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Importance of pharmacokinetics in the determination of withdrawal times

D Arnold

*Institute of Veterinary Medicine, Bundesgesundheitsamt,
Nordufer 20, 1000 Berlin 65, FRG*

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Summary — Models for the statistical determination of withdrawal times have been compared using computer-generated kinetic residue data. Estimates of withdrawal times obtained by direct evaluation of the 'known' frequency distributions of residue contents of very large samples have been compared to results obtained by regression analysis of the data on very small samples of the same populations. In this context, the hypothesis was tested that the natural logarithms of the residue contents were normally distributed and that the decrease of the natural logarithms was linear with time. Withdrawal times were then determined as the times when the upper limit of the (statistical) tolerance interval in a given percentile was below the acceptable daily intake. From the results obtained with computer-generated small data bases, it was concluded that adequate, but not necessarily precise, withdrawal times could be determined on a limited base of suitable kinetic residue data.

withdrawal time / statistical models / simulated data / distribution / regression

Résumé — **Importance de la pharmacocinétique dans la détermination des délais d'attente.** Des modèles statistiques destinés à la détermination des délais d'attente ont été comparés en utilisant des données simulées; les estimations des temps d'attente obtenues à partir d'échantillons de grandes tailles issus de populations à paramètres connus ont été comparées avec les résultats obtenus par analyse de régression de données de petits échantillons issus de la même population. Dans ce contexte, l'hypothèse testée est que les logarithmes de la teneur en résidu sont distribués normalement et que la décroissance est linéaire sur une échelle semi-logarithmique. Les délais d'attente ont été déterminés comme étant le temps correspondant à la limite supérieure de l'intervalle de confiance (pour un risque donné) qui permet d'être en-dessous de la dose journalière acceptable. A partir de ces résultats simulés, il est conclu que des temps d'attente adéquats, mais non nécessairement précis, peuvent être déterminés à partir d'un petit nombre de données cinétiques.

délai d'attente / modèles statistiques / données simulées / distribution / régression

INTRODUCTION

The withdrawal time of a veterinary drug is the interval necessary between the last administration to food-animals of the drug under approved conditions of use and the time when treated animals can be used for the production of safe food-stuffs. The withdrawal time should provide a high degree of statistical and real certainty, to both the producers and the consumers of animal-derived foods, that the amounts of daily-ingested residues do not exceed the acceptable daily intake (ADI). Therefore, the withdrawal times have to be determined from the results of suitable kinetic residue depletion studies as the time when a high percentile of the frequency distributions of the residues is at or below the ADI. Observance of the ADI is frequently monitored in practice by comparing the concentrations of a suitable 'marker' residue in a 'target' tissue with its permitted maximum residue limit (MRL). In these cases, the same concept can be followed for the MRL, with the target tissue playing the roles which are assigned to the ADI and the whole food-package, respectively, in this paper.

To apply pharmacokinetic principles to the determination of withdrawal times means primarily to describe mathematically the time-dependent changes in the concentrations of the residues in certain standard edible tissues of animals, such as muscle, liver, kidney and fat. In this context, it is a common approach to adopt certain equations originally developed from classical pharmacokinetic compartment concepts. Accordingly, the time courses of changes in the concentrations can be mathematically treated as a sum of exponential terms taking the form of equation 1:

$$c_t = \sum_{j=1}^n \alpha_j e^{-\beta_j t} \quad (1)$$

where c stands for concentration, e for the base of the natural logarithm and t for time. α and β are called the kinetic parameters in this text.

For a satisfactory description of the kinetics of the concentrations of the residues, over all phases of absorption, distribution and elimination of the drug, n , the number of exponential terms in equation 1 would usually exceed three. However, when dealing with the determination of withdrawal times, it is frequently sufficient to use only one such term for fitting a curve to the experimental data describing the 'terminal' elimination. By multiplying with appropriate consumption figures, concentrations can be transformed into ingested amounts of residues.

