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Simulation of human exposure to benzylpenicillin residues via pork originating from pigs fed with a dairy by-product

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The use of food industry by-products for feeding is restricted by the European Union (EU) by-product regulation (1774/2002). However, the actual public health risks involved in the use of such products are poorly recognized. This study focuses on bovine milk rejected at the dairy because of a positive result in antimicrobial drug testing and thereafter used as feed for finisher pigs in Finland. In theory, this current practice could expose pork consumers to antimicrobial drug residues. Raw bulk milk samples originating from rejected lots were analysed with a multi-residue method detecting five betalactams, including benzylpenicillin (BP). Based on the probabilistic simulation model developed, concentrations of BP in pork invariably remained below 1% of the maximum residue limit (MRL). Therefore the use of this by-product as feed with the current practice was considered to pose only a negligible risk to consumers of pork products.

Keywords: By-product, feed, antimicrobial drug residues, benzylpenicillin, pork, simulation model, exposure assessment, risk assessment, Finland

Introduction

The food industry produces extensive amounts of various by-products, many of which serve as animal feed. For example, in 2004, the dairy industry in Finland dispensed over 140 000 tons of by-products for feeding, most of which, 82%, consisted of whey and whey concentrate (National Food Administration [NFA] 2005). The new EU regulation on animal by-products (1774/2002) limits the use of such biomaterial as an animal feed, and member states must either ascertain the safety of such products as animal feed, or come up with sustainable solutions on how to dispose of these products (European Union [EU] 2002).

This precautionary approach is justified, e.g. BSE is generally believed to have spread by the recycling of the proteinaceous material from the carcasses of infected cattle into meat and bone meal. This permitted the amplification of what was previously a very rare cattle disease (Anderson et al. 1996, Wilesmith et al. 1988). However, many animal by-products have a high nutritional value and most likely do not pose any significant risks when used as feed. Only a few studies have evaluated the risks imposed by such products.

Finnish national legislation (Ministry of agriculture and forestry [MMM] 2001) demands that each raw milk lot arriving at dairy must be tested with a microbiological screening test for antimicrobial drug residues. National testing statistics indicate that antimicrobial drug residues are detected in 0.05% of milk lots (Finnish Association for Milk Hygiene [FAM] 2005). The most common residue is benzylpenicillin (BP), ensuing from treatment of cows for mastitis. Commercially available microbiological screening tests are very sensitive for

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3 this antimicrobial substance and usually detect BP at its MRL ($4 \mu\text{g kg}^{-1}$)
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5 (European Medicines Agency [EMA] 2005a). The efficient testing practice in
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7 Finland ensures safe milk products for consumers and reduces problems in
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9 cheese production.
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15 Milk rejected for human consumption is used, after mixing with other
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17 ingredients, as feed for finisher pigs. This long-standing practise is at odds with
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19 the new EU by-products regulation. In theory, such a practice has the potential
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21 to lead to BP residues in pork and indirectly expose consumers to the residues.
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23 A total exposure of as negligible as $3 \mu\text{g}$ of BP has been reported to elicit
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25 allergic reactions, such as rash or urticaria, in individuals previously sensitized
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27 to penicillin (Borrie and Barret 1961, Dewdney et al. 1991).
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34 The occurrence of test positive milk loads in Finland is a rare (ca 50 annually)
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36 and random event. Timely tracing of the farms receiving the rejected lots and
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38 representative sampling of the prepared feed, as well as reliable sampling and
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40 determination of the residue level in retail pork, were considered infeasible. The
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42 objective of this study was to construct a probabilistic dilution and exposure
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44 model for the residue, starting from the rejected milk and arriving to the
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46 concentration in pork. The aim was to assess the safety of the long-standing
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48 feeding practice to consumers by comparing the modelled probable distribution
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50 of BP residue concentration in pork with the appropriate Maximum Residue
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52 Limit (MRL) -value (European Community [EC] 1990; EMA 2005a).
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Materials and methods

