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Case Studies of Categorical Data-Derived Adjustment Factors

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ABSTRACT

Investigations were performed on representative compounds from five different therapeutic classes to evaluate the use of categorical data-derived adjustment factors to account for interindividual variability. The five classes included antidepressants, angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDS), cholesterol lowering agents, and antibiotics. Each of the case studies summarized the mode of action of the class responsible for both the therapeutic and adverse effects and the key pharmacodynamic (PD) and pharmacokinetic (PK) parameters that determine the likelihood of these responses for individual compounds in the class. For each class, an attempt was made to identify the key factors that determine interindividual variability and whether there was a common basis to establish a categorical default adjustment factor that could be applied across the class (or at least across specific subclasses within the class). Linking the PK and PD parameters to the critical endpoint used to establish a safe level of exposure was an important underlying theme throughout the investigations. Despite the wealth of PK and PD information in the published literature on the surrogate compounds representing these classes, it was difficult to derive a categorical adjustment factor that could be applied broadly within each class. The amount of information available may have hindered rather than helped the evaluations. Derivation of categorical defaults for different classes of "common" chemicals may be more straightforward if sufficient data are available. In a few cases (*e.g.*, tricyclic antibiotics, ACE inhibitors and selected antiinflammatory agents) categorical defaults could be proposed, although it is unclear whether the reduction in uncertainty resulting from their application would be offset by the additional uncertainties that may have resulted from their application. Residual uncertainties may remain depending on the level of confidence in the underlying assumptions used

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to support the categorical defaults. Regardless of the conclusions on the utility of categorical defaults, these investigations provided further support for the use of data-derived adjustment factors on a compound-specific basis.

Key Words: acceptable daily intake, occupational exposure limit, reference dose, tolerable intake, toxicokinetics, toxicodynamics, risk assessment, safety factors, uncertainty factors.

INTRODUCTION

Data-derived adjustment factors can be used to replace default uncertainty factors to establish safe levels of exposure whenever sufficient compound-specific data are available. The scheme originally proposed by Renwick (1991, 1993) provides a framework for incorporation of compound-specific toxicokinetic and toxicodynamic data when deriving regulatory and internal health-based limits such as acceptable daily intake values, tolerable intake values, reference doses/concentrations and occupational exposure limits. For some compounds, sufficient compound-specific data may not be available to support a data-derived adjustment factor (AF), but there may be enough information about the class of compounds they belong to which may be utilized. When limited data are available on a particular chemical, safe limits of exposure can be estimated by bridging to other similar compounds that have been more fully characterized by use of analogy and correlation (Galer *et al.* 1992). This would apply not only to the estimation of a no-effect level for the critical endpoint but also to the estimation of interindividual variability for that response.

When considering the use of a categorical default factor a number of criteria need to be satisfied. Renwick (1999) listed a number of considerations for use of compound-related data including whether the compound itself or a metabolite is the active species, the relevance of the toxicokinetic or toxicodynamic data to the critical endpoint, and how representative the data are of the human population. Meek *et al.* (1999) have proposed guidelines on the use of data-derived adjustment values to replace default uncertainty factors when sufficient compound-specific data are available.

Different approaches have been proposed for deriving categorical data-derived adjustment factors on the basis of common metabolic pathways (Walton 2000), physiological considerations (IPCS 2000) and dosimetric adjustments (Jarabek 1994). In this paper we describe the thinking process underlying the decision to apply a categorical default factor for interindividual variability based on similarity within a given therapeutic class of substances. Using published data on pharmaceuticals, five different therapeutic classes were investigated to show how we approached this question. For each category we assumed that we had a new compound in that class without sufficient data to establish a compound-specific adjustment factor. We tried to determine if the information available for the other (presumably well studied) compounds in that class supported a categorical default factor to apply to this new compound. A key determinant was whether there was a "common denominator" that applied to all compounds in that class. While the present investigation focussed on different classes of therapeutic agents, the same approach could be applied to other classes of "common" chemicals.

In this article we also discuss some of the issues that surfaced during these investigations. For example, can a categorical data-derived adjustment factor be applied generally across an entire class or just certain subclasses with precisely the same attributes? Under what circumstances can this default factor be applied? Is it necessary to know the precise mechanism-of-action or is a general understanding of the mode-of-action sufficient within the context of deriving compound- or class-specific adjustment factors to replace default uncertainty factors? Do the data-derived values encompass all of the variability or are there residual uncertainties? Do the data-derived values overstate the variability due to homeostatic/adaptive mechanisms or alternative pathways when a genetic polymorphism exists for a given pathway? What additional uncertainties are introduced by application of a categorical default factor?

METHODS

Interindividual differences were assessed using several pharmacokinetic (PK) and pharmacodynamic (PD) parameters indicative of systemic exposure and pharmacologic activity of the compounds evaluated. The PK parameters initially chosen as measures of internal dose were peak plasma concentration (C_{max}), area under the curve of blood concentration by time (AUC), steady state plasma concentration (SS), and elimination half-life ($t_{1/2}$). The first two, C_{max} and AUC, are considered the best indicators of body burden and systemic exposure since they are direct measures of the amount of compound in the blood. The pharmacodynamic parameters evaluated were appropriate for each therapeutic class. Since the focus of this paper was on interindividual differences (*i.e.*, healthy vs. sensitive individuals), only human *in vitro* and *in vivo* pharmacokinetic and/or pharmacodynamic data were evaluated.

For each therapeutic class an extensive literature search was conducted using Current Contents, MEDLINE and TOXLINE to return studies containing PK and PD data on pharmaceutical compounds of interest for different age groups and health status. The main key words used in the literature searches were related to pharmacokinetics, age and health status. The literature was then reviewed for studies that contained individual values or summary data (mean and standard deviation values) for the kinetic parameters C_{max} and AUC and various measures of pharmacologic activity (dynamics).

The method used to estimate the interindividual variability of a drug based on clinical trial data was adopted from work previously published by Naumann *et al.* (1997) and Silverman *et al.* (1999), which used the ratio of the tail of the distribution to the central tendency on a statistical and empirical basis, respectively, to obtain a data-derived adjustment factor (AF) to account for interindividual differences. The concept was based on the premise that, if a subpopulation (*e.g.*, tail of the distribution) was sufficiently different (*i.e.*, more susceptible based on significantly higher C_{max} or AUC values), their level of exposure needed to be adjusted downward to conform to the normal (average) healthy individual (Figure 1). Where two or more distinct subpopulations existed, the ratio of the upper tail of the most sensitive subpopulation over the mean of the healthy population was used to derive an appropriate adjustment factor (Figure 2).

In the present study, we used several methods for assessing interindividual variability and calculating data-derived adjustment factors using PK and PD information. Where individual values or a series of means from different studies were available we utilized percentiles to estimate data-derived adjustment factors. This approach was favored because the percentiles are easily interpreted in terms of the proportion of the population that is either covered or not covered by a given adjustment factor. Probability plots of either the log-transformed mean AUC or C_{max} values (corrected for dose and normalized for body weight) were used to estimate the 95th percentile and the 50th percentile for a specific population. If body weight was not given it was assumed to be 70 kg. For unimodal populations, with no known sensitive subpopulations, subtracting the 50th percentile from the 95th percentile for the chosen PK or PD parameter yields a log-transformed, empirically derived adjustment factor. The antilog of this difference is the arithmetic equivalent of the data-derived AF. For bimodal distributions (*i.e.*, when there is a recognized sensitive subpopulation) we also utilized percentiles but in this case, the 50th percentile for the healthy subpopulation was subtracted from the 95th percentile for the sensitive subpopulation to yield a log-transformed adjustment factor. Likewise, the antilog of this value represents an appropriate data-derived AF value. This method may be considered a more conservative approach to deal with sensitive subpopulations since it uses the 95th percentile of the sensitive subopulation rather than the combined population.

In most papers, only summary statistics for PK parameters (*e.g.*, mean and standard deviation) were available. Measures of variance for pharmacodynamic parameters (*e.g.*, IC_{50}s) were only rarely provided and only measures of central tendency (*e.g.*, means) were presented. A data-derived adjustment factor was calculated using summary statistics by dividing the mean plus two standard deviations by the mean (*i.e.*, (mean + 2SD)/mean). Occasionally, standard errors needed to be converted to standard deviations by multiplying the former by $\sqrt{N}$. This ratio approximates a 95%/50% ratio for parameters that are normally distributed. The ratios derived for individual compounds in a class were used to determine if the variability for a given PK or PD parameter was sufficiently similar to support a categorical data-derived adjustment factor.

The five therapeutic classes evaluated were antidepressants, angiotensin converting enzyme (ACE) inhibitors, nonsteroidal antiinflammatory drugs (NSAIDs), cholesterol lowering agents and antibiotics. Each of the five authors investigated a different therapeutic class and applied their own approach for assessing the suitability of a categorical data-derived adjustment factor for the class.

CASE STUDIES: FIVE THERAPEUTIC CLASSES INVESTIGATED

Antidepressants: Mode of Action

The first two subclasses of therapeutic agents used in the treatment of major depression were tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors. Since their introduction several other subclasses of antidepressants have been introduced, including selective serotonin reuptake inhibitors (SSRIs) and several others that are described as having atypical mechanisms (Feighner 1999). Tricyclic antidepressants such as amitriptyline and imipramine (tertiary amines)

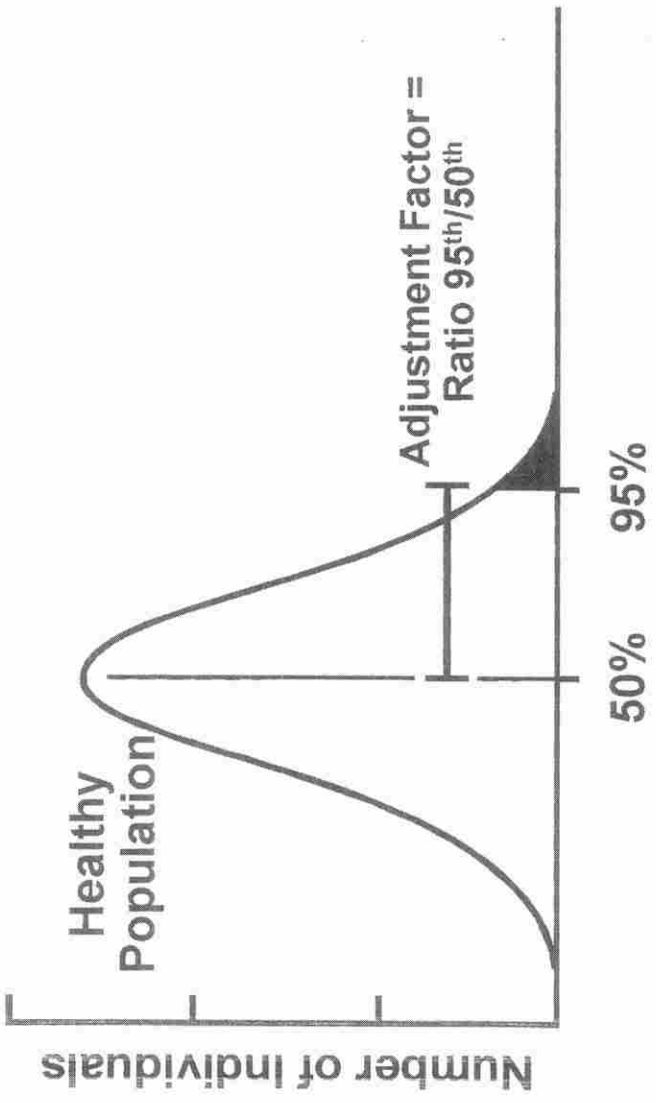

Figure 1. Unimodal population distribution. An alternative adjustment factor (AF) may be expressed as the (Mean + 2SD)/Mean ratio.

