] | 19 | 3.1 | 1.3 | 42 | 2.5 | 1.5 | 41 | 0.51 | 1.4 |
| Infants | Cefpirome | 1 | 1[13] | 3 | 2.4 | 0.36 | 15 | 2.38 | 1.2 | 15 | 0.75 | 0.84 |
| | Fluconazole | 1 | 1[5] | 14 | 0.63 | 0.22 | 36 | 0.59 | 1.4 | 36 | 0.58 | 1.1 |
| | Piperacillin | 1 | 1[14] | 12 | 4.7 | 1.8 | 38 | 4.4 | 1.5 | 38 | 0.93 | 0.71 |
| Children | Cefazolin | 1 | 1[15] | 6 | 1.02 | 0.14 | 14 | 1.0 | 1.1 | 14 | 1.1 | 0.57 |
| | Cefpirome | 1 | 1[13] | 10 | 2.1 | 0.76 | 37 | 1.9 | 1.4 | 37 | 0.91 | 2.1 |
| | Piperacillin | 2 | 1[6] | 18 | 5.7 | 3.5 | 61 | 4.9 | 1.7 | 57 | 0.83 | 1.1 |
| | Trobamycin | 1 | 1[16] | 38 | 3.0 | 0.80 | 27 | 2.9 | 1.3 | 27 | 0.45 | 0.88 |
| CL ($mlmin^{-1}1.73m^{-2}$) | | | | | | | | | | | | |
| Neonates | Acyclovir | 2 | 2[17] | 14 | 106 | 42 | 39 | 99 | 1.4 | 36 | 2.3 | 1.3 |
| | Gentamycin | 2 | 1[18] | 23 | 30 | 7.9 | 26 | 29 | 1.3 | 25 | 2.7 | 0.61 |
| Infants | Acyclovir | 1 | 1[19] | 4 | 330 | 76 | 23 | 320 | 1.3 | 23 | 0.72 | 0.80 |
| Children | Acyclovir | 1 | 1[19] | 6 | 350 | 140 | 40 | 350 | 1.5 | 40 | 0.66 | 1.39 |
| CL ($mlmin^{-1}$) | | | | | | | | | | | | |
| Children | Cefpirome | 1 | 1[20] | 33 | 180 | 57 | 32 | 170 | 1.4 | 32 | 0.36 | 1.5 |
| | Trobamycin | 1 | 1[21] | 7 | 62 | 21 | 33 | 59 | 1.4 | 33 | 1.4 | 1.4 |

[a]**Ns** Number of studies; **Np,** Number of publications; **n**, number of subjects; $\mathbf{X_W}$, Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$, Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$), **J** Japanese.

[1]Nahata *et al.*,1995; [2]Lonnerholm *et al.*,1982; [3]Reed *et al.*,1994;[4]Kildoo *et al.*,1984 (2); [5]Kildoo *et al.*,1984; [6]Reed *et al.*,1994 (2); [7]Lonnerholm *et al.*,1982, Huisman-De Boer *et al.*,1995; [8]Deguchi *et al.*,1988; [9]Assael *et al.*,1980, Giacoia *et al.*,1986 (2), Watterberg *et al.*,1987 (2), Murphy *et al.*,1998; [10]Kacet *et al.*,1992 (3), Reed *et al.*,1994; [11]Nahata *et al.*,1983 (3), Arbeter *et al.*,1983, Nahata *et al.*,1984 (3); [12]Yoshioka *et al.*,1979, Fukuci *et al.*,1984;[13]Nahata *et al.*,1995; [14]Krzeska *et al.*,1993; [15]Koshida *et al.*,1987;[16]Bauer *et al.*,1983; [17]De Miranda and Blum, 1983, Hintz *et al.*,1982; [18]Zenk *et al.*,1984 (2); [19]De Miranda and Blum, 1983; [20]Kearns *et al.*,1995; [21]Bragonier *et al.*,1998.