It is exceedingly difficult to decide by which mathematical model a given set of kinetic residue data should be treated, particularly since practically no adequate information on the true shapes of the frequency distributions of the residue contents in the tissues of treated animals exists. It is not uncommon, therefore, that the available data do not allow us to discriminate between hypothetical models.

In this paper, problems in the calculation of withdrawal times are discussed using examples taken from a large hypothetical data base generated with a microcomputer.

MATERIALS AND METHODS

A Hewlett-Packard 9836A desktop calculator was used for all calculations.

The terminal depletion of total drug residues from tissues has been calculated using equation 1 with one exponential term ($n = 1$). It has been assumed that the pharmacokinetic parameters were normally distributed. The population means and standard deviations (SD) of the hypothetical kinetic parameters which were used

throughout all computer experiments are given in table I.

Class frequencies of the distributions of the above kinetic parameters (5×10^7 items in 1000 classes between $\mu \pm 5.09\sigma$) have been calculated for each parameter. Upper class limits of the α 's or β 's have been defined according to equations (2a and 2b):

$$\alpha_i = \mu_\alpha - 5.09\sigma_\alpha + k_\alpha \times 10.18\sigma_\alpha / 1000 \quad (2a)$$

$$\beta_i = \mu_\beta - 5.09\sigma_\beta + k_\beta \times 10.18\sigma_\beta / 1000 \quad (2b)$$

with $k_\alpha, k_\beta = 1, 2, 3, \dots, 1000$.

The following arbitrary daily consumptions per adult human were used: 300 g of muscle, 100 g of liver, 50 g of fat and 50 g of kidney. A fictive acceptable daily intake (ADI) of 15 $\mu\text{g}/60$ kg human/d has been set in this example. The total amounts of residues contained in the arbitrary daily 'meat-package' have been calculated for a given time, t (d) as:

$$A_t = \sum_{i=1}^4 D_{Ti} \alpha_i e^{-\beta_i t} \quad (3)$$

where A_t stands for the time-dependent amounts and D_T for the tissue-specific consumption figures.

Table I. Population means and standard deviations of hypothetical pharmacokinetic parameters.

Tissue	Parameters			
	μ_α ($\mu\text{g}/\text{kg}$)	σ_α	μ_β ($1/\text{d}$)	σ_β
Muscle	30.6	6.01	0.1258	0.02472
Fat	279	54.8	0.0907	0.01782
Kidney	114	22.4	0.1424	0.02798
Liver	684	134	0.1432	0.02814

Statistical parameters of the pharmacokinetic parameters used for the computer-generation of kinetic tissue residue data.

Samples of at least 50 000 items per sampling time have been generated according to equation 3 in order to calculate approximate frequency distributions of total residue contents in the meat consumed daily. In these calculations, the individual α_i ' and β_i 's were allowed to assume any random value between the limits of the distributions truncated as indicated above. The sampling-times used were 7, 14, 21, 28, 32, 36, 40, 44, 48 and 52 d. Estimates of the withdrawal times have been obtained from these frequency distributions as the time at which a given percentile was below the ADI.

Smaller subsamples (5 times of sampling, 1–5 replicates per time) have been generated in order to estimate withdrawal times by 'least squares' curve fitting. The residue contents of the subsample used for the preparation of figure 5 are given in table II.

Linear regression lines and corresponding estimates of their statistical parameters were calculated on the basis of known equations (Documenta Geigy, 1980).

RESULTS

In order to illustrate the possible effects of the variability of the pharmacokinetic parameters on frequency distributions of residues, a few simplistic assumptions have

Table II. Example of kinetic residue data.