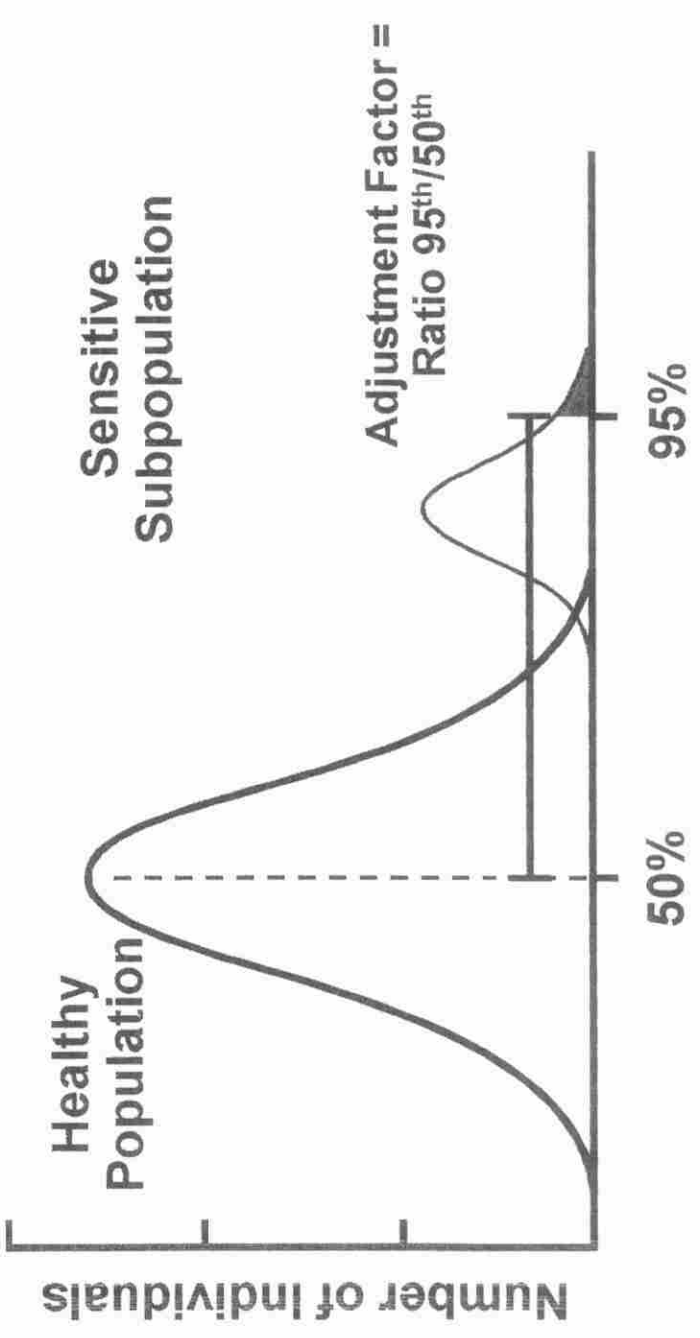

Figure 2. Bimodal population distribution. An alternative adjustment factor (AF) may be expressed as the $(Mean_{Sensitive} + 2SD)SD/Mean_{Healthy}$ ratio.

and their *N*-demethyl derivatives, nortriptyline and desipramine (secondary amines) have been used for 4 decades, and their pharmacodynamics and pharmacokinetics have been studied extensively. All tricyclic antidepressants have the capability of inhibiting the reuptake of norepinephrine and serotonin (5-hydroxytryptamine, 5-HT) by synaptic neurons. The tertiary amines inhibit neuronal uptake of serotonin preferentially, whereas the secondary amines tend to be more potent inhibitors of norepinephrine (NE) uptake. The MAO inhibitors regulate the degradation of catecholamines and serotonin in neural tissues (Baldessarini 1989). Currently marketed MAO inhibitors are site-directed irreversible (suicide) inhibitors and, hence, interfere with amine metabolism (Bonhomme and Esposito 1998). Selective serotonin reuptake inhibitors are a series of antidepressant compounds that are structurally unrelated to TCAs and MAO inhibitors and, as their name implies, preferentially inhibit the reuptake of the neurotransmitter serotonin (Hyttel 1993; Preskorn 1997; Goodnick and Goldstein 1998). The mode of action of all antidepressants involves the increase in serotonergic neurotransmission, although the exact mechanism of action of different subclasses differs (Stahl 1998). It is likely that the efficacy of antidepressants depends on a complex interplay of neurotransmitter uptake, metabolism and receptor binding, with cascading events and multiple feedback mechanisms (DeVane 1998; Sanchez and Hyttel 1999). As a rule, a 2 to 3 week delay in the onset of therapeutic effects is observed with all of the antidepressants, although many of the side effects are manifested at the onset of therapy. Despite the years of experience and research into the understanding of the antidepressant actions of these drugs, the precise mechanistic basis for the efficacy of these compounds is not fully understood (Westenberg 1999). This may not be surprising considering the complexity of the brain and the multiplicity of hormonal and biochemical factors that determine mood and behavior.

Antidepressants: Pharmacodynamics

It seemed reasonable to approach the possible establishment of a categorical data-derived adjustment factor for antidepressants by initially narrowing the evaluation to tricyclic antidepressants, because they dominated the class for many years, are structurally similar, and appear to have similar effects on amine uptake (Table 1). It is well recognized that a reduction in the uptake of key neurotransmitters (*e.g.*, norepinepherine and serotonin) by neurons in specific parts of the brain is the key first step in a cascade of neurochemical responses that ultimately leads to the desired therapeutic effect for tricyclic antidepressants.

When considering the use of a categorical data-derived adjustment factor it is necessary to demonstrate a common mode of action and to evaluate this activity in light of the critical endpoint used as the basis for establishing a safe level of exposure. In other words, the pharmacodynamic endpoint used to characterize interindividual variability must be relevant to the no-effect level for the endpoint used to derive the safe exposure limit. If a new tricyclic antidepressant were compared to other compounds in this class to determine if a categorical default adjustment factor could be applied, it would be necessary to demonstrate that there was a common denominator with respect to the endpoint of concern. In general, within the pharmaceutical industry, the practice is to establish occupational exposure

Table 1. Pharmacodynamic data for antidepressants.

Compound	Subclass	Equilibrium Dissociation Constants (K_d, nM) for Human Brain Receptors					
		$5HT_{1A}$	$5HT_2$	Dopamine, D-2	Histamine, H_1	Muscarinic	α_1-Adrenergic
Amitriptyline	TCA[1]	450 ± 35*	18 ± 2	1460 ± 156	0.95 ± 0.05	9.6 ± 0.5	24.0 ± 3.5
		(1.2)**	(1.2)	(1.2)	(1.1)	(1.1)	(1.3)
Nortriptyline	TCA	294 ± 6.9	41± 7	2570 ± 87	6.3 ± 1.6	37 ± 2	55 ± 3
		(1.0)	(1.3)	(1.1)	(1.5)	(1.0)	(1.1)
Imipramine	TCA	5,800 ± 870	150 ± 3	620 ± 156	37 ± 7	46 ± 3	32 ± 9
		(1.3)	(1.0)	(1.5)	(1.4)	(1.1)	(1.5)
Desipramine	TCA	6,400 ± 520	350 ± 35	3,500 ± 350	60 ± 2	66 ± 3	100 ± 17
		(1.2)	(1.2)	(1.2)	(1.1)	(1.1)	(1.5)
Fluoxetine	SSRI[2]	32,400 ± 15,600	280 ± 87	12,000 ± 1,700	5,400 ± 870	590 ± 120	3,800 ± 520
		(1.1)	(1.6)	(1.3)	(1.3)	(1.4)	(1.3)
Paroxetine	SSRI	>35,000	19,000 ± 1,700	32,000 ± 6,900	22,000 ± 6,900	108 ± 8.7	4,600 ± 9
			(1.2)	(1.4)	(1.3)	(1.2)	(1.0)
Sertraline	SSRI	>35,000	9,900 ± 1,700	10,700 ± 1,400	24,000 ± 8,700	630 ± 52	380 ± 87
			(1.3)	(1.1)	(1.7)	(1.2)	(1.5)
Bupropion	ATYP[3]	N/A	N/A	N/A	6,600 ± 400	48,000 ± 9,000	4,600 ± 500
					(1.1)	(1.4)	(1.0)
Nefazodone	ATYP	80 ± 35	26 ± 3	910 ± 69	24,000 ± 1,700	11,000 ± 3,500	48 ± 3
		(1.9)	(1.3)	(1.2)	(1.1)	(1.6)	(1.1)
Trazodone	ATYP	96 ± 8.7	25 ± 1	3,500 ± 1,040	1,100 ± 350	>35,000	42 ± 5
		(1.2)	(1.1)	(1.6)	(1.6)		(1.2)

[1]TCA-Tricyclic Antidepressant

[2]SSRI-Selective Serotonin Reuptake Inhibitor

[3]ATYP-Atypical Mechanisms

* Mean ± SD

** Numbers in parentheses are (Mean + 2SD)/Mean ratios

N/A Not Available

From Cusack *et al.* 1994

limits (OELs) to protect against all potential adverse effects, including the therapeutic effects (Naumann and Sargent, 1997). These effects are the desired effects in patients, but not in workers that are not under the supervision of a physician. The OEL is also designed to protect against any possible adverse effects associated with the drug. In the case of tricyclic antidepressants, sedation is the most prominent side effect of therapy and is the critical endpoint used to derive the OEL. Drowsiness is an effect that is undesirable in workers because of the obvious implications with respect to worker safety. The stimulating or mood-elevating effects of tricyclic antidepressants do not occur in normal subjects. At least in the case of tricyclic antidepressants, there is a common mechanistic basis for both therapeutic effects and side effects. Table 1 summarizes pharmacodynamic data (human brain receptor binding constants) for a series of antidepressants. Some of the more recent compounds in this class exploit the known structural determinants of drug-induced side effects. For example, the secondary amine tricyclics (*e.g.*, desipramine and nortriptyline) are generally less sedating and have more limited anticholinergic and autonomic side effects than the older tertiary amine tricyclics (*e.g.*, amitriptyline and imipramine). The selective serotonin-reuptake inhibitors are generally well tolerated but also produce sedative effects. Table 1 also provides additional pharmacodynamic data for other subclasses of antidepressants.

Available *in vitro* data on the pharmacodynamics of norepiniephrine and serotonin reuptake and receptor binding at receptors (*e.g.*, 5-HT_{1A}, 5-HT_2, D-2) that are important for therapeutic effects or other receptors that are responsible for the side effects (*e.g.*, histamine, muscarinic, or α_1-adrenergic) suggest that the interindividual variability is relatively low. A categorical data-derived adjustment factor calculated from these pharmacodynamic data (*e.g.*, histamine, H_1) could be as low as 1.1 to 1.7 (see Table 1) (compared to the default value of 3.2) based on the range of (mean + 2SD)/mean ratios for this PD endpoint. However, it may not be appropriate to apply this to the class as a categorical default because of the uncertainties regarding the possible variability in subsequent neurobiochemical mechanisms that ultimately lead to the drug-induced effects. If it was determined that a single receptor (*e.g.*, histamine, H_1) was responsible for the critical effect (*e.g.*, sedation), a data-derived adjustment factor (*e.g.*, average ratio was 1.4 in this case) could apply to all compounds in the class with significant affinity for this receptor. This would include the tricyclics and selected compounds from other subclasses depending on a predetermined threshold for PD activity (*e.g.*, < 1000 n*M*). If adopted, the categorical data-derived AF of 1.4 would replace the default value of 3.2 for interindividual differences in pharmacodynamics.

Antidepressants: Pharmacokinetics

A categorical default factor for pharmacokinetics could also be considered for tricyclics (and perhaps other subclasses of antidepressants) if there is a common determinant of kinetic behavior. Table 2 summarizes the available data on several key PK parameters for a number of antidepressants from different subclasses. Clinically, the interindividual variability in various measures of systemic exposure is considered to be relatively high for antidepressants and dosage adjustments are often recommended for young and elderly patients. Despite this well-established practice, there

Table 2. Pharmacokinetic data for antidepressants.