## III. 6. The Elderly

**Table 6. Pharmacokinetics of compounds eliminated via renal excretion: comparison between healthy adults and elderly after oral and intravenous administration[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | | |
| CLr($ml\,min^{-1}kg^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 2 | 2[1] | 30 | 2.8 | 1.6 | 59 | 2.4 | 1.8 | 62 | 1.8 | 2.9 |
| CLr($ml\,min^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[2] | 12 | 150 | 54 | 36 | 140 | 1.4 | 36 | 2.03 | 0.87 |
| CL($ml\,min^{-1}kg^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[3] | 20 | 6.7 | 3.7 | 56 | 5.8 | 1.7 | 56 | 1.5 | 2.9 |
| CL($ml\,min^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[2] | 12 | 280 | 73 | 26 | 270 | 1.3 | 26 | 2.9 | 0.62 |
| Lomefloxacin | 1 | 1[4] | 12 | 150 | 34 | 24 | 140 | 1.3 | 24 | 1.8 | 1.6 |
| Ofloxacin | 3 | 3[5] | 40 | 109 | 37 | 34 | 98 | 1.4 | 33 | 2.1 | 1.5 |
| AUC/dose ($ngml^{-1}\,h$)[a] | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[6] | 10 | 2090 | 680 | 33 | 2000 | 1.4 | 33 | 1.5 | 0.99 |
| Lomefloxacin | 1 | 1[7] | 11 | 10500 | 2800 | 26 | 10200 | 1.3 | 26 | 2.1 | 2.0 |
| Cmax/dose ($ngml^{-1}$)[a] | | | | | | | | | | | |
| Ampicillin | 1 | 1[8] | 6 | 920 | 370 | 40 | 860 | 1.5 | 40 | 2.6 | 1.1 |
| Ciprofloxacin | 3 | 3[9] | 42 | 540 | 201 | 38 | 502 | 1.4 | 34 | 1.7 | 1.0 |
| Ofloxacin | 3 | 3[5] | 40 | 1100 | 370 | 33 | 1060 | 1.4 | 32 | 1.5 | 1.2 |
| Lomefloxacin | 2 | 2[10] | 23 | 790 | 210 | 27 | 770 | 1.3 | 27 | 1.2 | 1.3 |
| *Intravenous administration* | | | | | | | | | | | |
| CLr ($ml\,min^{-1}1.73m^{-2}$) | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[11] | 8 | 220 | 21 | 9 | 210 | 1.1 | 9 | 1.5 | 0.44 |
| CLr ($ml\,min^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[12] | 12 | 160 | 65 | 40 | 150 | 1.5 | 0.40 | 2.3 | 1.4 |
| CL ($ml\,min^{-1}kg^{-1}$) | | | | | | | | | | | |
| Ampicillin | 1 | 1[8] | 6 | 1.3 | 1.0 | 75 | 1.1 | 2.0 | 75 | 3.8 | 2.4 |
| Gentamycin | 2 | 2[13] | 100 | 1.2 | 0.37 | 31 | 1.1 | 1.4 | 31 | 1.02 | 0.79 |
| Ofloxacin | 2 | 1[14] | 16 | 1.6 | 0.98 | 63 | 1.3 | 1.7 | 58 | 2.4 | 1.7 |
| Piperacillin | 1 | 1[15] | 15 | 2.9 | 0.97 | 34 | 2.7 | 1.4 | 34 | 1.5 | 0.6 |
| Trobamycin | 1 | 1[16] | 29 | 1.3 | 0.36 | 29 | 1.2 | 1.3 | 29 | 1.1 | 0.9 |
| Trobamycin[J] | 2 | 1[17] | 16 | 1.5 | 0.54 | 37 | 1.2 | 1.3 | 25 | 1.1 | 0.83 |
| CL ($ml\,min^{-1}1.73m^{-2}$) | | | | | | | | | | | |
| Acyclovir | 1 | 1[18] | 20 | 330 | 80 | 24 | 320 | 1.3 | 24 | 0.73 | 0.85 |
| Ampicillin | 2 | 2[19] | 24 | 190 | 60 | 32 | 180 | 1.4 | 33 | 1.5 | 0.99 |
| Ciprofloxacin | 1 | 1[11] | 8 | 430 | 54 | 12 | 430 | 1.1 | 12 | 1.3 | 0.6 |
| CL ($ml\,min^{-1}$) | | | | | | | | | | | |
| Amoxicillin | 1 | 1[20] | 9 | 220 | 60 | 27 | 210 | 1.5 | 40 | 1.1 | 1.0 |
| Ciprofloxacin | 1 | 1[12] | 12 | 410 | 87 | 21 | 405 | 1.2 | 21 | 1.5 | 0.96 |
| Gentamycin | 3 | 3[21] | 82 | 43 | 19 | 45 | 38 | 1.5 | 44 | 1.8 | 1.06 |
| Trobamycin | 1 | 1[22] | 10 | 84 | 28 | 39 | 80 | 1.4 | 33 | 1.0 | 1.4 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$, Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mgkg^{-1}$), **J** Japanese.