1
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3 Data about the amounts of milk containing antimicrobial drug residues rejected
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5 at dairies and the amount of other dairy by-products mixed with the milk prior to
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7 the delivery to the pig farms were obtained from the National Food Agency. The
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9 data about the feed processing practices on the farms, consumption data and
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11 the duration of the time when milk was used on farms were obtained from the
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13 Plant Production Inspection Centre. In addition, laboratory analyses were
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15 carried out to obtain information on the BP concentrations in the rejected bulk
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17 milk lots. Since no data on the concentration of BP in the final feed mixture were
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19 available, a simulation model was developed to estimate the daily exposures of
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21 fattening pigs and thereafter the amount of BP residues in pork meat.
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29 Other parameters taken into consideration in the simulation model were the,
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31 oral bioavailability and metabolism of BP. Based on literature, benzylpenicillin is
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33 not chemically stable at the low pH present in the stomach. The gastric acid
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35 hydrolyses the beta-lactam ring and only a minor proportion, 15–30%, of the
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37 orally ingested BP dose is bioavailable (Plumb 1991). Additionally, the half-life
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39 of BP in serum is comparatively short, 1.7 hours (Luthman et al. 1988). These
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41 parameters that reduce the possible amount of residues in pork meat were
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43 included into the evaluation (see Figure 1).
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51 [insert Figure 1 about here]
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55 *Sample collection*

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57 Twenty raw milk samples, drawn from bulk milk lots which were positive in the
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59 microbiological screening tests, were collected during 2001-2003 and their BP
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concentrations were determined. The samples were stored at -70°C and analysed within two months.

Chemical analysis

Benzympenicillin in milk samples was analysed using a multiresidue method detecting also phenoxymethylpenicillin, amoxicillin, ampicillin, oxacillin and cloxacillin. The method was based on the one used for meat products devised by Verdon and Coëdor (1999) and was applied for milk with some modifications. Briefly, the milk samples were centrifuged at 10°C for defatting. The sample tubes were kept at -18°C for 10 min and the fat button was removed with a spatula. The defatted milk samples were transferred with sodium phosphate buffer (3x5 ml; 0.1M at pH 8) into ultracentrifuge tubes, ensuring that all of the precipitate on the bottom was transferred. The pH was adjusted to 8.0-8.1 and the capped tubes were shaken horizontally for 10 min. The samples were clarified by centrifugation (12 000 g for 15 min at 10°C) and vacuum filtration using glass fibre filters (Millipore). The extracts were further purified with C18 solid phase extraction (SPE). The eluents were derivatized with benzoic acid anhydride and mercuric chloride, diluted with phosphate buffer (1:1; 0.1M pH 8) and analysed with high performance liquid chromatography (HPLC) using a reversed phase column (Hypersil BDS C18 5 μm 250x4 mm Agilent Technologies, Germany) and UV (diode array) detection. The SPE, derivatization and HPLC procedures followed in general the method of Verdon and Coëdor (1999). Positive samples were confirmed with UV spectrum and penicillinase treatment.

The limit of detection (LOD) was calculated on the basis of a 3:1 S/N ratio from blank milk and standard solution ($10 \mu\text{g l}^{-1}$) taking into account correction for the recovery. The limit of quantification (LOQ) was calculated similarly based on a 6:1 S/N ratio. To determine the recovery, blank milk samples were spiked at a level of $10 \mu\text{g l}^{-1}$ with six replicates. The measurement uncertainty was 3%.

Construction of the simulation model

The model consisted of five consecutive steps. Three steps described the dilution processes, one step simulated the exposure of fattening pigs and the final step estimated the amount of residues in pork meat and its relation to the MRL-value. The calculations in the five steps were as follows:

Step 1. Residue concentration in dairy silo was calculated by multiplying the respective concentration in truck or trailer (a distribution) with the ratio of the quantity of the milk on truck or trailer (a distribution) to the quantity of milk in silo (a distribution).