Compound	Group	N	PK Parameter	Mean ± SD	Ratio (Mean + 2SD)/Mean	Reference
Amitriptyline	Adult	15	SS (ug/L-mg)	0.49 ± 0.39	2.59	Braithwaite *et al.* 1972
	Adult	12	SS (ug/L-mg)	0.64 ± 0.23	1.83	Hucker *et al.* 1975
	Adult	16	SS (ug/L-mg)	0.73 ± 0.43	2.17	Kupfer *et al.* 1977
	Adult	12	SS (ug/L-mg)	0.54 ± 0.27	1.98	Garland *et al.* 1979
	Adult	47	SS (ug/L-mg)	0.57 ± 0.30	2.05	Robinson *et al.* 1979
	Adult	28	SS (ug/L-mg)	0.84 ± 0.48	2.15	Jungkunz and Kuss 1980
	Adult	15	SS (ug/L-mg)	0.53 ± 0.15	1.58	Milkoviz *et al.* 1996
	Adult Females > 50 yrs	110 (both sexes)	SS (ug/L-mg)	2.03 ± 0.59	1.58	Preskorn and Mac 1985
	Adult Males > 50 yrs	110 (both sexes)	SS (ug/L-mg)	1.76 ± 0.78	1.89	Preskorn and Mac 1985
	Depressed Young	6	SS (ug/L)	81.7 ± 41	2.00	Nies *et al.* 1977
	Depressed Elderly	6	SS (ug/L)	138.7 ± 59	3.02 (bimodal)	Nies *et al.* 1977
	Depressed Elderly	6	AUC (ng·hr/ml) - mg	46.4 ± 5.6	1.24	Henry *et al.* 1981
	Adult	24	AUC (ng·hr/ml) - mg	16.9 ± 8.4	1.99	Gupta *et al.* 1998
Citalopram	Adult	18	SS (ug/L-mg)	1.95 ± 0.65	1.67	Pedersen *et al.* 1982
	Adult	55	SS (ug/L-mg)	1.98 ± 0.85	1.86	Fredricson 1982
	Adult	13	SS (ug/L-mg)	1.67 ± 0.56	1.67	Oyehaug *et al.* 1984
	Adult	18	SS (ug/L-mg)	2.30 ± 1.08	1.93	Bouchard *et al.* 1987
	Adult	48	SS (ug/L-mg)	2.00 ± 1.00	2.00	Montgomery *et al.* 1993
	Adult	57	SS (ug/L-mg)	1.68 ± 1.18	2.41	Van Bemmel *et al.* 1993
	Adult	16	SS (ug/L-mg)	2.04 ± 0.84	1.82	Van Bemmel *et al.* 1993
	Adult	61	SS (ug/L-mg)	2.34 ± 1.09	1.94	Baumann *et al.* 1996
	Alcoholic Adults	20	SS (ug/L-mg)	2.05 ± 0.70	1.69	Naranjo *et al.* 1987
Fluoxetine	Adult	13	SS (ug/L-mg)	4.53 ± 1.87	1.83	Kelly et al. 1989
	Adult	14	SS (ug/L-mg)	2.37 ± 0.88	1.74	Nelson *et al.* 1991
	Adult	23	SS (ug/L-mg)	4.13 ± 2.57	2.34	Norman *et al.* 1993
	Adult	19	SS (ug/L-mg)	5.14 ± 2.66	2.03	Goff *et al.* 1995
	Adult	12	$t_{1/2}$ (days)	2.2 ± 1.7	2.55	Schenker *et al.* 1988
	Cirrhotics	13	$t_{1/2}$ (days)	6.6 ± 4.9	7.45 (bimodal)	Schenker *et al.* 1988
Nortriptyline	Adult Female EMs[1]	14	SS (ug/L)	3.8 ± 1.1	1.58	Dahl et al. 1996
	Adult Male EMs	7	SS (ug/L)	2.1 ± 0.5	1.48	Dahl et al.1996

Compound	Group	N	PK Parameter	Mean ± SD	Ratio (Mean + 2SD)/Mean	Reference
	Adult (CYP2D6*1/*1)	5	AUC (nmol·hr/L)	1817 ± 131	1.14	Yue *et al.* 1998
	Adult (CYP2D6*10/*10)	5	AUC (nmol·hr/L)	4002 ± 627	2.89 (bimodal)	Yue *et al.* 1998
Paroxetine	Adult	20	SS (ug/L-mg)	1.93 ± 1.23	2.28	Kuhs *et al.* 1992
	Young EMs	22	AUC (ug·hr/ml)	0.065 ± 0.048	2.48	Findling *et al.* 1999
	Young PMs[2]	2	AUC (ug·hr/ml)	0.39	6.0 (bimodal)	Findling *et al.* 1999
	Young EMs & PMs	24	AUC (ug·hr/ml)	0.09 ± 0.10	3.22	Findling *et al.* 1999

[1]Extensive Metabolizers

[2]Poor Metabolizers

were only anecdotal reports and few quantitative assessments of the variability in plasma levels beyond statements of ranges (*e.g.*, 8 to 30-fold differences) that would permit calculation of ratios. For healthy patients, the (mean + 2SD)/mean ratios for steady state plasma concentrations ranged from 1.1 to 2.6. Bimodal (mean + 2SD)/mean ratios for various PK parameters for sensitive subpopulations ranged from 2.9 to 7.5. Two of the five bimodal ratios exceeded the default PK value of 3.2.

The interindividual differences in the pharmacokinetics of tricyclic antidepressants has been attributed primarily to a genetic polymorphism in oxidative metabolism by hepatic Cytochrome P450 enzymes, predominantly CYP2D6. An estimated 7% of Caucasians have an isoform of CYP2D6 that is much less efficient at oxidizing xenobiotic substrates compared to the rest of the population (Bertilsson 1995). These so-called "poor metabolizers" can be phenotyped using debrisoquine as a probe. Table 2 includes the AUC values for paroxetine in poor and extensive metabolizers. In this case the PK differences between poor and extensive metabolizers overshadow the "normal" variability in extensive metabolizers (Findling *et al.* 1999). The P450 enzyme subtype CYP2D6 is primarily responsible for the metabolism of paroxetine, which also inhibits this drug-metabolizing enzyme (DeVane 1994). A categorical data-derived adjustment factor of 6.0 was calculated by dividing the (mean + 2SD) for poor metabolizers by the mean of the distribution for extensive metabolizers (normal healthy individuals). This categorical default factor could apply to any compound in the class that relies on metabolism by CYP2D6 for removal. This "common denominator" for antidepressants could also apply to other therapeutic classes, including anti-arrhythmics, beta-blockers, and neuroleptics whose pharmacokinetics are determined by CYP2D6 metabolism (Vincent-Viry *et al.* 1991).

Angiotensin Converting Enzyme (ACE) Inhibitors: Mode of Action

Angiotensin converting enzyme (ACE) inhibitors are a major class of therapeutics for treatment of hypertension and heart disease, with more than 10 oral products approved by the FDA (Verme-Gibboney, 1997). ACE inhibitors act on the renin-angiotensin-aldosterone system, which plays a major role in maintenance of blood pressure, electrolyte balance, and blood volume. ACE is a zinc-containing enzyme that is widely distributed throughout the body, including the lungs, kidneys, brain, and blood vessels (Cushman *et al.* 1989). ACE converts the inactive prohormone, angiotensin I to the potent vasoconstrictor angiotensin II. Angiotensin II stimulates the release of aldosterone to promote the reabsorption of sodium and water and to increase the excretion of potassium. Its presence also inhibits the release of renin via a negative feedback loop, thus blocking the renin-angiotensin-aldosterone system leading to vasoconstriction, increased blood volume, and systemic blood pressure. ACE inhibitors prevent the conversion of angiotensin I to angiotensin II thus lowering vascular resistance, lowering blood pressure and improving cardiac function. As ACE also breaks down bradykinin, ACE inhibitors also preserve bradykinin, which is a vasodilator.

ACE Inhibitors: Pharmacodynamics

The hemodynamic endpoint of significance in establishing an occupational exposure limit for each of the ACE inhibitors is systemic reduction in blood pres-

sure. There are three chemically different classes of ACE inhibitors, sulfhydryl-containing, nonsulfhydryl-containing, and phosphorus-containing compounds, although the hemodynamic action of each compound is dependent on its intrinsic potency to bind with ACE and pharmacokinetic properties (Thind 1990). An estimate of age-related differences in both PK and PD was obtained from the data in Table 3. In two separate studies, three different ACE inhibitors were administered orally to healthy, normotensive young (21 to 39) and elderly (66 to 76) volunteers. Plasma ACE inhibiting activity was measured and is shown here as a comparison of the maximum inhibition concentration (I_{max}) and median inhibition concentration (IC_{50}) values. Based on the data shown there appears to be little difference in interindividual variability between the young and elderly. It should be noted that, because both of these studies were *in vivo* the interindividual variability estimate accounted for differences in both pharmacokinetics and pharmacodynamics. Animal studies using *in vitro* design were available to evaluate variability in pharmacodynamics for a number of different tissues (Cushman *et al.* 1989) but similar *in vitro* human data were not available. Consequently, a categorical data-derived adjustment factor for interindividual differences in pharmacodynamics could not be established for ACE inhibitors.

ACE Inhibitors: Pharmacokinetics

Pharmacokinetic variability has been estimated using the parameters AUC and C_{max}. There is a correlation between ACE inhibitor concentration, ACE inhibition and blood pressure reduction (Fyhrquist 1986) that is seen in both healthy normotensives and in hypertensive individuals that can be evaluated using both of these parameters. In defining a possible categorical default factor for interindividual variability it was necessary to first determine whether sensitive subpopulations might exist that would require analysis using a bimodal distribution. Therefore, for the purposes of this evaluation the target group for therapeutic use of ACE inhibitors, hypertensives, was initially considered a potential sensitive subpopulation. Two of the drugs, captopril and lisinopril, require metabolic activation to the active metabolite. All of the others are administered as prodrugs in order to increase bioavailability, rate of absorption, or duration of action (White 1998). Patients with hepatic dysfunction such as cirrhosis may not be able to adequately metabolize the prodrug or eliminate the active metabolite and therefore could also be considered a sensitive subpopulation. ACE inhibitors are primarily cleared via the kidney, and treatment dosages must be adjusted according to renal function (Burnier and Biollaz 1992). A number of studies have been conducted comparing the pharmacokinetics of ACE inhibitors in healthy patients to patients with insufficient renal clearance. Thus, these latter individuals were also considered a potential sensitive subpopulation. Hypertension is seen in individuals in all age brackets and studies have been conducted which have compared the pharmacokinetics in infants, children, adults and elderly. Finally, ACE inhibitors have been shown to improve hemodynamic measurements, provide symptomatic relief, and improve survival in patients with congestive heart failure (Reid *et al.* 1989). Studies comparing pharmacokinetics of several drugs in these patients were available and they were also evaluated as a sensitive subpopulation.

Table 3. Pharmacodynamic data for angiotensin converting enzyme (ACE) inhibitors in the young and elderly.

Compound	Age Status	Plasma I_{MAX} (%)	Plasma IC_{50} (nmol/L)	Ratios (Mean + 2SD/Mean)		Reference
				I_{MAX}	IC50	
Enalaparil	Young	106.7 ± 17.1	22.9 ± 6.5	1.32	1.57	MacDonald *et al.* 1993
Enalaparil	Elderly	95.6 ± 14.2	19.4 ± 5.0	1.30	1.52	MacDonald *et al.* 1993
Benzalepril	Young	97.9 ± 5.2	12.4 ± 4.9	1.10	1.79	MacDonald *et al.* 1993
Benazapril	Elderly	98.9 ± 3.1	14.0 ± 3.5	1.06	1.50	MacDonald *et al.* 1993
Perindopril	Young	N/A	1.5 ± 0.5[1]	N/A	1.67	Lees *et al.* 1988
Perindopril	Elderly	N/A	1.8 ± 0.8[1]	N/A	1.89	Lees *et al.*. 1988

[1]Values in ng/ml

N/A Not Available

Table 4 lists the pharmacokinetic data found from 48 references published on 13 different ACE inhibitors. Shown are the mean and standard deviations for AUC and C_{max} along with the age and the health status of the population studied. The unused references usually did not provide standard deviations or the individual values needed to calculate them. Both C_{max} and AUC data were corrected for dose and body weight. From corrected C_{max} and AUC data, unimodal (mean + 2SD)/Mean ratios were estimated for each drug, age group and health. For purposes of this evaluation, the ages were grouped into adult (19 to 65 years), elderly (greater than 65 years), child (5 to 18 years), and infant (less than 6 months). Some grouping of health status was also done for the purposes of this evaluation. Several studies examined pharmacokinetic differences as a function of the severity of renal failure. Patients with mild, moderate and severe renal failure, renal insufficiency, and on renal dialysis were grouped together under renal failure. Data on healthy fasted and fed volunteers and healthy Caucasian and Chinese volunteers were also grouped.