Withdrawal time (d)	Amounts (ng)					
	6151	14150	37339	40088	32551	
36	6151	14150	37339	40088	32551	
40	2495	4055	667	20022	12316	
44	1534	6593	1890	22.2	271	
48	29.3	357	67.5	505	542	
52	4347	667	20.7	51.1	83.1	

Residue contents in 300 g of muscle + 100 g of liver + 50 g of kidney + 50 g of fat. The data were used to explain the estimation of withdrawal times by semilogarithmic linear regression. See also fig 5.

been made in the first computer-'experiment': the composite pharmacokinetic parameters α and β and normally distributed; case 1: the α 's and β 's are independent (in the computer experiment: individual values combine randomly); case 2: the α 's and β 's are interdependent (in the computer experiment they combine in such a way that k_{α_i} , 2, 3, 4; k_{β_j} , 1, 2, 3, 4 = k_{α_1} (see equations 2a, b); case 3: the α 's and β 's are interdependent (in the computer experiment they combine in such a way that $k_{\beta_j} = 1000 - k_{\alpha_i}$ (see equations 2a, b).

The results obtained with a sample size of 50 000 for each of the three cases and for d 7 post administration are presented graphically in figure 1, where class frequencies of residue contents of the resulting distributions are compared to normal frequency distributions with the same mean, standard deviation (SD) and area under the curve. Under the conditions of the three cases examined here, the deviation from normality was evident. All three distributions were characterized by long

'tails' at high residue contents, with highest probability densities in the tail portion in case 3.

The influence of variation of the time of sampling on the frequency distributions has been studied in the same way as described above for the first experiment. The results obtained are given in figures 2 and 3, respectively.

Figure 2 shows the time-dependent cumulative frequencies of items below the ADI in percent of total observations. Three bars at each point of time represent the results obtained for the model cases 1, 2 and 3 from left to right. Cumulative frequencies increased with time, but with different initial rates, depending upon the model. The highest initial rate was observed for case 3. The corresponding frequency distributions (for case 1 only) are given in figure 3. In this figure, the amounts of residues contained in the whole meat-package are expressed as multiples of the ADI and are plotted as logarithmic distributions. At short withdrawal times, they tend to approximate

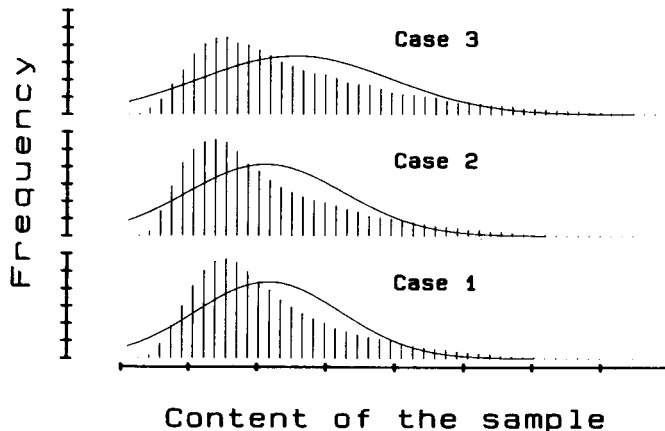


Fig 1. Influence of the variability of pharmacokinetic parameters on the hypothetical frequency distributions of residue contents in arbitrary 'meat' packages. Discontinuous frequency distributions obtained for cases 1, 2 and 3 in the computer experiment described in the text are compared to continuous normal frequency distributions with the same mean, SD and area under the curve.

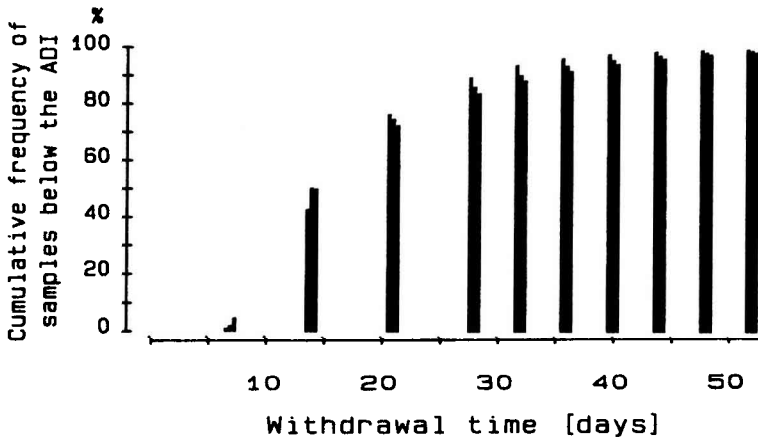


Fig 2. Influence of the various model assumptions on the variability of kinetic parameters on time-dependent cumulative frequencies of samples below the ADI. Bars for each time period represent cases 1, 2 and 3 from left to right, as described in the text. The results are based on 50 000 items generated per point of time.