Step 2. The concentration in feed was calculated by dividing the concentration in silo (step 1) with the final feed dilution factor (a distribution).

Step 3. Daily exposure of pigs was calculated as the product of concentration in feed (step 2) and quantity of feed fed per day. The total exposure of pigs was calculated as a product of concentration in feed (step 2), quantity of feed fed per day and number of days fed.

Step 4. The maximum amount of residue in 1 kg of pork was calculated as a product of daily exposure of pigs (step 3) and bioavailability, divided by approximate weight of pig carcasses.

Step 5. The maximum amount of residue in 1 kg of pork (step 4) in relation to the appropriate MRL was calculated as the percentage of the latter.

The input for parameters of the model were given as probability distributions based on observed data points, or as fixed point estimates, i.e. means of the observed data and literature references (see Table 1). The goodness of fit of the observed data with the representative input distributions is given in Table 1. The model employed Monte-Carlo sampling of the input distributions and the final concentration of the residues in feed was hence also obtained in the form of probability distributions.

[insert Table I about here]

Each model run consisted of 10 000 simulation runs. The simulation model was implemented on commercial spreadsheet software (Excel 2002, Microsoft Corporation, USA), with a commercial Excel add-in module for risk analysis (@Risk, version 4.5.2, Palisade Corporation, USA).

Statistical procedures

The goodness of fit of the observed data with the employed probabilistic distributions to represent them was tested with Chi square test for the concentration in truck or trailer, and Kolmogorov-Smirnov test for the quantity of milk in truck or trailer, quantity of milk in dairy silo and final feed dilution factor. The p-value of the latter three was obtained by Smirnov's chi square

approximation. The calculations were performed with Statistix for Windows software (Analytical Software, USA).

Results

BP residues in rejected bulk milk

The LOD and LOQ for benzylpenicillin were determined to be $2 \mu\text{g l}^{-1}$ and $4 \mu\text{g l}^{-1}$, respectively. The mean recovery of benzylpenicillin in the recovery study was 113 % and the relative standard deviation was 1.5 %.

The average concentration of BP in the analysed bulk milk samples was $16.9 \mu\text{g l}^{-1}$ (median $6.9 \mu\text{g l}^{-1}$, 90% probability interval 2.3–37.9). The distribution of the observed values conformed to Lognormal distribution (@Risk module), with the parameters calculated from the observed data.

[insert Table II about here]

Simulated exposure of pigs to BP residues via feed

On average, each bulk milk lot rejected at the dairy, was diluted 13-fold (median 8.3, 90% probability interval 1.7–40.7) before it was fed to pigs. According to the simulation model, the average BP concentration in feed was $3.1 \mu\text{g l}^{-1}$ (median $1.2 \mu\text{g l}^{-1}$, 90% probability interval 0.1–11.9 $\mu\text{g l}^{-1}$). Approximately 80% of the results for the BP residue concentration in feed remained under the MRL of BP ($4 \mu\text{g l}^{-1}$) set for milk for human consumption (EMEA 2005a) (see Figure 2).

[insert Figure 2 about here]

According to the model, the average daily exposure of fattening pigs to BP residues was $31.9 \mu\text{g day}^{-1}$ (median $12.0 \mu\text{g day}^{-1}$, 90% probability interval $1.2\text{--}119.2 \mu\text{g day}^{-1}$) during the time that they were fed with the feed containing rejected milk. In the current situation, exposure to BP residues at this level continued on average for 3.6 days (maximum of 7 days) resulting in a total exposure to BP residues during the pigs lifetime of an average of $111.0 \mu\text{g}$ (median $42.9 \mu\text{g}$, 90% probability interval $4.5\text{--}411 \mu\text{g}$).