[1]Bayer *et al.*,1987, Guay *et al.*,1988; [2] Le Bel *et al.*,1986; [3]Guay *et al.*,1988; [4]Crome and Morrison., 1991; [5]Veyssier *et al.*,1986, Rademaker *et al.*,1989, Molinaro *et al.*,1992; [6]Bayer *et al.*,1987; [7]Cowling *et al.*,1991; [8]Triggs *et al.*,1980; [9]Bayer *et al.*,1987,Guay *et al.*,1988, Le Bel *et al.*,1986; [10]Cowling *et al.*,1991, Crome and Morrison., 1991; [11]Ljungberg and Nilsson-Ehle, 1989; [12]Shah *et al.*,1995; [13]Bauer *et al.*,1982, Lackner *et al.*,1990; [14]Bardin *et al.*,1992 (2); [15]Fourtillan *et al.*,1986; [16]Bauer and Blouin., 1981; [17]Mineshita *et al.*,1988; [18]De Miranda and Blum , 1983;[19]Sjovall *et al.*,1986, Rho *et al.*,1989; [20]Arancibia *et al.*,1980; [21]Lawson *et al.*,1982, Matzke *et al.*,1987, El Sayed *et al.*,1989; [22]Champoux *et al.*,1996.

## III. 7. Patients with liver disease

**Table 7. Pharmacokinetics of compounds eliminated via renal excretion: comparison between healthy adults and patients with liver disease after oral and intravenous administration[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | | |
| CLr($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Ofloxacin | 1 | 1[1] | 8 | 1.50 | 50 | 33 | 1.4 | 1.4 | 33 | 1.4 | 0.80 |
| CLr($ml min^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[2] | 8 | 240 | 87 | 36 | 230 | 1.4 | 36 | 1.3 | 0.89 |
| Ofloxacin | 1 | 1[3] | 12 | 77 | 59 | 77 | 61 | 1.98 | 77 | 2.7 | 2.9 |
| CL($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Ofloxacin | 1 | 1[1] | 8 | 2.30 | 0.30 | 13 | 2.28 | 1.1 | 13 | 1.2 | 0.60 |
| CL($ml min^{-1}$) | | | | | | | | | | | |
| Ofloxacin | 1 | 1[3] | 12 | 96 | 50 | 51 | 85 | 1.6 | 52 | 2.5 | 2.4 |
| AUC/dose ($ng ml^{-1} h$)[a] | | | | | | | | | | | |
| Ciprofloxacin | 1 | 1[2] | 8 | 2500 | 1400 | 57 | 2200 | 1.7 | 57 | 1.7 | 1.7 |
| Lomefloxacin | 1 | 1[4] | 12 | 7800 | 2700 | 35 | 7400 | 1.4 | 35 | 1.5 | 2.7 |
| Cmax/dose ($ng ml^{-1}$)[a] | | | | | | | | | | | |
| Ciprofloxacin | 4 | 2[5] | 27 | 340 | 104 | 30 | 330 | 1.3 | 29 | 1.1 | 0.82 |
| Lomefloxacin | 1 | 1[4] | 12 | 630 | 190 | 31 | 600 | 1.3 | 31 | 0.98 | 1.4 |
| Ofloxacin | 2 | 2[6] | 20 | 1200 | 360 | 30 | 1100 | 1.3 | 30 | 1.6 | 1.1 |
| *Intravenous administration* | | | | | | | | | | | |
| CLr ($ml min^{-1}$) | | | | | | | | | | | |
| Ampicillin | 1 | 1[7] | 9 | 180 | 90 | 46 | 170 | 1.6 | 46 | 1.6 | 1.8 |
| CL ($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Cefazolin | 2 | 1[8] | 20 | 1.1 | 0.35 | 33 | 0.99 | 1.4 | 34 | 1.1 | 1.4 |
| Piperacillin | 2 | 2[9] | 19 | 3.8 | 1.5 | 40 | 3.5 | 1.5 | 40 | 1.2 | 0.75 |
| Fluconazole | 1 | 1[10] | 9 | 0.16 | 0.08 | 50 | 0.14 | 1.6 | 50 | 2.4 | 1.5 |
| CL ($ml min^{-1}$) | | | | | | | | | | | |
| Ampicillin | 1 | 1[7] | 9 | 280 | 140 | 49 | 252 | 1.6 | 0.49 | 1.4 | 3.1 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$).