Pertinent data from Table 4 are presented in summary form in Table 5. Shown here are the average unimodal (mean + 2SD)/mean ratios for the healthy individuals and the average bimodal ($mean_{subpopulation}$ + 2SD)/$mean_{healthy}$ ratios for six different potentially sensitive subpopulations. The average unimodal ratios for a healthy adult population fall within a relatively narrow range (1.19 to 2.39) which is well below the default value of 3.2. This leads to the conclusion that a categorical data-derived adjustment factor could be derived for this class of compounds as long as the adjustment factor was applied to a risk estimate aimed at a population of exposed healthy adults. Such an adjustment factor could be used in the derivation of an occupational exposure limit for a new ACE inhibitor since it can be assumed that extremes of age and unhealthy individuals would not be found in the workplace. The bimodal ratios showed much greater variability, ranging from less than 1 to greater than 16. Based on the variability in these data a categorical adjustment factor could not be derived for this class of compounds that would be applicable to all sensitive subpopulations. The highest value of 16 was based on a single study with a limited number of coronary heart failure patients and its use for the general population would be overly conservative.

Nonsteroidal Antiinflammatory Drugs (NSAIDS): Mode of Action

Nonsteroidal antiinflammatory drugs (NSAIDs) are a heterogeneous group of compounds, which are widely used as analgesic, antiinflammatory, and antipyretic drugs. The NSAIDs are among the most prescribed and most widely used over-the-counter drugs in the world, but their long-term use has been limited by gastrointestinal side effects (Baum *et al.* 1985; Coles *et al.* 1981). It is widely accepted that NSAIDs exert their therapeutic effects by inhibiting the activity of cyclooxygenase (COX), the enzyme involved in the biosynthesis of prostaglandins and related prostanoids (Vane 1971). Over the last several decades, it has also become clear that important differences in side effects exist among various NSAIDs, which can not be explained by their physical and chemical properties and pharmacokinetics. In recent years two isoforms of COX, COX-1 and COX-2, have been identified. COX-1, the constitutive form of COX has been found in many tissues, including platelets and gastric mucosa. COX-2, the inducible form of COX is short-lived and is induced by a variety of

Table 4. Pharmacokinetic data for angiotensin converting enzyme (ACE) inhibitors.

Compound	N	Age	Health Status	C_{MAX} ng/ml Mean ± SD	AUC ng·hr/ml Mean ± SD	C_{MAX} Ratio Mean + 2SD / Mean	AUC Ratio Mean + 2SD / Mean	Reference
Alacepril	7	Adult	Healthy	226 ± 53	861 ± 47	2.25	1.29	Onoyama *et al.* 1986
Alacepril	7	Adult	Healthy	266 ± 53	807 ± 41	2.05	1.27	Onoyama *et al.* 1985
Alacepril	7	Adult	Healthy	247 ± 41	746 ± 77	1.33	1.21	Onoyama *et al.* 1985
Alacepril	9	Adult	Renal Failure	239 ± 33	763 ± 56	1.83	1.44	Onoyama *et al.* 1986
Altiopril	8	Adult	Healthy	63 ± 6*	177 ± 18	1.19	1.20	Onoyama *et al.* 1990
Altiopril	8	Adult	Renal Failure	110 ± 25*	397 ± 70	1.45	1.35	Onoyama *et al.* 1990
Benazoprilat	9	Adult	Healthy	476 ± 152	2765 ± 775	1.64	1.56	MacDonald *et al.* 1993
Benazoprilat	9	Elderly	Healthy	444 ± 114	3867 ± 1340	1.51	1.69	MacDonald *et al.* 1993
Captopril	5	Adult	Healthy	143 ± 35	725 ± 84	1.49	1.23	Duchin *et al.* 1982
Captopril	6	Adult	Healthy	163 ± 72	364 ± 93	1.88	1.51	Jankowski *et al.* 1995
Captopril	6	Adult	Healthy	190 ± 143	537 ± 125	1.99	1.47	Jankowski *et al.* 1995
Captopril	12	Adult	Healthy Females	554 ± 230	728 ± 181	1.84	1.50	Massana *et al.* 1997
Captopril	12	Adult	Healthy Males	587 ± 236	718 ± 214	1.80	1.60	Massana *et al.* 1997
Captopril	12	Elderly	Healthy	803 ± 232	1394 ± 204	1.58	1.29	Creasey *et al.* 1986
Captopril	10	Infant	Chronic Heart Failure	350 ± 184	1019 ± 331	2.05	1.64	Pereira *et al.* 1991
Captopril	6	Adult	Chronic Heart Failure	94 ± 12	7734 ± 1154	1.26	1.29	McElnay *et al.* 1996
Captopril	8	Adult	Hypertensive	447 ± 889	437 ± 229	4.98	2.05	Drummer *et al.* 1987
Captopril	10	Adult	Hypertensive	1210 ± 569	1673 ± 673	1.94	1.63	Giudicelli *et al.* 1984
Captopril	10	Adult	Hypertensive	1310 ± 632	N/A	1.96	N/A	Richer *et al.* 1984
Captopril	6	Adult	Hypertensive/Renal Failure	181 ± 466	1350 ± 2131	6.15	3.93	Drummer *et al.* 1987
Captopril	10	Adult	Hypertensive/Renal Failure	1050 ± 474	2043 ± 1068	1.90	2.05	Giudicelli *et al.* 1984
Captopril	9	Adult	Hypertensive/Renal Failure	1000 ± 420	1934 ± 1170	1.84	2.21	Giudicelli *et al.* 1984
Captopril	8	Child	Renal Failure	267 ± 168	637 ± 519	2.25	2.63	Levy *et al.* 1991
Captopril	4	Adult	Renal Failure	800 ± 400	1900 ± 600	2.00	1.63	Duchin *et al.* 1984
Captopril	8	Adult	Renal Failure	1100 ± 566	7100 ± 283	2.02	1.08	Duchin *et al.* 1984
Captopril	6	Adult	Renal Failure	800 ± 245	2600 ± 735	1.61	1.57	Duchin *et al.* 1984
Captopril	5	Adult	Renal Failure	387 ± 167	711 ± 321	1.86	1.90	Fujimura *et al.* 1986
Captopril	8	Adult	Renal Failure	500 ± 283	8200 ± 1981	2.13	1.48	Duchin *et al.* 1984
Delaprilat	6	Adult	Healthy	442 ±123	1110 ± 176	1.55	1.32	Onoyama *et al.* 1987
Delaprilat	9	Adult	Hypertensive	635 ± 168	1859 ± 480	1.53	1.51	Shionoiri *et al.* 1987
Delaprilat	4	Adult	Hypertensive/Renal Failure	797 ± 202	6400 ± 3362	1.51	2.05	Shionoiri *et al.* 1987

Delaprilat	6	Adult	Renal Failure	929 ± 355	4225 ± 2298	1.76	2.09	Onoyama *et al.* 1987
Compound	**N**	**Age**	**Health Status**	**C_{MAX} ng/ml Mean ± SD**	**AUC ng·hr/ml Mean ± SD**	**C_{MAX} Ratio Mean + 2SD / Mean**	**AUC Ratio Mean + 2SD / Mean**	**Reference**
Delaprilat	12	Adult	Renal Failure	780 ± 408	5983 ± 5269	1.74	2.76	Onoyama *et al.* 1988
Enalaprilat	9	Adult	Healthy	128 ± 63	1272 ± 215	1.98	1.34	MacDonald *et al.* 1993
Enalaprilat	4	Adult	Healthy	88.1 ± 16.6	710 ± 102	1.38	1.29	McLean *et al.* 1989
Enalaprilat	9	Adult	Healthy	68 ± 29	722 ± 188	1.85	1.52	Hockings *et al.* 1986
Enalaprilat	10	Adult	Healthy	108.9 ± 29.1	951 ± 188	1.53	1.40	Hayes *et al.* 1989
Enalaprilat	9	Elderly	Healthy	199 ± 105	2709 ± 1459	2.05	2.07	MacDonald *et al.* 1993
Enalaprilat	9	Elderly	Healthy	101 ± 54	997 ± 332	2.07	1.67	Hockings *et al.* 1986
Enalaprilat	7	Elderly	Chronic Heart Failure	10.3 ± 4.8	218.3 ± 126	1.93	2.15	Johnston and Duffin 1992
Enalaprilat	9	Elderly	Hypertensive	119 ± 53	289 ± 221	1.89	2.53	Weisser *et al.* 1992
Enalaprilat	10	Elderly	Renal Failure	23.3 ± 11	386 ± 155	1.47	1.82	Sica *et al.* 1991
Enalaprilat	8	Adult	Cirrhotic	152.7 ± 114.1	1660 ± 1363	2.49	2.64	Hayes *et al.* 1989
Fosinprilat	6	Adult	Healthy	144 ± 62	940 ± 400	1.86	1.85	Ford *et al.* 1995
Fosinprilat	10	Adult	Healthy	177 ± 64	1489 ± 619	1.72	1.83	Kostis 1995
Fosinprilat	12	Adult	Healthy	183 ± 59	1556 ± 586	1.64	1.75	Ding *et al.* 2000
Fosinprilat	10	Adult	Chronic Heart Failure	195 ± 67	1716 ± 808	1.69	1.94	Kostis 1995
Fosinprilat	4	Adult	Renal Failure	165 ± 11	2135 ± 327	1.27	1.68	Hui *et al.* 1991
Fosinprilat	5	Adult	Renal Failure	136 ± 23	2052 ± 286	1.75	1.62	Hui *et al.* 1991
Fosinprilat	4	Adult	Renal Failure	127 ± 22	2405 ± 668	1.69	2.11	Hui *et al.* 1991
Fosinprilat	12	Adult	Cirrhotic	140 ± 51	1255 ± 434	1.73	1.69	Ford *et al.* 1995
Lisinopril	4	Adult	Healthy	64 ± 13	767 ± 132	1.40	1.34	McLean *et al.* 1989
Lisinopril	6	Adult	Healthy	N/A	526 ± 191	N/A	1.72	Gautam *et al.* 1987
Lisinopril	18	Adult	Healthy	86 ± 48	1231 ±620	2.12	2.01	Mojaverian *et al.* 1986
Lisinopril	16	Adult	Healthy	31 ± 22.1	347 ± 223	2.43	2.28	Neubeck *et al.* 1994
Lisinopril	10	Adult	Healthy	80.4 ± 38.7	1047 ± 340	1.96	1.65	Hayes *et al.* 1989
Lisinopril	6	Elderly	Healthy	N/A	870.4 ± 341	N/A	1.78	Gautam *et al.* 1987
Lisinopril	12	Adult	Chronic Heart Failure	N/A	530 ± 377	N/A	2.42	Till *et al.* 1989
Lisinopril	6	Elderly	Chronic Heart Failure	N/A	1195.9 ± 357	N/A	1.59	Gautam *et al.* 1987
Lisinopril	6	Elderly	Chronic Heart Failure	11.5 ± 6.1	192.3 ± 50.5	2.06	1.53	Johnston and Duffin 1992
Lisinopril	6	Adult	Hypertensive	74.2 ± 82.3	848 ± 828	3.22	2.95	Van Schaik *et al.* 1988
Lisinopril	9	Adult	Hypertensive	41.8 ± 22.2	523.6 ± 243.3	2.06	1.93	Shionoiri *et al.* 1990

Table 4. (cont.)