Possible BP residues in pork

Only a fraction of the ingested BP in feed is absorbed and BP is quickly eliminated from the body, mainly via urine. Prior to its elimination, the average amount of the orally ingested BP absorbed was $9.3 \mu\text{g day}^{-1}$. (median 3.6 , 90% probability interval $0.4\text{--}34.4 \mu\text{g day}^{-1}$). As the daily feed proportion is broken down into 3-4 meals, the average amount of BP absorbed during each meal varies between $3.1\text{--}2.3 \mu\text{g/meal}$. The figure 3 demonstrates a feeding schema where pigs are fed 3 times a day. In case of other feeding schemes, such as four meals per day, the exposure per meal is even lower as the proportions diminish when pigs are fed more often. In view of the rapid elimination, accumulation of BP at such low exposure levels is negligible (see Figure 3).

[insert Figure 3 about here]

Risk estimate for BP

To assess the potential health risk of BP residues in pork for humans a risk estimate was created by comparing the maximum concentration of BP in pork and the MRL of BP set for meat. Residue levels in meat below the MRL are considered to be safe for human consumption (EMEA 2005b).

According to the model, the BP concentration in pork would remain well below the MRL: after 3.5 days of feeding, the average total amount of BP in the pigs immediately after the last feeding would be 9.3 µg (median 0.4, 90% probability interval 3.6–35.8 µg), which would be distributed throughout the body, mainly to stomach and duodenum (McKellar et al. 1987). Pork was estimated to contain on average 0.2% of the MRL concentration (median 0.09%, 100% of the results less than 1%).

Discussion

The route of the exposure in this study has a novel perspective. If animal by-products are used as animal feed then they still have the possibility of gaining access to the human food chain. Therefore, there is clearly an increased need for realistic assessments of risks involved in the use of animal by-products. In this research we have concentrated on benzylpenicillin as one of the potential hazards involved in the process. Other measured antimicrobials are seldom detected in milk. The half-life of these other measured betalactams is short and they do not bioaccumulate more readily than BP. As other betalactam antimicrobials are better tolerated by consumers than BP, they are not expected to pose a greater risk and are not evaluated in this study.

1 If BP was deliberately added to feed, a normal withdrawal period should be
2 applied prior to the slaughter. However, if feed contains rejected milk, there is
3 no withdrawal period. Exposed pigs are allowed to be slaughtered immediately
4 and residues of BP may thus occur in meat. Thereafter the exposure of pigs to
5 BP was only evaluated via this route of using dairy by-products as feed.

In order to assess the risk, reliable data on the level of hazard in commodities are needed. The benzylpenicillin analysis method, modified from a method used for muscle samples, worked well for milk. The sample preparation was rather straight-forward and the recovery and relative standard deviation were good in the recovery study. The method has been used in Finland for many years at the EU National Residue Control Program to detect and quantify BP in milk and has been shown to be a reliable method for this purpose, in several proficiency and intercalibration tests it has produced z-scores between ± 2 .

No MRL for BP residues in feed has been established. However, if the same concentration of BP residues was found in milk as estimated in the pig feed with current practice in Finland, this milk would be approved for human consumption. This study employed probabilistic distributions instead of average point estimates used in many other exposure studies for concentrations and intake values (e.g. Park et al. 2004, Caldas and Souza 2004, Rao et al. 2004). This approach permits a more realistic estimation of the variability in the exposure, and the ensuing residue levels. Risk assessment based on the described variation in the factors is well in line with the transparency objective (Codex Alimentarius Commission [CAC] 1999).

Based on the model, due to the current practice pork was estimated never to contain over 1% of the MRL for BP, even if the animals were to be slaughtered immediately after feeding. This level of BP residues in pork is below the detection limits. In normal practice pigs are not fed for several hours before they are slaughtered and therefore due to the active elimination, the actual BP concentration in meat at slaughter would be even lower than estimated. According to our data, pigs are exposed to this type of feed only once during their lifetime. Therefore this exposure can be considered as an acute instead of a continuous exposure.