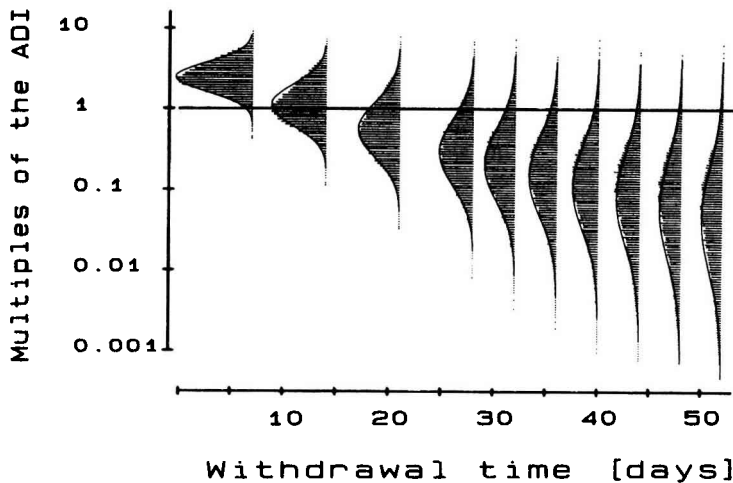


Fig 3. Time-dependent frequency distributions of the decimal logarithms of the residue contents in arbitrary 'meat' packages in comparison with the ADI. Discontinuous frequency distributions of 50 000 items per time point obtained for case 1 in the computer experiment described in the text are compared to the continuous normal frequency distributions with the same mean, SD and area under the curve.

sharp symmetrical distributions with tails at high contents. With increasing time, they become broader, slightly more asymmetric and more long-tailed at lower residue contents. The probability density functions of normal distributions with the same mean, standard deviation, and area under the curve are also given in figure 3, for comparison. The areas under the curve overlap considerably and peak frequencies are observed in closely adjacent classes, depending upon time. The distance between the locations of the mean and the median of the experimental distributions is apparently small and increases with time. In order to confirm these visual observations for the longer withdrawal times, distributions with up to 700 000 items have been generated for the times 36, 40, 44, 48 and 52 d. Certain characteristics of these distributions are given in table III. These results clearly demonstrate that for model case 1 (independent pharmacokinetic parameters), the resulting residue contents in the arbitrary meat-packages are well described by normal distributions of their nat-

ural logarithms, with means and standard deviations depending upon the time of sampling.

During the computer-generation of these 700 000 items, the classes of the 99th percentile of the nascent distributions were determined every time 1000 new items per distribution had been generated. The resulting class numbers were compared to the number of the class which included the ADI itself. At the same intervals, the times at which the upper limit of the tolerance interval in the 99th percentile was below the ADI have been calculated by (semi-logarithmic) linear regression using all accumulated data from these last five sampling times. Figure 4 shows how these estimates of the withdrawal time decreased depending upon the accumulated sample size. Some relevant additional numerical results of these calculations are summarized in table IV. Although even this large sample size was insufficient to estimate precisely enough the probability densities of the tails of the frequency distributions to obtain stable estimates of the

Table III. Certain characteristics of computer-generated frequency distributions.

Time (d)	Mean (log _e)		SD (log _e)		Overlap of the areas (%)	
	a ^a	b ^a	a	b	a	b
36	7.56	7.51	0.996	0.943	95.2	95.3
40	7.22	7.16	1.086	1.027	94.2	94.5
44	6.87	6.80	1.175	1.112	93.3	93.6
48	6.54	6.46	1.265	1.197	92.4	92.8
52	6.21	6.12	1.355	1.284	91.7	92.0

^a Items per sampling time: a: 400 000, b: 700 000.