Compound	N	Age	Health Status	C_{MAX} ng/ml Mean ± SD	AUC ng·hr/ml Mean ± SD	C_{MAX} Ratio Mean + 2SD / Mean	AUC Ratio Mean + 2SD / Mean	Reference
Lisinopril	6	Adult	Hypertensive/Renal Failure	66.9 ± 39.6	1210 ± 662	2.18	2.09	Van Schaik *et al.* 1988
Lisinopril	6	Adult	Hypertensive/Renal Failure	41.1 ± 13.6	590 ± 139	1.66	1.47	Van Schaik *et al.* 1988
Lisinopril	8	Adult	Hypertensive/Renal Failure	73.9 ± 23.8	1108.8 ± 365	1.64	1.66	Shionoiri *et al.* 1990
Lisinopril	8	Adult	Renal Failure	4.7 ± 2.5	75 ± 39	2.09	2.04	Neubeck *et al.* 1994
Lisinopril	10	Elderly	Renal Failure	47.4 ± 21	8164 ± 361	1.89	1.09	Sica *et al.* 1991
Lisinopril	8	Adult	Cirrhotic	150 ± 164.8	1584 ± 834	3.20	2.05	Hayes *et al.* 1989
Pentoprilat	8	Adult	Healthy	420 ± 170	1800 ± 481	1.81	1.53	Rakhit *et al.* 1985
Pentoprilat	8	Adult	Healthy	370 ± 537	1620 ± 509	3.90	1.63	Rakhit *et al.* 1985
Pentoprilat	6	Adult	Hypertensive	488 ± 271	2200 ± 2675	2.11	3.44	Rakhit *et al.* 1988
Pentoprilat	9	Adult	Hypertensive/Renal Failure	1643 ± 738	2620 ± 7470	1.90	6.7	Rakhit *et al.* 1988
Perindoprilat	8	Adult	Healthy	N/A	119.7 ± 83	N/A	2.39	Lees *et al.* 1988
Perindoprilat	8	Elderly	Healthy	N/A	295 ± 286	N/A	2.93	Lees *et al.* 1988
Perindoprilat	6	Adult	Hypertensive	8.5 ± 6.4	93 ± 34	2.50	1.69	Verpooten *et al.* 1991
Perindoprilat	4	Adult	Hypertensive/Renal Failure	30.1 ± 11	361 ± 92	1.73	1.62	Verpooten *et al.* 1991
Perindoprilat	6	Adult	Hypertensive/Renal Failure	12.6 ± 8.6	217 ± 97	2.39	1.88	Verpooten *et al.* 1991
Perindoprilat	6	Adult	Hypertensive/Renal Failure	19.5 ± 8.6	398 ± 243	1.88	2.22	Verpooten *et al.* 1991
Perindoprilat	4	Adult	Hypertensive/Renal Failure	32.6 ± 21	1106 ± 496	2.31	2.10	Verpooten *et al.* 1991
Ramiprilat	5	Adult	Hypertensive	4.7 ± 1.1	86.5 ± 23.2	2.05	2.20	Shionoiri *et al.* 1987
Ramiprilat	5	Adult	Hypertensive/Renal Failure	19.0 ± 3.7	325.2 ± 104.9	1.87	2.44	Shionoiri *et al.* 1987
Zofenoprilat	18	Adult	Healthy	726 ± 229	1191 ± 279	1.63	1.47	Marzo *et al.* 1999

N/A Not Available

proinflammatory cytokines, mitogens and growth factors (Hawkey 1999). With the discovery of COX-2 selective inhibitors, it is now possible to show that differential inhibition of COX-1 and COX-2 by NSAIDs is the basis for the differences in gastrointestinal side effects among various NSAIDs. Inhibition of gastric mucosal COX-1 by NSAIDs is regarded as the major cause of gastrointestinal side effects of NSAIDs: gastric perforation, ulceration, and bleeding (Hawkey 1999). The antiinflammatory, antipyretic, and analgesic effects of NSAIDs are mostly related to the inhibition of COX-2. Overall, most if not all NSAIDs share a common mode of action *i.e.*, the inhibition of cyclooxygenase; however, differential inhibition of the two isoforms of COX enzymes is responsible for the differences in their therapeutic efficacy and adverse effects (Hawkey 1999; Mitchell *et al.* 1993; O'Neill *et al.* 1994).

Nonsteroidal Antiinflammatory Drugs (NSAIDS): Pharmacodynamics

Invariably, all NSAIDs show antiinflammatory, analgesic, and antipyretic activities; however, these effects vary significantly among various NSAIDs possibly due to varying COX-1 vs. COX-2 inhibitory activities and mechanistic differences (Mitchell *et al.* 1993; O'Neill *et al.* 1994; Ansel 1996). For example, acetaminophen has strong analgesic and antipyretic activity but has very poor antiinflammatory activity possibly owing to a weak inhibition of COX. Aspirin significantly differs from other marketed NSAIDs in its mechanism of COX inhibition. Unlike most NSAIDs, aspirin is an irreversible inhibitor of COX isoenzymes by virtue of its covalent binding to COX proteins and the duration of the pharmacodynamic effects of aspirin are related to different turnover of COX enzymes in various target tissues. Antithrombolytic properties of aspirin are related to its ability to inhibit COX-1 (formation of thromboxane) throughout the life of the platelet (8 to 10 days) providing a strong anticlotting effect (Ansel 1996). The antipyretic and antiinflammatory effects of aspirin are related to an irreversible inhibition of COX-2 (Ansel 1996). Most other marketed NSAIDs (excluding COX-2-specific inhibitors) are reversible inhibitors of COX. Recently approved COX-2-specific inhibitors are believed to be slowly reversible noncompetitive inhibitors of COX-2. Overall, gastrointestinal toxic effects of NSAIDS are dependent on their ability to differentially inhibit the two isoforms of COX (Ansel, 1996; Donnelly and Hawkey 1997).

The side effects of NSAIDs include (but are not limited to) gastrointestinal ulceration, blockade of platelet aggregation through inhibition of thromboxane synthesis, inhibition of prostaglandin-mediated renal function, and hypersensitivity reactions. Important clinically significant differences in toxicity exist among various marketed NSAIDs (Ansel 1996; Fries *et al.* 1991). It has been shown that local irritation and/or continued inhibition of gastric prostaglandin synthesis are responsible for the gastrointestinal side effects of various NSAIDs, including gastric perforation, ulceration and bleeding. Table 6 shows a comparison of gastrointestinal toxicity with COX-2 vs. COX-1 selectivity for selected NSAIDs (Donnelly and Hawkey 1997). Although efficacy of various NSAIDs can vary widely, clinical experience indicates that large differences in average efficacy are uncommon.

In setting occupational exposure limits for workers involved in the manufacturing of NSAIDs, it is imperative that workers are protected from both pharmacological (antiinflammatory, antipyretic, and analgesic effects) and toxic effects. NSAIDs may also produce idiosyncratic hypersensitivity reactions. Table 6 also shows the

Table 5. Pharmacokinetic data for angiotensin converting enzyme (ACE) inhibitors on potentially susceptible subpopulations.

Unimodal Ratios* $(Mean_{Healthy} + 2SD)/Mean_{Healthy}$	Bimodal Ratios* $(Mean_{Subpop} + 2SD_{Subpop})/Mean_{Healthy}$													
	Healthy		Elderly		CHF		Hypertensive		Renal Failure		Hypertensive + Renal Failure		Cirrhosis	
Compound	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Alacepril	1.88	1.28	N/A	N/A	N/A	N/A	N/A	N/A	1.24	1.09	N/A	N/A	N/A	N/A
Altiopril	1.19	1.20	N/A	N/A	N/A	N/A	N/A	N/A	0.04	3.03	N/A	N/A	N/A	N/A
Benzoprilat	1.64	1.56	1.41	2.36	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Captopril	1.80	1.46	3.87	2.93	0.36	16.35	6.87	4.45	4.22	9.23	5.05	7.64	N/A	N/A
Delaprilat	1.55	1.32	N/A	N/A	N/A	N/A	2.20	2.54	3.66	11.41	2.72	11.82	N/A	N/A
Enalaprilat	1.70	1.39	4.17	6.16	0.20	0.51	2.30	0.80	0.45	0.76	N/A	N/A	3.89	4.80
Fosinoprilat	1.74	1.81	N/A	N/A	1.96	2.51	N/A	N/A	1.08	2.29	N/A	N/A	1.44	1.60
Lisinopril	1.98	1.80	N/A	2.53	N/A	1.63	2.49	2.24	0.15	0.20	1.74	2.23	7.38	4.15
Penrindoprilate	N/A	2.39	N/A	7.22	N/A	N/A	N/A	1.34	N/A	N/A	N/A	8.20	N/A	N/A
Pentoprilat	2.86	1.58	N/A	N/A	N/A	N/A	2.61	4.42	N/A	N/A	7.90	10.27	N/A	N/A
Zofenoprilat	1.63	1.47	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A - Not Available

* Average ratios for given ACE Inhibitor and Subgroup

Table 6. Pharmacodynamic data for nonsteroidal antiinflammatory drugs (NSAIDS).

NSAID	IC_{50} (nM)[1]		IC_{50} COX-2 / IC_{50} COX-1	Relative Risk for GI Toxicity
	COX-1	COX-2		
Indomethacin	13.5 ± 3.5[2]	> 1000	> 74	18.0 (8.2-39.6)[3]
Suldinac Sulfide	1.3 ± 1.0	50.7 ± 6.6	39	-
Piroxican	17.7 ± 3.3	> 500.0	28	6.3 (3.3-12.2)
Diclofenac	2.7 ± 1.0	20.5 ± 6.4	7.6	3.9 (2.3-6.5)
Flubiprofen	0.5 ± 0.1	3.2 ± 1.6	6.5	-
Mectofenamate	1.5 ± 0.6	9.7 ± 1.8	6.4	-
Naproxen	4.8 ± 1.8	28.4 ± 7.6	6.3	3.1 (1.7-5.9)
Ibuprofen	4.0 ± 1.0	12.4 ± 2.1	5.9	2.9 (1.7-5.0)
Ketorolac	31.5 ± 9.2	60.5 ± 14.8	3.1	-
Etodolac	74.4 ± 7.6	60.0 ± 8.4	1.9	-
Salicylic Acid	> 1000	> 1000	~ 1.0	-
Phenylbutazene	16.0	> 100	0.8	-

[1]Inhibition of Human Cyclooxygenase Isoenzymes

[2]Mean ± SD

[3]95% Confidence Interval

COX-1 and COX-2 inhibitory activities of selected NSAIDs. In this regard it is essential to know the no-effect level for efficacy as well as for toxic effects. Exposure limits for workers must provide an adequate margin of safety relative to both no-effects levels. Since the gastric tolerability of NSAIDs vary widely and the interindividual variability in (local) gastric exposure to oral NSAIDs is expected to be low, it is likely that individual susceptibility factors may be important. These may include distribution of bacterial population, age (elderly people are generally less tolerant to NSAIDs), and disease status (Ansel 1996; Day *et al.* 1987). Additionally, there are some individuals that may experience idiosyncratic hypersensitivity with certain NSAIDs. Because of the above noted reasons, replacement of the default factor of 3.2 (WHO 1994) for inter-individual variability with a categorical data-derived adjustment factor seems inappropriate for NSAIDS as a class. However, a categorical data-derived adjustment factor for the PD variability may be appropriate for the new generation of COX-2 selective inhibitors, which are likely to show a low degree of gastrointestinal toxicity.