[1]Orlando *et al.*, 1992; [2]Ruhnke *et al.*, 1990; [3]Silvain *et al.*, 1989; [4]Lebrec *et al.*, 1992; [5]Esposito *et al.*, 1989 (3), Ruhnke *et al.*, 1990; [6]Silvain *et al.*, 1989, Orlando *et al.*, 1992; [7]Lewis *et al.*, 1975; [8]Ohashi *et al.*, 1986(2); [9]Ruhnke *et al.*, 1995; [10]Hary *et al.*, 1991(2).

## III. 8. Patients with renal disease

**Table 8. Pharmacokinetics of compounds eliminated via renal excretion: comparison between healthy adults and patients with renal disease after oral and intravenous administration[a].**

| Drug | Ns | Np | n | $X_w$ | $SD_w$ | $CV_N$ | $GM_w$ | $GSD_w$ | $CV_{LN}$ | Ratio $H/S_{LN}$ | Ratio $CV_{LN}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Oral administration* | | | | | | | | | | | |
| CLr($ml min^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 4 | 2[1] | 30 | 46 | 46 | 100 | 26 | 1.8 | 0.68 | 11 | 1.7 |
| Ofloxacin | 2 | 2[2] | 15 | 14 | 8.3 | 61 | 10.4 | 1.7 | 57 | 16 | 2.1 |
| CL ($ml min^{-1} 1.73m^{-2}$) | | | | | | | | | | | |
| Lomefloxacin | 9 | 3[3] | 54 | 83 | 27 | 33 | 69 | 1.3 | 28 | 3.2 | 1.4 |
| CL($ml min^{-1}$) | | | | | | | | | | | |
| Ciprofloxacin | 4 | 2[1] | 30 | 443 | 166 | 38 | 411 | 1.4 | 36 | 1.9 | 0.8 |
| Ofloxacin | 5 | 4[4] | 38 | 31 | 16 | 51 | 18 | 1.5 | 44 | 11.4 | 2.0 |
| Cmax/dose ($ng ml^{-1}$)[a] | | | | | | | | | | | |
| Ciprofloxacin | 4 | 2[1] | 30 | 420 | 103 | 25 | 400 | 1.3 | 27 | 1.3 | 0.74 |
| Lomefloxacin | 9 | 3[3] | 54 | 770 | 230 | 30 | 740 | 1.3 | 30 | 1.2 | 1.4 |
| Ofloxacin | 5 | 5[4] | 38 | 1100 | 360 | 31 | 1000 | 1.3 | 29 | 1.4 | 1.1 |
| *Intravenous administration* | | | | | | | | | | | |
| CLr($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Amoxicillin | 3 | 1[5] | 17 | 0.55 | 0.20 | 36 | 0.33 | 1.5 | 46 | 7.5 | 1.5 |
| CLr ($ml min^{-1} 1.73m^{-2}$) | | | | | | | | | | | |
| Piperacillin | 4 | 1[6] | 24 | 53 | 53 | 100 | 30 | 2.37 | 105 | 4.8 | 4.9 |
| CLr ($ml min^{-1}$) | | | | | | | | | | | |
| Ampicillin | 3 | 1[7] | 14 | 49 | 23 | 48 | 11.4 | 2.0 | 79 | 23 | 3.2 |
| Piperacillin | 6 | 2[8] | 54 | 39.8 | 9.7 | 0.25 | 33 | 1.3 | 29 | 4.3 | 1.3 |
| Trobamycin | 1 | 1[9] | 4 | 12 | 10.1 | 84 | 9.1 | 2.1 | 85 | 7.0 | 2.1 |
| CL($ml min^{-1} kg^{-1}$) | | | | | | | | | | | |
| Acyclovir | 1 | 1[10] | 6 | 0.77 | 0.14 | 18 | 0.76 | 1.2 | 18 | 4.8 | 0.59 |
| Amoxicillin | 3 | 1[11] | 16 | 0.87 | 0.28 | 32 | 0.70 | 1.3 | 24 | 4.9 | 0.74 |
| Gentamycin | 1 | 1[12] | 65 | 0.51 | 0.33 | 65 | 0.43 | 1.8 | 65 | 2.7 | 1.6 |
| Trobamycin | 2 | 2[13] | 54 | 0.47 | 0.26 | 56 | 0.50 | 1.6 | 50 | 2.6 | 1.64 |
| CL ($ml min^{-1} 1.73m^{-2}$) | | | | | | | | | | | |
| Acyclovir | 1 | 1[14] | 6 | 29 | 9.5 | 33 | 27 | 1.4 | 0.33 | 8.5 | 1.1 |
| Lomefloxacin | 9 | 3[15] | 54 | 83 | 27 | 33 | 69 | 1.3 | 0.28 | 3.2 | 1.4 |
| Piperacillin | 6 | 2[16] | 34 | 18 | 10.4 | 0.6 | 97 | 1.6 | 0.46 | 2.1 | 1.4 |
| CL ($ml min^{-1}$) | | | | | | | | | | | |
| Ampicillin | 4 | 2[17] | 18 | 86 | 35 | 41 | 52 | 1.5 | 41 | 6.7 | 2.7 |
| Cefpirome | 4 | 1[18] | 22 | 31 | 14 | 46 | 31 | 1.5 | 42 | 2.0 | 1.9 |
| Gentamycin | 1 | 1[19] | 6 | 41 | 7.8 | 19 | 40 | 1.2 | 19 | 1.7 | 0.46 |
| Piperacillin | 9 | 2[20] | 72 | 93 | 16 | 17 | 82 | 1.3 | 26 | 2.7 | 1.1 |
| Trobamycin | 1 | 1[9] | 4 | 27 | 11 | 39 | 25 | 1.5 | 39 | 3.2 | 1.7 |