Statistical parameters of computer-generated frequency distributions of the residue contents in 500 g of meat (300 g of muscle + 100 g of liver + 50 g of kidney + 50 g of fat). The parameters were determined for two different sample sizes per sampling time (400 000 and 700 000 items, respectively). The overlapping parts of the 'experimental' distributions and normal distributions with the same mean, SD and area under the curve have been compared.

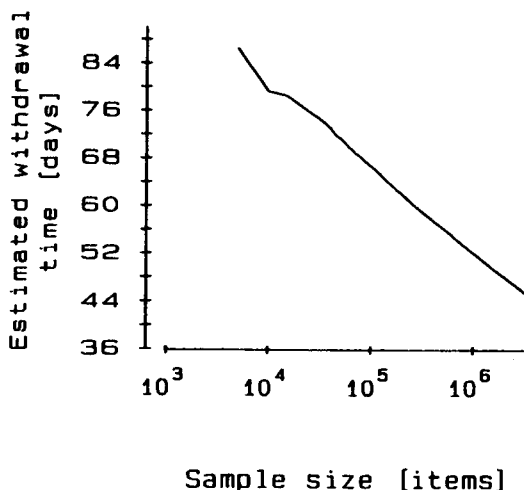


Fig 4. The influence of sample size on the approximation of the 'true' withdrawal time by semi-logarithmic linear regression.

withdrawal times, it is apparent from the examples given in table IV and figure 4 that the length of withdrawal times is over-

estimated when linear regression is used for the estimation. The deviation from normality of the distributions caused less than

Table IV. Comparison of withdrawal times obtained using different methods of calculation and different sample sizes.

Time (d)	Quantile below the ADI			Withdrawal time (d) obtained from					
				frequency distribution			linear regression		
	a ^a	b ^a	c ^a	a	b	c	a	b	c
36	96.30	98.52	99.40	<48	<40	<36	56.3	49.8	44.9
40	97.82	99.24	99.69						
44	98.72	99.58	99.82						
48	99.26	99.76	99.89						
52	99.52	99.84	99.93						

^a a : 50 000 items per sampling time; b: 300 000 items per sampling time; c: 700 000 items per sampling time. Cumulative frequencies of items below the ADI and withdrawal times estimated using two different methods are compared for 3 sample sizes, 50 000, 300 000 and 700 000 items per sampling time, respectively.

0.1% of the observed discrepancies. At the observed degree of non-uniformity of the variances, the use of unweighted regression caused about 10% discrepancy. The remaining difference was due to the selection of the upper limit of the tolerance interval in the 99th percentile as the basis for the determination of withdrawal times by linear regression.

The regression model is graphically explained in figure 5, where the semi-logarithmic (\log_e) regression line is given together with the two limits of the tolerance interval and the data points from table II which were used for the calculations. Using unweighted regression, the results were as follows: intercept 20.9 \log_e units, slope $-0.316 \log_e$ units/d, coefficient of correlation -0.7576 , average depletion

time to residue contents below the ADI 36 d and withdrawal time 51 d.

Twenty thousand of such small samples with 5, 4, 3, 2 and 1 replicates at each of the five sampling times have also been generated with truncation of the original frequency distributions of the pharmacokinetic parameters at either $\mu \pm 5.09\sigma$ or $\mu \pm 3.00\sigma$. The following tests have been performed: linearity of \log_e of the residue contents over time has been tested for all cases with ≥ 2 replicates per time-point; the statistical significance of the coefficients of correlation and their negative sign and the uniformity of variances has been tested. Samples were either rejected according to the results of the above tests or were used to calculate additional estimates of the withdrawal time by linear regression. The