Nonsteroidal Antiinflammatory Drugs (NSAIDS): Pharmacokinetics

It has been suggested that interindividual variability in pharmacokinetics may also contribute to variability in therapeutic response and tolerability to various NSAIDs (Famey 1985; Day *et al.* 1987; Simkin 1988). Certain NSAIDs show a weak correlation between dose and therapeutic effect. The lack of pharmacokinetic-pharmacodynamic correlation for various NSAIDs may be due to the fact that the plasma concentrations of NSAIDs are only distantly related to drug concentrations at sites of efficacy (*e.g.*, inflamed tissues, synovial fluid etc.) and toxicity (*e.g.*, gastrointestinal tissues) (Sinkin 1988). Additional factors that may contribute to a poor pharmacokinetic-pharmacodynamic relationship include differences in pharmacokinetics between responders and non-responders, variable plasma protein binding, concentrations in target sites, variable elimination half-lives, metabolic activation, disease status, and age (Famey 1985; Day *et al.* 1987; Simkin 1988). The pharmacodynamic mechanisms (*e.g.*, reversible/slowly reversible/irreversible inhibition of COX isoenzymes) by which NSAIDs inhibit COX activity also may be an important factor in understanding the plasma concentration-effect relationship for various NSAIDs.

In reviewing the pharmacokinetics of NSAIDs as a class, the best correlation exists for salicylates. Mild analgesia was observed at a plasma concentration of 100 μg/mL, and concentrations of 75 to 300 μg/ml provided strong antiinflammatory activity against rheumatoid arthritis. Toxic effects, including headache, nausea, and vomiting, were observed between 300 to 400 μg/ml and a concentration of 900 μg/ml was associated with death (Famey 1985; Day *et al.* 1987). Despite this correlation between plasma concentration and therapeutic and toxic effects, there are significant interindividual variations in the pharmacokinetics of salicylates and significant overlap exists between the therapeutic and toxic concentrations. Indomethacin shows a good correlation between plasma concentration and the inhibitory effects on prostaglandin synthesis (Famey 1985); however, a similar correlation does not exist between plasma indomethacin concentration and antiinflammatory activity in rheumatoid diseases. Additionally, high and variable concentrations of indometha-

cin seem to be associated with a high degree of gastrointestinal toxicity. Many propionic acid NSAIDs show a good correlation between plasma concentration and prostaglandin inhibition, however, they fail to show a similar correlation between plasma concentration and antiinflammatory activity in arthritis. Half-lives of various NSAIDs range from 1.5 to 29 hours for various NSAIDS (Famey 1985; Heel and Avery 1980). It has been observed that NSAIDs with short and intermediate half-lives equilibrate rapidly between plasma and target tissues when compared to their elimination; however, peak concentrations in target tissues (*e.g.*, synovial fluid) occur later giving rise to a poor correlation between plasma concentration and efficacy. Generally, NSAIDs with a longer half-life also show a lower C_{max} and delayed T_{max} in synovial fluid; however, synovial fluid approaches a closer equilibrium with blood because of the smaller fluctuations in plasma concentrations. It appears that NSAIDs with a long half-life may show a better correlation between plasma concentration and effect(s) than NSAIDs with a short half-life; however, such a correlation has not been demonstrated consistently for NSAIDs with a long plasma half-life (Day *et al.* 1987; Netter *et al.* 1989). Given the poor correlation between plasma pharmacokinetics and efficacy/toxicity, and lack of information on drug concentration in synovial fluid or other target sites, it is difficult to establish a precise relationship between plasma concentrations and effects. For certain NSAIDS such as salicylates, which show a fairly good correlation between plasma concentration and effects (therapeutic and toxic), a categorical data-derived adjustment factor may be appropriate.

Cholesterol-Lowering Agents: Mode of Action

The 'statins' are a class of cholesterol-lowering agents used as the first line of therapy for the treatment of hypercholesterolaemia. They inhibit the rate-limiting step in cholesterol biosynthesis by reversibly inhibiting the microsomal enzyme, HMG-CoA reductase (Goldstein and Brown 1990). This enzyme converts HMG-CoA to mevalonate in the cholesterol biosynthetic pathway. Inhibition of HMG-CoA reductase by statins decreases intracellular cholesterol synthesis and eventually increases cell surface LDL receptors. Subsequently, additional cholesterol is provided to the cell by *de novo* synthesis and by receptor-mediated uptake of LDL-C from the blood. This mechanism resets intracellular cholesterol homeostasis in extrahepatic tissues. The liver is the target organ for the statins, since it is the major site of cholesterol biosynthesis, lipoprotein production and LDL catabolism. However, cholesterol biosynthesis in extrahepatic tissues is also necessary for normal cell function. The potential adverse effects of HMG-CoA reductase inhibitors during chronic treatment depends in part upon the degree to which they exert their inhibitory activity in extrahepatic tissues such as muscle (Sirtori 1993), although elevations in liver enzymes are also important adverse events that must be monitored. Both the cholesterol lowering therapeutic effects and the potential adverse effects in hepatic and extrahepatic tissues need to be considered when establishing a categorical data-derived AF for statins as a class.

The statins evaluated were fluvastatin, lovastatin, pravastatin and simvastatin. The last three are all derived from fungi and are structurally similar. Fluvastatin is a

synthetic material with a structure distinct from that of the others. The pharmacological mode of action is well defined and is the same for each of these.

Cholesterol-Lowering Agents: Pharmacodynamics

The statins share the same basic mode of action in lowering cholesterol, *i.e.*, they act by reversibly inhibiting HMG-CoA reductase. The rare but potential serious adverse effects (*e.g.*, hepatotoxicity, rhabdomyolisis, and developmental toxicity) associated with these drugs are critical endpoint(s) that may be used as the basis for establishing safe exposure levels.

In vitro pharmacodynamic studies show that the variability in inhibition of HMG-CoA reductase activity in various cell lines from various species, including humans, is low (Cohen *et al.* 1993). For example, the IC_{50}s (Mean $\pm$ SD) in cultured human myoblasts for lovastatin, simvastatin, and pravastatin were 19 $\pm$ 6, 4.0 $\pm$ 2.3, and 110 $\pm$ 38 n*M*, respectively (Van Vliet *et al.* 1996). Pravastatin was less active compared with lovastatin and simvastatin in human hepatoma cells (IC_{50} = 1900 n*M*) than in homogenates of these cells (IC_{50} = 95 n*M*), suggesting that differential uptake was a factor. Uptake and intracellular metabolism are considered under pharmacodynamics in the current scheme for data-derived adjustment factors.

When determining if a categorical default adjustment factor for pharmacodynamics is appropriate, variability in healthy individuals and any potentially sensitive subpopulations need to be taken into consideration. Data were collected from studies in the published literature comparing the efficacy of the statins in several, possibly sensitive, hypercholesterolemic subpopulations (Table 7). These data, which reflect both pharmacokinetics and pharmacodynamics, suggest that sensitive subpopulations do not exist for the statins as a class. The therapeutic reductions in LDL-C achieved with a statin in hypercholesterolemic healthy individuals are similar to those achieved in healthy subpopulations. Clinical efficacy and tolerability profiles were similar among the subpopulations (*i.e.*, male vs. female) for all four statins investigated (data not shown). It is not possible to identify, *a priori*, susceptible individuals that may experience idiosyncratic adverse events involving the muscle or liver. A composite factor to account for PD interindividual variability could not be calculated for the statins due to the lack of data in the published literature on the variability among individuals in potential sensitive subpopulations.

A key question is whether the critical endpoint is manifested at the same level of tissue exposure and via the same mode of action for all the agents in this class. Pharmacodynamic factors do not appear to be as important as PK factors when comparing drugs of this class due to the fact that the four statins investigated in this study have similar PD properties. The data collected demonstrate that a categorical data-derived adjustment factor for pharmacodynamics is not recommended, but that use of compound-specific data-derived adjustment factors is appropriate.

Cholesterol-Lowering Agents: Pharmacokinetics

The possibility of calculating a categorical data-derived adjustment factor to account for interindividual variability in PK for the statins was also investigated. The statins are administered orally. Fluvastatin and pravastatin are administered as active

hydroxy acid drugs, whereas lovastatin and simvastatin are administered as their inactive lactone precursors, which undergo conversion to the corresponding open hydroxy acids by carboxyesterases. These statins undergo metabolism after they enter the enterocytes that line the alimentary tract that contain a variety of metabolizing enzymes. The inactive lactone precursors are also metabolized by various enzyme systems in the plasma and liver. These activities vary between individuals and are highly dependent on age, nutrition, sex, health status, etc. Pharmacokinetic properties such as degree of systemic exposure, hepatic extraction, metabolism, and elimination half-life of active compound(s) are important when comparing a class of drugs. The effective elimination half-lives of the hydroxy acid forms of the four statins range from 0.7 to 3.0 hours. Protein binding is >90% for fluvastatin, lovastatin, and simvastatin, but only 50% for pravastatin. Fluvastatin is greatly absorbed from the small intestine, followed by extensive metabolism via CYP2C9 in the liver with metabolites excreted in the bile (Lindahl *et al.* 1996). In contrast to fluvastatin, 31% of oral doses of lovastatin and pravastatin are absorbed intestinally. Lovastatin is a hydrophobic material, which does not allow for complete dissolution in the intestinal fluid. Pravastatin is very hydrophilic, restricting effective intestinal permeability. The carboxyesterases in the liver and plasma that activate statins show large variations between individuals (Tang and Kalow 1995). Cytochrome P4503A4 plays a role in the metabolism of lovastatin, simvastatin and, to a lesser extent, pravastatin. None of these PK parameters (protein binding, metabolism, hydrophilicity, and absorption) that influence the disposition of statins provided a common determinant of kinetic behavior that could be used to define a categorical data-derived adjustment factor.

Several other key PK parameters were evaluated as an attempt to determine if they can be used to develop a categorical default. A thorough search of the published literature resulted in several studies comparing the PK parameters of several statins in healthy patients to potential sensitive subpopulations. Table 8 summarizes data available (means and standard deviation) for the dose- and body weight-normalized AUC and C_{max} parameters for the four statins we investigated. Numerous references did not report standard deviations and therefore could not be used in this exercise.

These normalized PK parameters were used to determine the existence of potential sensitive subpopulations with significantly different normalized AUC and C_{max} values. The average unimodal (mean + 2SD)/mean ratios were calculated for each individual statin for healthy individuals, each age group, sex, and disease state. Table 8 summarizes the PK comparisons for the various statins. No subpopulation data were available for pravastatin. Average unimodal ratios of 1.9 and 1.7 could be calculated for the four statins from the normalized C_{max} and AUC values, respectively, for healthy adults. These values are below the current default value of 3.2 for interindividual differences in pharmacokinetics and could be used to calculate an OEL for a healthy population of workers. The average bimodal (mean + 2SD)/mean ratios for the various potentially sensitive subpopulations (sex, age, and diseased state) were estimated by calculating the mean plus two standard deviations of the sensitive subpopulation mean divided by the mean of the healthy group. The bimodal ratios for males, females, young, and the elderly also showed low variability for both parameters and were similar to the values calculated for the healthy

Table 7. Pharmacokinetic data for cholesterol-lowering drugs.

Statin	Hypercholesterolemic Population Status	Cmax (ng/ml-mg)	AUC (ng-hr/ml-mg)	Reference
Simvastatin	Healthy	60 ± 30	179 ± 79	Desager and Horsmans 1996
	Healthy	64 ± 26	217 ± 72	Desager and Horsmans 1996
	Healthy	102 ± 49	102 ± 31	Lennernäs and Fager 1997
	Healthy	-------	139 ± 41	Arnadottir *et al.* 1993
	Elderly	217 ± 91	614 ± 296	Cheng *et al.* 1992
	Elderly	145 ± 46	490 ± 152	Cheng *et al.* 1992
	Young	161 ± 65	474 ± 382	Cheng *et al.* 1992
	Young	99 ± 43	301 ± 86	Cheng *et al.* 1992
	Female	217 ± 91	614 ± 296	Cheng *et al.* 1992
	Female	161 ± 65	474 ± 382	Cheng *et al.* 1992
	Male	145 ± 46	490 ± 152	Cheng *et al.* 1992
	Male	99 ± 43	301 ± 86	Cheng *et al.* 1992
Fluvastatin	Healthy	207 ± 140	382 ± 165	Deslypere 1994
	Healthy	471 ± 235	532 ± 213	Deslypere 1994
	Healthy	186 ± 95	389 ± 144	Deslypere 1994
	Healthy	641 ± 263	585 ± 235	Deslypere 1994
	Elderly	256 ± 179	613 ± 186	Deslypere 1994
	Elderly	203 ± 175	627 ± 186	Deslypere 1994
	Young	203 ± 116	648 ± 151	Deslypere 1994
	Young	189 ± 105	490 ± 147	Deslypere 1994
	Female	203 ± 175	613 ± 186	Deslypere 1994
	Female	256 ± 179	648 ± 151	Deslypere 1994
	Male	189 ± 105	627 ± 186	Deslypere 1994

Table 7. (cont.)