Instead of using a model to assess the probable distribution of concentration of BP residues in pork, there is the theoretical possibility of obtaining actual samples of retail pork and performing the chemical analyses. However, the number of samples to confidently detect the residues, the concentration of which most likely would lie below the detection limit of the method, was considered prohibitive.

Usually the safety of the long-term exposure to different compounds found in human diets is evaluated by comparing the estimated intake with acceptable daily intake values (ADI) (Reynolds et al. 2004, Rao et al. 2004, Caldas and Souza 2004), or with no observed adverse effect levels (NOAEL) (Poole et al. 2004). The consumption of pork in Finland was not estimated in this study and therefore the safety estimation was made by comparing the estimated BP residue concentrations in meat with MRL. The smallest amount of BP (3 µg)

which has been observed to elicit allergic reactions in previously sensitized individuals would require, according to our model, a consumption of about 25 kg of pork before any adverse health effects would be expected even in the most sensitive individuals. The Finnish practice of disposing of this dairy by-product as feed can therefore be considered as safe from the residue point of view for pork consumers.

Animal by-products may pose a risk for consumer, if used for animal feeding. Our study has shown that the risk can be vanishingly small and nutritionally valuable feed raw material should not be summarily rejected without a careful assessment of the situation in each case.

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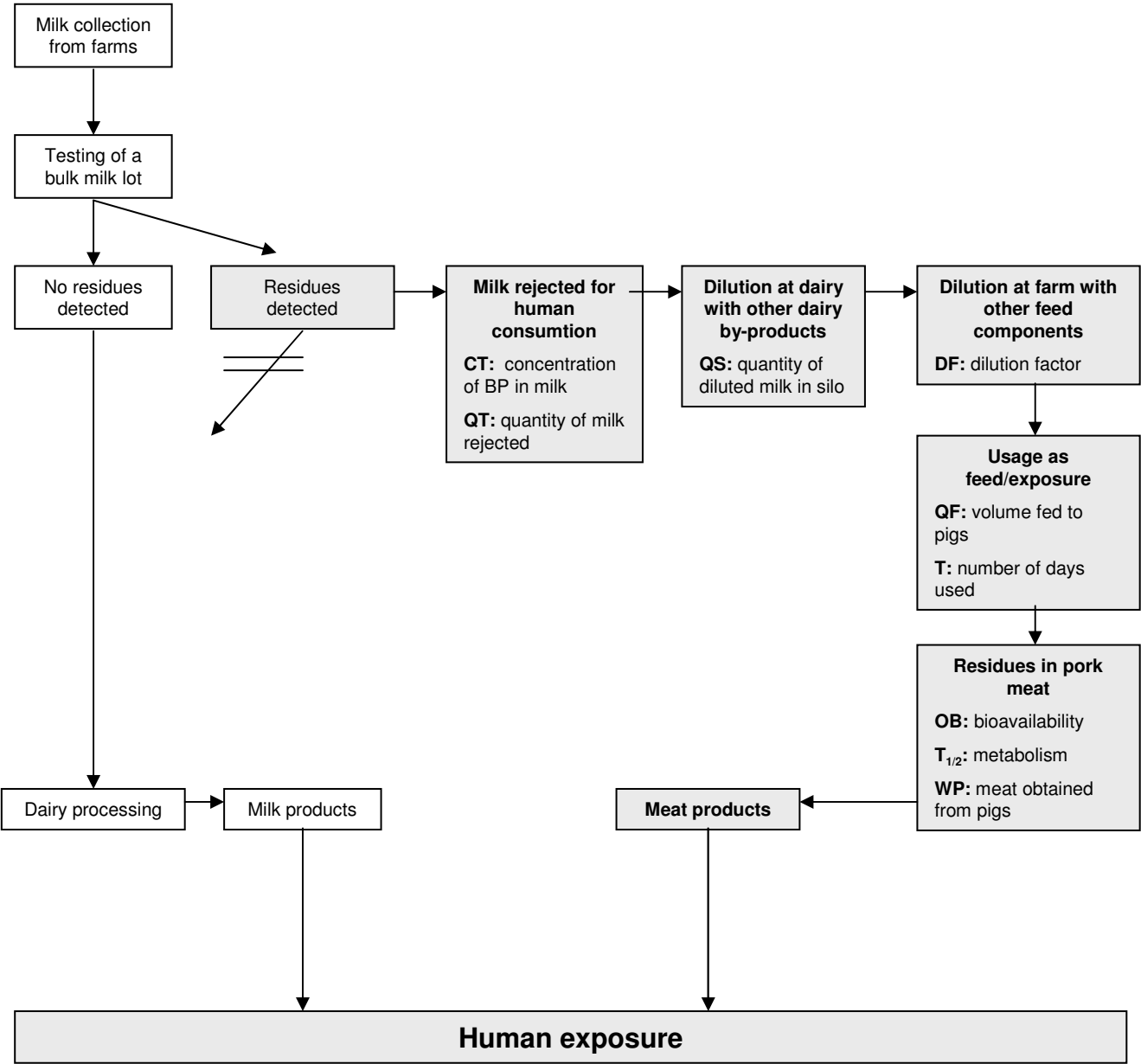
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Step in the model	Inputs	Symbol in Figure 1	Description	unit
STEP 1: Rejected milk lots	Quantity in transport truck	QT	Quantity of milk in transport truck rejected due to a test positive result	litres