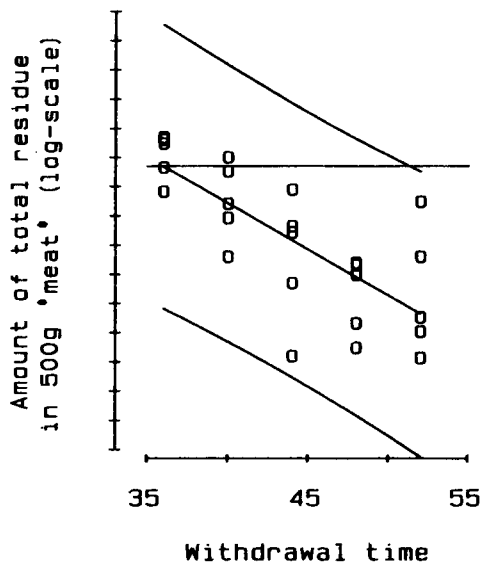


Fig 5. Relationship between experimental data points, 'best fitting' residue-depletion curve (semi-logarithmic regression line), average depletion time, tolerance intervals and withdrawal time. The numerical data are given under Materials and Methods. For explanations see the text.

tolerance intervals in both the 95th and the 99th percentiles were alternatively used in this experiment. The frequency distributions of the withdrawal times are given graphically in figure 6. Other relevant results of this experiment are summarized in table V.

The majority of samples was rejected, usually because the (negative) coefficient of correlation was above its limits of significance. The minimum number of replicates which gave relatively stable estimates of withdrawal times with non-rejected samples was 2 items per sampling time.

Truncation of the original frequency distributions at their very far ends ($\mu \pm 5.09\sigma$) caused moderate 'tailing' of the frequency distributions of the withdrawal times based on tolerance intervals in the 95th percentile; excessively long tails were seen when withdrawal times were calculated from the

same data but using the tolerance intervals in the 99th percentile.

Shorter and less variable withdrawal times were obtained for the cases for which the original frequency distributions of the pharmacokinetic parameters were truncated at $\mu \pm 3.00\sigma$.

DISCUSSION

The objective of this study was to address the suitability of certain statistically based procedures to estimate withdrawal times for veterinary drugs used in food-producing animals. It was postulated that the withdrawal time should be established in such a way that it guarantees that a high percentile of the frequency distributions of the residue contents in foods ingested daily is at or below the ADI. The term ADI was

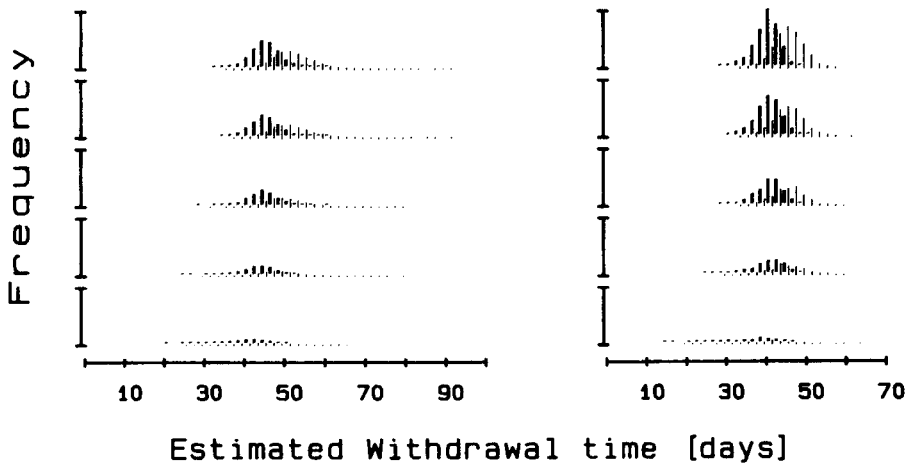


Fig 6. Frequency distributions of withdrawal times estimated by semi-logarithmic linear regression on the basis of tolerance intervals on either the 95th (thin bars) or 99th percentile (thick bars). The data were generated using truncated frequency distributions of pharmacokinetic parameters (left side: truncation at $\mu \pm 5.09\sigma$; right side: truncation at $\mu \pm 3.00\sigma$). The number of replicates per sampling time decreases from top ($n = 5$) to bottom ($n = 1$).

Table V. Influence of the number of replicates per time point on the suitability of kinetic residue data for the calculation of withdrawal times.