Statin	Hypercholesterolemic Population Status	Cmax (ng/ml-mg)	AUC (ng-hr/ml-mg)	Reference
Lovastatin	Healthy	132 ± 94	499 ± 241	Quérin *et al.* 1991
	Healthy	71 ± 37	423 ± 116	Rogers *et al.* 1999
	Healthy	95 ± 55	400 ± 202	Desager and Horsmans 1996
	Male	64 ± 26	545 ± 216	Cheng *et al.* 1992
	Male	43 ± 7	337 ± 94	Cheng *et al.* 1992
	Female	91 ± 41	668 ± 346	Cheng *et al.* 1992
	Female	53 ± 23	471 ± 180	Cheng *et al.* 1992
	Young	43 ± 7	337 ± 94	Cheng *et al.* 1992
	Young	53 ± 23	471 ± 180	Cheng *et al.* 1992
	Elderly	64 ± 26	545 ± 216	Cheng *et al.* 1992
	Elderly	91 ± 41	668 ± 346	Cheng *et al.* 1992
	Chronic renal failure	210 ± 87	1060 ± 554	Quérin *et al.* 1991
Pravastatin	Healthy	34 ± 6	109 ± 18	Pan *et. al.* 1990a
	Healthy	41 ± 7	111 ± 17	Pan *et. al.* 1990a
	Healthy	46 ± 10	105 ± 14	Pan *et. al.* 1990a
	Healthy	105 ± 41	657 ± 110	Singhvi *et al.* 1990
	Healthy	122 ± 13	291 ± 26	Pan *et. al.* 1990b
	Healthy	142 ± 20	332 ± 41	Pan *et al.* 1991
	Male	203 ± 175	490 ± 147	Deslypere 1994
	Hepatic Insufficiency	1195 ± 598	1391 ± 557	Deslypere 1994

Table 8. Data-derived adjustment factors describing the variability in C_{max} and AUC for cholesterol-lowering drugs.

	Unimodal Ratios* ($Mean_{healthy}+2SD_{healthy}$) / $Mean_{healthy}$		Bimodal Ratios* ($Mean_{subpop} + 2SD_{subpop}$)/ $Mean_{healthy}$									
	Healthy		Male		Female		Young		Elderly		Diseased State	
Compound	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
Fluvastatin	2.1	1.8	1.3	1.9	1.4	2.1	1.1	1.8	1.6	2.1	6.4 (hepatic insufficiency)	5.3 (hepatic insufficiency)
Lovastatin	2.2	1.8	0.9	1.7	1.4	2.5	0.8	1.5	1.5	2.7	3.9 (chronic renal failure)	4.9 (chronic renal failure)
Pravastatin	1.5	1.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Simvastatin	1.7	2.0	1.4	1.4	2.2	2.6	1.5	1.8	2.0	2.1	N/A	N/A
Average	1.9	1.7	1.2	1.7	1.7	2.4	1.1	1.7	1.7	2.3	5.2	5.1

* Average ratios for given Statin and subgroup

N/A Not Available

population. However, the bimodal ratio for the diseased states was significantly greater than the healthy value and higher than the default value of 3.2. The findings indicate that the disposition of fluvastatin and lovastatin and its metabolites is altered in patients with hepatic insufficiency and chronic renal failure, respectively, compared with control subjects. The potential for accumulation of these drugs in patients cannot be ruled out. These values indicate that sensitive subpopulations do exist for some, but not all statins. A categorical adjustment factor (*e.g.*, 6.4) could be derived that would apply to all compounds in this class if it is assumed that hepatic and renal insufficiency would be common susceptibility factors.

Antibiotics: Mode of action

Historically antibiotics have been classified on the basis of their chemical structure and proposed mode of action (Chambers *et al.* 1996). In this section we studied six different antibiotics representative of four antibiotic classes. The classes studied were the macrolides (azithromycin, clarithromycin and erythromycin); the cephalosporins (cefixime); the aminoglycosides (gentamicin); and the glycopeptides (vancomycin). Several of the antibiotics studied have been associated with toxic side effects believed to be a result of high plasma concentrations. The aminoglycosides and vancomycin have both been associated with ototoxicity and nephrotoxicity. These toxicities are potentiated when the two classes of antibiotics are administered simultaneously (Keller *et al.* 1994). Erythromycin, at higher doses, has been associated with unpleasant gastrointestinal (GI) side effects (Sefton *et al.* 1990), while the newer macrolides, such as clarithromycin and azithromycin, are generally well tolerated and cause fewer GI side effects (Guay 1996).

Aminoglycoside-induced nephrotoxicity complicates a significant number (10 to 20%) of all therapeutic courses (Swan 1997). This class of antibiotic is almost entirely eliminated by the renal route, which contributes to their toxicity especially in patients with renal insufficiency. Aminoglycosides exert their toxic effect by binding to and disrupting plasma membranes, leading to proximal tubular injury and eventually tubular cell necrosis. Frequently the damage is not detected until extensive injury has occurred (Swan 1997). Uptake of aminoglycosides into the tubular cells appears to be an active process dependent on calcium but one that is saturable (Triggs *et al.* 1999). The fact that a saturation level is reached suggests that high peak serum concentrations may not necessarily lead to greater nephrotoxicity than a lower serum concentration (Barclay *et al.* 1995). The duration of exposure therefore may be a better indicator of toxicity than C_{max}, although one would also expect high peak concentrations to contribute to toxicity. Nephrotoxicity induced by aminoglycoside administration is usually reversible after stopping the drug but renal dysfunction may persist due to renal accumulation (Rankin *et al.* 1989).

The reported incidence of aminoglycoside induced ototoxicity ranges from 0% to 47%. This large variability is at least partially due to different sensitivities in the subjective methods used to detect ototoxicity. The literature suggests that aminoglycoside induced ototoxicity can take two forms: a largely irreversible, chronic type and a reversible, acute type. The former causes degeneration of hair cells in the cochlea. Aminoglycoside induced ototoxicity is very unpredictable, sometimes with a severe onset, and some researchers have suggested susceptibility to this adverse

effect may be genetically determined (Barclay *et al.* 1995). The therapeutic target peak concentration for aminoglycosides is 6 to 10 mg/L and the target trough concentration is less than 2 mg/L (Triggs *et al.* 1999). Ototoxicity is observed when aminoglycosides accumulate in the perilymph and endolymph of the inner ear when plasma levels are persistently high (Huy *et al.* 1983). Overall it appears that duration of exposure above a certain threshold concentration is the most important determinant of aminoglycoside induced toxicity (Paterson *et al.* 1998).

Cephalosporins are a subclass of β-lactam antibiotics and adverse effects associated with their use are usually mild and reversible (Grassi 1995). The majority of cephalosporins are eliminated by the renal route except for cefixime (a third generation cephalosporin) in which renal elimination accounts for only 20% of all elimination (Klepser *et al.* 1995). Cefixime-related GI disturbances are the most common adverse events seen in patients (Wu 1993). Several older cephalosporins had been reported to be potentially nephrotoxic, a problem not associated with modern cephalosporins (Norrby 1987).

Vancomycin, a glycopeptide antibiotic, is not absorbed significantly from the GI tract and must be given intravenously. It is not metabolized and is cleared from the blood by renal excretion (Fogarty *et al.* 1989). Vancomycin has been reported to have ototoxic and nephrotoxic side effects particularly in the higher dose ranges. Like the aminoglycosides, this toxicity is more dependent on persistent high concentrations and the cumulative dose rather than on the daily dose (Gendeh *et al.* 1998). Initially ototoxicity was reported in patients with renal insufficiency whose serum levels of vancomycin were greater than 80 mg/L. Concomitant therapy with other ototoxic agents such as aminoglycosides may have exacerbated this toxic side effect. Vancomycin ototoxicity starts by affecting the hair cells of the cochlea leading to complete hair loss. This degeneration is irreversible and the deafness produced is therefore permanent (Fogarty *et al.*, 1989). The toxic effect of vancomycin is dose-dependent and has occurred at serum levels between 80 and 100 mg/L. It is rarely observed at serum levels less than 30 mg/L; however, peak serum concentrations as low as 38 mg/L have been associated some degree of hearing loss (Gendeh *et al.* 1998). Currently, the desired peak therapeutic serum concentration is 30 to 40 mg/L and the desired trough serum concentration is 5 to 10 mg/L (Fogarty *et al.* 1989; Gendeh *et al.* 1998).

Unfortunately, the role of vancomycin in producing nephrotoxicity is not as straightforward as its role in ototoxicity (Fogarty *et al.* 1989). The general consensus in the literature is that the toxic reactions seen with vancomycin, especially the nephrotoxicity, may have originally been due to impurities present in the early preparations of vancomycin that have been removed in the more purified product today (Levine 1987; Gendeh *et al.* 1998).

Early macrolide antibiotics, such as erythromycin, were characterized by a number of drawbacks, including poor gastrointestinal (GI) tolerability. The macrolide antibiotics are well distributed into body fluids and tissues, penetrate intracellularly and inhibit protein synthesis by binding to the 50S ribosomal subunit and interfering with the translocation reaction during protein synthesis in susceptible bacteria (Guay 1996). Erythromycin exerts its GI side effects primarily by its motilin agonist activity on smooth muscle receptors in the gut although alterations in the normal gut flora also occur during therapy. Approximately 60%

of patients receiving 1 g of erythromycin per day suffer from GI side effects (Anastasio *et al.* 1992). With high doses of erythromycin, side effect rates close to 73% have been observed, suggesting this is a dose-related adverse effect (Carter *et al.* 1987).

Azithromycin remains essentially unchanged in the body, has no known metabolites (Nightingale 1997), and its C_{max} and area under the plasma concentration-time curve (AUC) tend to rise with age (Langtry and Balfour 1998). Azithromycin distributes rapidly into fluids, tissues, and cells where it is slowly released back into the serum (Nightingale 1997). Intracellular azithromycin concentrations are maintained at therapeutically relevant concentrations long after plasma concentrations have diminished (Langtry and Balfour 1998). Azithromycin pharmacokinetics are not significantly affected by mild to moderate hepatic impairment (Langtry and Balfour 1998) and azithromycin does not induce P450 enzymes (Nightingale 1997). Studies have shown that approximately 5% of patients experience adverse GI side effects (Langtry and Balfour 1998).

Clarithromycin is a macrolide antibiotic that is structurally similar to erythromycin. First pass metabolism of clarithromycin produces a 14-hydroxy metabolite that is microbiologically active (Langtry and Brogden 1997). The pharmacokinetics of clarithromycin are nonlinear and at doses above 600 mg the formation of the active metabolite begins to overcome the rate of hepatic elimination resulting in a decrease in total body clearance and an increase in elimination half-life (Langtry and Brogden 1997). This type of saturation kinetics will increase exposure to the parent compound and the active metabolite, which may result in an increase in toxicity. As with azithromycin, concentrations of clarithromycin in tissues and fluids greatly exceed those in plasma (Langtry and Brogden 1997). Clarithromycin pharmacokinetics are not significantly affected by mild to moderate hepatic impairment (Langtry and Brogden 1997). Clarithromycin is a weak inducer of cytochrome P_{450} (Nightingale 1997) and drug interactions related to the cytochrome P_{450} system may occur with clarithromycin use (Langtry and Brogden 1997).

Numerous clinical studies have suggested a potential synergistic nephrotoxic effect when aminoglycoside and cephalosprin therapy was given concomitantly. The synergistic effect may be exacerbated simply because patients receiving this therapy are critically ill and are suffering renal impairment subsequent to therapy with another drug (Rankin *et al.* 1989). Concomitant administration of vancomycin and an aminoglycoside, especially for a long duration of time, has been shown to cause nephrotoxicity and ototoxicity (Paterson *et al.* 1998).