	BP concentrations in transport truck	CT	Samples were drawn from the test positive milk lots and BP concentrations were analysed	$\mu\text{g litre}^{-1}$
STEP 2: Dilution at dairy	Quantity in dairy silo	QS	Quantity of rejected milk and other dairy by-products mixed together in dairy silo	litres
STEP 3: Dilution at farm	Dilution factor at farms	DF	A factor indicating the dilution of rejected milk at farms due to the mixing with other feed components	
STEP 4: Exposure	Quantity of feed eaten daily	QF	The total amount of feed fed to the pigs daily	litres day^{-1}
	Number of days fed	T	Duration of time when feed contains rejected milk	days
STEP 5: Residues in meat	Oral bioavailability	OB	Bioavailability of BP when ingested orally	%
	Elimination $t_{1/2}$	$T_{1/2}$	Half life of BP	h
	Weight of the pig carcasses	WP	The average amount of meat which is obtained from each pig at slaughter	kg
	MRL for BP in meat		The maximum residue limits in meat set by the European Medicines Agency	$\mu\text{g kg}^{-1}$

1 p-value: probability of the data given the parametrized distribution

Employed distributions of fit of data	Source of data	Outputs
Lognorm(9,911;6,219) Smirnov's chi square p = 0.618 ¹	National Food Agency	
Lognorm(16.9;22.8) Chi square p = 0.611 ¹	Laboratory analyses	
Lognorm(36,380;28,147) Smirnov's chi square p = 0.443	National Food Agency	Dilution factor in silo Residue concentration in silo
Lognorm(2.56;0.84) Smirnov's chi square p = 1.000	Plant Production Inspection Centre	Concentration in final feed
Point estimate:10	Plant Production Inspection Centre	Daily exposure
Point estimate 3.6	Plant Production Inspection Centre	Total exposure
30	Plump (1991)	The amount of absorbed BP/day
1.7	Luthman et al. (1988)	The amount after elimination (24 h)
80	Rantala (2004)	% of MRL set for BP in meat
50	EMEA (2005a)	

Sample	BP ($\mu\text{g l}^{-1}$)
1	29
2	65
3	4
4	10
5	6
6	6
7	9
8	24
9	14
10	17
11	6
12	8
13	3
14	6
15	92
16	22
17	0
18	5
19	6
20	5
Average	16.9
Stdev	22.8