No of replicates	Samples rejected (%)	Withdrawal times			
		<i>a</i> ^a		<i>b</i> ^a	
		mean (d)	cv (%)	mean (d)	cv (%)
A ^a 1	97.3	45.4	14.2	39.4	11.5
A 2	93.4	49.5	11.9	42.8	8.2
A 3	88.6	51	11.4	43.7	7.8
A 4	83.5	52	10.9	44.1	7.7
A 5	78.1	52.6	10.8	44.3	7.7
B ^a 1	96.3	40.6	18.3	35.1	18.8
B 2	87.8	45	10.6	39.6	9.3
B 3	78.7	45.5	8.9	39.8	7.8
B 4	67.2	45.6	8.4	39.5	7.6
B 5	57.8	45.7	8	39.2	7.4

^a **A**: truncation of the frequency distributions of the pharmacokinetic parameters at $\mu \pm 5.09\sigma$; **B**: truncation of the frequency distributions of the pharmacokinetic parameters at $\mu \pm 3.00\sigma$; **a**: withdrawal times based on tolerance intervals in the 99th percentile; **b**: withdrawal times based on tolerance intervals in the 95th percentile.

Samples with 1, 2, 3, 4 and 5 replicates per sampling time were generated with frequency distributions of the pharmacological parameters truncated at either $\mu \pm 5.09\sigma$ (**A**) or $\mu \pm 3.00\sigma$ (**B**). Samples were rejected or used for the calculation of withdrawal times, depending upon the results of statistical tests (eg, significance of the coefficient of correlation). Estimates of the withdrawal times were based on tolerance intervals in either the 99th (**a**) or 95th (**b**) percentile. See also fig 6.

used here as an estimate of the amount of drug residue, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk. This is in analogy to the original definition of the ADI (WHO, 1987). Since the ADI is related to kg body weight, a figure of 60 kg was adopted for the average human body weight (WHO, 1989).

The amount of residues ingested daily is a function of the amount of residue-contaminated food items consumed. Consumption data based on scientifically reliable surveys are difficult, if not impossible, to come by. For the lack of a better database, somewhat exaggerated daily con-

sumptions have been used in accordance with current practice of the Joint FAO/WHO Expert Committee of Food Additives (FAO, 1988; WHO, 1989).

Relevant information on frequency distributions of drug residue contents in tissues were unavailable and have not been found in the literature. This led to the idea to generate a database with the aid of a computer. However, it was again impossible to make the indispensable assumptions on biological variabilities of pharmacokinetic parameters in the absence of sufficient published data. Therefore, it would have been necessary, in order to predict the shape of frequency distribu-

tions, to know quantitatively all the many individual factors which influence absorption, distribution and elimination of a drug. Such factors include, for example, membrane permeabilities, transport processes and enzyme activities, which in turn are genetically controlled at the level of the synthesis of the proteins involved and, in addition, are usually influenced by a great variety of other regulatory mechanisms. Conditions which would tend to produce normal frequency distributions of such biological phenomena would include *inter alia* that there exist many influencing factors which are independent in occurrence and effect and make equal contributions to the variance (Sokal and Rohlf, 1981).

Since no example exists for which such information is known, a few simplistic assumptions have been made, for example, that the distributions of the 8 composite pharmacokinetic parameters used were of the Gaussian type with the same relative standard deviation of 0.2, and that they could vary either dependently or independently, in principle.

The frequency distributions of the pharmacokinetic parameters used for the subsequent computer experiments had to be truncated for the following reasons: individual values of the pharmacokinetic parameters were to be selected by using normally distributed random numbers. Their normal distribution was to be controlled with the aid of known expected frequencies. With continuous frequency distributions, absolute frequencies can only be calculated between class limits. With 5×10^7 items in 1000 classes and truncation of the distributions at $\mu \pm 5.09\sigma$, however, only approximately 35 additional items would fall into classes outside those limits. Expected frequencies per additional class (of the same class width), however, would be below 1.