[a]**Ns** Number of studies; **Np** Number of publications; **n** Number of subjects; $\mathbf{X_W}$ Arithmetic weighted mean (normal distribution); $\mathbf{SD_w}$ Weighted standard deviation (normal distribution); $\mathbf{CV_N}$ Coefficient of variation (normal distribution); $\mathbf{GM_W}$ Geometric weighted mean (lognormal distribution); $\mathbf{GSD_w}$ Weighted geometric standard deviation (lognormal distribution); $\mathbf{CV_{LN}}$ Coefficent of variation; (lognormal distribution); **(n)** in reference, number of studies in the publication entering the weighted mean/weighted standard deviation calculation; [a]Mean data corrected for dose expressed per mean body weight ($mg kg^{-1}$).

[1]Gasser *et al.*,1987, Singlas *et al.*,1987 (2); [2] Bandai *et al.*,1989, Flor *et al.*,1991; [3]Nilsen *et al.*,1982, Blum *et al.*,1990, Leroy *et al.*,1990; [4]Chan *et al.*,1987, Bandai *et al.*,1989, Flor *et al.*,1991(2), Kampf *et al.*,1992; [5]Horber *et al.*,1986(3); [6] Welling *et al.*,1983 (4); [7]Blum *et al.*,1989(4); [8]Aronoff *et al.*,1983 (2), Jonhson *et al.*,1992 (4); [9]Pechere and Dugal, 1976; [10]Boelaert *et al.*,1987; [11]Francke *et al.*,1979; [12]El Sayed *et al.*,1989; [13]Matzke *et al.*,1989, Aronoff *et al.*,1990; [14]Laskin *et al.*,1982b; [15]Nilsen *et al.*,1982, Blum *et al.*,1990, Leroy *et al.*,1990; [16]Giron *et al.*,1981(2), Welling *et al.*,1983 (4); [17]Jusko *et al.*,1973, Blum *et al.*,1989(3); [18]Lameire *et al.*,1992(4); [19]Letourneau-Saheb *et al.*,1977; [20]Aronoff *et al.*,1983 (3), Jonhson *et al.*,1992 (6).