Antibiotics: Pharmacodynamics

Since antibiotics exhibit their effect on microorganisms rather than on a receptor or active site in the body we must assume that human toxicological sensitivity to the macrolides themselves will be less than the sensitivity of various microorganisms to the macrolides. Therefore a data-derived adjustment factor based on a bacterial inhibition can not easily be extrapolated to estimate human sensitivity and is not appropriate in setting an exposure limit. Individual differences in susceptibility to the toxic effects of the drugs would have been more appropriate to characterize. However, increased susceptibility is usually attributed to the pharmacokinetics of

these drugs. Pharmacokinetic data should therefore be utilized whenever possible to calculate data-derived adjustment factors for antibiotics.

Antibiotics: Pharmacokinetics

None of the studies examined showed any evidence of a significant health-sensitive or age- subpopulation. This is intriguing due to the high dependency that the antibiotics we studied have on renal clearance. One would anticipate decreasing renal function with age and unwarranted and unmonitored exposure to an antibiotic could lead to toxicity.

Probability plots of the log-transformed mean PK parameters were used to estimate the 95th percentile and the 50th percentile from the pooled data gained from clinical trials published in the literature. For example, Figure 3 shows the cumulative frequency distribution plot for azithromycin. Note that the straight line indicates the underlying distribution is log-normal. Subtracting the 50th percentile from the 95th percentile and then taking the anti-log of the result led to the data-derived adjustment factors listed in Table 9.

The aminoglycoside peak concentrations ranged from 6.75 to 39.8 mg/L and the vancomycin peak concentrations ranged from 23 to 48 mg/L in the published reports reviewed. As mentioned earlier, the therapeutic target aminoglycoside peak concentration is 6 to 10 mg/L and vancomycin peak serum concentration is 30 to 40 mg/L. In one study (Demczar *et al.* 1997) 100 patients received a course of treatment with an aminoglycoside that resulted in a C_{max} of greater than 20 mg/L. Two patients (2%) had elevated serum creatinine concentrations indicative of nephrotoxicity and five had symptoms consistent with ototoxicity. However, it should be noted that the case for ototoxicity may have been complicated due to concurrent treatment with other ototoxic drugs and past treatment with aminoglycosides. It was difficult to correlate observed toxicities with peak and trough serum concentrations because the published reports on toxic responses rarely report serum concentrations of the drug.

Pharmacokinetic data for various antibiotics evaluated suggest that, in general, interindividual differences in measures of systemic exposure are relatively low with unimodal adjustment factors ranging from 1.3 to 4.7. The average value for the compounds investigated was 2.2. This categorical AF could be considered to replace the default factor of 3.2 for antibiotics. However, due to the nephrotoxic and ototoxic properties of the aminoglycosides, and the relationship between high plasma levels and these adverse effects, it may be appropriate to establish a separate categorical default for this subclass of antibiotics.

DISCUSSION

We have already identified a number of class-specific issues regarding the applicability of categorical data-derived adjustment factors that surfaced during our case study evaluations of five different therapeutic classes. Answers to the questions posed earlier are given below to provide some additional insights and generalizations:

Can a categorical data-derived adjustment factor be applied generally across an entire class or just certain subclasses with precisely the same attributes? The breadth

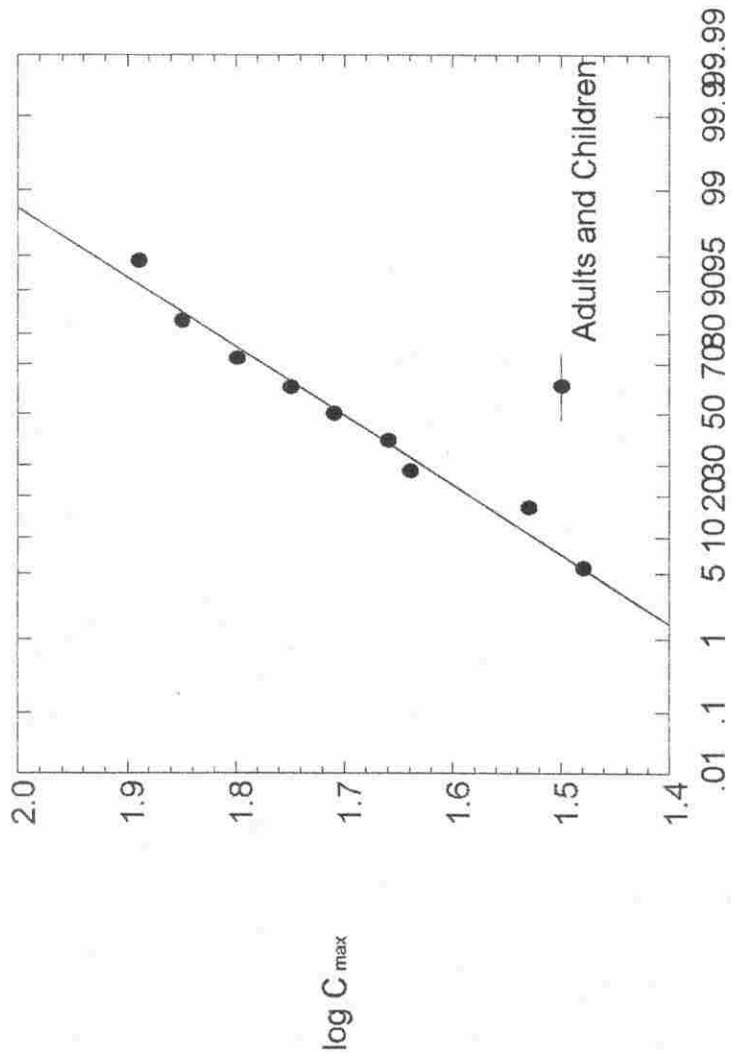

Figure 3. Probability plot for the C_{max} values for Azithromycin

Table 9. Data-derived adjustment factors for individual differences in pharmacokinetics for antibiotics.

Antibiotic	Subclass	Subpopulation	Unimodal AF
Azithromycin	Macrolide	Adults & children	1.7 [a]
Azithromycin	Macrolide	Adults & children	1.3 [b]
Clarithromycin	Macrolide	Adults & children	2.4 [a]
Erythromycin	Macrolide	Adults	1.8 [a]
Erythromycin	Macrolide	Adults	2.4 [b]
Cefixime	Cephalosporin	Adults	2.3 [a]
Cefixime	Cephalosporin	Adults	4.7 [b]
Vancomycin	Glycopeptide	Adults	1.9 [a]
Gentamicin	Aminoglycoside	Adults	1.9 [a]
Gentamicin	Aminoglycoside	Adults	1.1 [b]

[a] Calculation based on data obtained at C_{max}

[b] Calculation based on AUC

of application of a categorical default will depend on similarity of compounds in the class with regard to disposition and activity. Available data for selected, well-characterized compounds in a class with structural similarities and toxicity profile may suggest that the individual differences in PK and PD parameters can be applied widely. When there are structural differences within the class, the likelihood that they may be handled differently by certain subpopulations increases. The tricyclic antidepressants and selective serotonin reuptake inhibitors (Table 1) exemplify this distinction.

Under what circumstances can a categorical default factor be applied? The application of a categorical data-derived adjustment factor should be confined to the PK and/or PD factors, and the critical endpoint used to establish the exposure limits, for the surrogate compounds used to justify the categorical default. The boundaries and limitations of use should be clearly documented in a narrative summarizing the basis of the categorical factor (IPCS 2000). The new compound being considered a candidate for application of the categorical default must conform to these inclusion criteria and have the same "common denominator" as the reference compounds. The dependence of systemic exposure on renal clearance for ACE inhibitors is an important consideration for like compounds in this class.

Is it necessary to know the precise mechanism-of-action or is a general understanding of the mode-of-action sufficient within the context of deriving compound- or class-specific adjustment factors to replace default uncertainty factors? An adjustment factor can apply to an entire class if all compounds within the class produce effects via the same mode-of-action. A full understanding of the precise mechanism of action should not be necessary to derive adjustment factors that account for the major sources of variability in kinetics or dynamics. For the compounds evaluated, the variability associated with a particular enzyme or receptor was relatively low. Of greater importance was identifying the "correct" pharmacodynamic parameter to evaluate (*i.e.*, the one responsible for the critical effect). Correct linkage between the PD parameter and the critical endpoint is a potential source of uncertainty (Meek *et al.* 1999). For example, the level of COX-1 activity is a key determinant of the potential for adverse gastrointestinal side effects for antiinflammatory agents.

Do the data-derived adjustment factors encompass all of the variability or are there residual uncertainties? The availability of data for key, representative compounds in a class greatly reduces the uncertainties regarding interindividual PK and PD differences and can support compound-specific adjustment factors for those individual compounds. Residual uncertainties represent the possibility that the surrogate compounds evaluated may differ from the new compound in some unknown manner. It is also possible that the data available for the well-studied compounds were derived from targets or groups that may not be representative of the entire population or subpopulations that would be covered by the health-based limit being derived. The standard deviations of the distributions are influenced by sample size. Ideally, the calculated ratio should be from as broad a cross-section of the population as possible. The

extent that "known" differences are more important than subtle differences between subpopulations that have not yet been identified will limit any residual uncertainties.

Do the data-derived values overstate the variability due to homeostatic/adaptive mechanisms or alternative pathways when a genetic polymorphism exists for a given pathway? The extent that the mode of action is understood will determine whether compensatory mechanisms could modify the variability in response, primarily on a pharmacodynamic basis. For complex biological responses, many receptor- or enzyme-based activities do not directly affect a pharmacodynamic outcome because they only represent the first in a series of cascading reactions within the body that lead to the ultimate effect. Regulatory feedback mechanisms can mute the effects of a single pharmacodynamic endpoint. Likewise, in terms of pharmacokinetics, genetic polymorphisms in metabolism (*e.g.*, poor metabolizers via CYP2D6) may not be more susceptible if alternate elimination pathways are available. The extent that these "deficiencies" are used as the basis for an adjustment factor, the true contribution to the population variability in response may be overestimated. The kind of complex interplay of pharmacokinetics of antidepressants (*e.g.*, induction or inhibition of metabolism by the liver) and alternative pharmacodynamic pathways (*e.g.*, amine uptake or receptor binding efficiency) is difficult to evaluate, but must be considered, for example, to come to an understanding of individual susceptibilities and human resiliency (Westenberg 1999).

What additional uncertainties are introduced by application of a categorical default adjustment factor? Data-derived adjustment factors reflect an improved understanding of the underlying bases of the interindividual differences for individual compounds. A sound scientific rationale is required to bridge from a series of compounds to another compound based on a common determinant of variability. If the underlying assumptions are incorrect, or if the data used to support the extrapolation are flawed or inadequate, the use of a categorical default may actually introduce uncertainty depending on the quality of data and level of professional judgement introduced. This uncertainty may be less than or greater than that represented by the default uncertainty factor.

CONCLUSIONS

The published data for compounds in the five therapeutic classes investigated provided valuable insights into the potential for establishing categorical data-derived adjustment factors. Each therapeutic class had unique issues, although the general approach used by each of the assigned co-authors was similar in each case. Linking the critical endpoint that would be used to establish the exposure limit to specific pharmacokinetic and pharmacodynamic determinants for individual compounds was challenging and establishing a common denominator for all compounds in a class or subclass was difficult. In a few cases, categorical default adjustment factors could be esti-

mated. To the extent that the underlying assumptions are valid, the use of this categorical default adjustment factor for new members of the class that satisfies criteria for its use should reduce uncertainties regarding interindividual variability. The wealth of information available for review for these five therapeutic classes may actually have hindered more than helped the evaluations. It may actually be easier to establish categorical defaults for chemical classes with less robust databases. Further investigations on different classes of chemicals will be required to support the broader use of categorical defaults in environmental risk assessment. Regardless of the conclusions regarding the utility of categorical default adjustment factors, these investigations provide further support for the use of compound-specific data-derived adjustment factors.

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