From the results of the first experiment (see fig 1), which tested three different

cases, it may be concluded that, in the absence of relevant information on the biological variability, it is not justified to assume that the summarized residue contents in the above-defined 'meat-package' are normally distributed. Although the three different model assumptions resulted in slightly different initial depletion rates of the residues, the times when the 99th percentile of the distributions was below the ADI were nearly identical. Consequently, subsequent experiments have been performed under the assumptions made in case 1 only (*ie*, pharmacokinetic parameters vary independently).

Further experiments have clearly demonstrated that, under the given conditions of simulated biological variability, the logarithms of the residue contents were nearly normally distributed during the relevant phase of 'terminal elimination' of the residues, although a small fraction of the computer-generated items formed rather long tails. Both the length and the probability density of the tail portions were influenced by the extent of truncation of the distributions of the pharmacokinetic parameters. In terms of biological variability, this would mean that higher variabilities of the pharmacokinetic parameters would cause more extended tails of the frequency distributions of residues.

Unfortunately, these tails caused specific problems. On the one hand, it was mandatory to estimate certain higher percentiles of the distributions as precisely as possible in order to estimate the 'true' withdrawal times as reference values. On the other hand, this was equivalent to cutting the low-density tails of the distributions at their extreme ends. Therefore, it was not possible to obtain stable estimates of the withdrawal times from inspection of the time-dependent frequency distributions within reasonable calculation times. For

any given sample size, however, the lengths of the withdrawal times were considerably overestimated, when they were determined by semi-logarithmic linear regression based on the calculation of the tolerance intervals in the 99th percentile of the population. Only a minor part of this discrepancy could have been eliminated by using weighted linear regression. Unweighted regression was used here primarily because the sponsors of veterinary drugs usually have to provide the registration authorities with suitable kinetic residue data for the calculation of withdrawal times. Frequently, sample sizes which can be realistically required (eg, in 'total-residue' studies with large animals and isotopically labeled drug) are too small to unequivocally allow the identification of any 'outlier' or to obtain valid estimates of the variances or to test the hypothesis of uniformity over time of the variances of the residue data. Therefore, the registration authority has frequently no other choice but to apply unweighted regression analysis when determining withdrawal times. The results of the above computer experiments, however, suggest that — even at the very flat end of the residue-depletion curves — variances change somewhat with time.

The withdrawal times calculated from a limited set of kinetic residue data depend mainly upon pharmacokinetic parameters, biological variability, sample size and the quantile of the population which should be below the ADI at the end of the withdrawal time. The computer experiments have shown that responsibility fell mainly on the high biological variabilities combined with the request that, at withdrawal times, the tolerance intervals in the 99th percentile should be below the ADI, which caused long tails and increases variability in the distributions of the estimates of withdrawal times obtained from small samples. At low

biological variability, it became apparent that sample size in the range of 15–25 items which were appropriately spaced in time and including an appropriate number of replicates could satisfy realistic requirements.

However, it is also apparent from the examples given that even with 25 animals slaughtered for a residue study, the confidence bands of the calculated limits of the tolerance intervals could be rather broad. It could, therefore, be preferable to calculate, for example, upper 95% confidence limits (FDA, 1986) and use these figures as the official withdrawal times. This would mean using the resulting extended time span as an additional 'safety span', in practice. Alternatively, safety spans could also be added to the upper limits of the tolerance intervals calculated without confidence limits on a case by case basis, by submitting the question of the necessity of such a safety span to scientific judgement. In the latter case, factors, such as safety margins contained in the ADI, likelihood of consumer exposure to residues, sample size and practicability of (longer) withdrawal times would be considered.

In practice, the selection of animals from small groups of well-defined breeds kept under standardized conditions of animal husbandry would probably lead to an underestimate of the biological variability. On the other hand, the requirement that the upper limit of the tolerance interval in the 99th percentile of the population should be below the ADI could possibly cause the establishment of unnecessarily long withdrawal times. Both trends would probably compensate each other to some extent. In conclusion, withdrawal times set as the upper 95% confidence limit of the upper limit of the tolerance interval in the 99th percentile of the population should normally provide adequate safety to the consumers of food of animal origin.

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