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Multicriteria-based Ranking Model for Risk Management of Animal Drug Residues in Milk and Milk Products

Food and Drug Administration
U.S. Department of Health and Human Services

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ABBREVIATIONS AND ACRONYMS

Acronym	Definition
ADI	Acceptable Daily Intake
ALAM	Additive linear aggregation model
AMDUCA	Animal Medicinal Drug Use Clarification Act
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CVM	Center for Veterinary Medicine
DHHS	Department of Health and Human Services
ELDU	Extra label drug use
FARAD	Food Animal Residue Avoidance Databank
FDA	Food and Drug Administration
FR	Federal Register
FSIS	Food Safety Inspection Service
GAO	Government Accountability Office
IMS	Interstate Milk Shipper
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
Papp	Apparent Partition Coefficient
MCDA	Multi-Criteria Decision Analysis
NADA	New Animal Drug Application
NCIMS	National Conference on Interstate Milk Shipments
NAHMS	National Health Monitoring System
NHANES	National Health and Nutrition Examination Survey
NMDRD	National Milk Drug Residue Database
NSAID	Nonsteroidal anti-inflammatory drugs
NTP	National Toxicology Program
OTC	Over-the-counter
PMO	Pasteurized Milk Ordinance
Rx	Prescription
TBD	To be determined
USDA	United States Department of Agriculture
UK	United Kingdom
US	United States
VRC	Veterinary Residues Committee
WHO	World Health Organization

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EXECUTIVE SUMMARY

The U.S. Food and Drug Administration (FDA or "we") developed a multicriteria-based ranking model for risk management of animal drug residues in milk and milk products. This risk assessment serves as a decision-support tool to assist with re-evaluating which animal drug residues should be considered for inclusion in milk testing programs. The risk assessment also may be used to identify and prioritize research needs. FDA undertook this project in response to a request from the National Conference on Interstate Milk Shipments (NCIMS), a coalition of the federal and state governments and Puerto Rico, the dairy industry, academia, and consumers. A key question is whether residues of animal drugs other than beta-lactam antibiotics – currently the focus of milk-sampling programs – warrant monitoring. The multicriteria-based ranking model we developed ranks selected animal drugs according to specific criteria used in the model.

FDA collaborates with the NCIMS under a memorandum of understanding between the two entities. Since 1991, Appendix N of the Pasteurized Milk Ordinance (PMO) has required that all bulk-milk pickup tankers delivering milk to a milk plant be tested for residues of beta-lactam antibiotics, which are commonly used in dairy cows. However, other kinds of drugs also are administered to dairy cows. Reports published by the National Milk Drug Residue Database (a third-party system that captures, under contract to FDA, the milk industry's voluntary reporting on results of drug-residue tests) and FDA (Milk Drug Residue Sampling Survey, 2015) confirm the presence of residues from drugs other than beta-lactam antibiotics in some samples from bulk tank or bulk milk pickup tanker in the United States.

Considerations

FDA selected 54 animal drugs and their various formulations for evaluation. The multicriteria-based ranking model is based on four overarching criteria that collectively contribute to a drug's score and rank within the group: (1) the likelihood that it would be administered to lactating dairy cows; (2) the likelihood that, following administration, drug residues would be present in milk (bulk tank or bulk milk pickup tanker); (3) the relative extent to which consumers could be exposed to drug residues via consumption of milk and milk products; and (4) the potential for a human health hazard given exposure to the drug residue.

We used a wide range of data and information, from a variety of sources to inform the scoring for these criteria, including, for example, government conducted surveys, the published literature, and an external expert elicitation. The risk assessment model approach has undergone an independent external peer review.

Results & Conclusions

The multicriteria-based model evaluated an overall score for each of the selected animal drugs based on the four criteria. The group of animal drugs were ranked, from a food safety perspective, on the basis of the overall score. Drugs in a variety of drug classes scored high, with drugs in eight different drug classes ranked among the top 20 highest-scoring drugs. These eight classes include beta-lactam antibiotics, antiparasitics, macrolides, aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonamides, tetracyclines, and amphenicols. Based on three different analytics (the rank of the highest scoring drug in each class, the rank of each drug in the class evaluated in the model, and the number of drugs in each class that were among the top 20 highest-scoring drugs), beta-lactam antibiotics and antiparasitic drugs (especially avermectins) were the two highest ranked drug classes.

Avermectins were among the highest-ranking antiparasitic drugs, although other antiparasitics also ranked comparatively high. Among the other comparatively high-ranking drug classes, tulathromycin (a macrolide), gentamicin (an aminoglycoside), flunixin (an NSAID), sulfaquinoxaline (a sulfonamide), tetracycline (a tetracycline), and florfenicol (an amphenicol) were among the highest-ranked drugs in their classes.

In light of the resolution afforded by this multicriteria-based ranking model and uncertainties in the data informing the model, we focused on drug clusters (by score) or drug classes when analyzing these results.

This risk assessment provides a science-based analytical approach to collate and incorporate relevant available data and information. The results of the risk assessment provide information for FDA, the NCIMS, and other stakeholders, regarding potential changes to the PMO. The risk assessment report documents the methodology used to develop the model, the model structure, and model results. The report also collects, provides, and analyzes all the currently available data and information for each of 54 animal drugs that were used to evaluate scores for each of the four criteria.

1. INTRODUCTION

1.1 Background

The United States Department of Health and Human Services Food and Drug Administration (FDA) developed this risk assessment to serve as a decision-support tool to assist with re-evaluating which animal drug residues should be considered for inclusion in milk testing programs.

FDA undertook this project in response to a request from the Appendix N Modification Committee of the National Conference on Interstate Milk Shipments (NCIMS), a voluntary coalition that includes representatives from federal and state governments and Puerto Rico, the dairy industry; academia; and consumers. The Appendix N Modification Committee of the NCIMS requested that we conduct an assessment of animal drug residues in the milk supply, to inform potential changes to milk testing program requirements.

FDA collaborates with the NCIMS under a memorandum of understanding between the two entities. The NCIMS meets every two years to propose and discuss potential changes to milk-regulation policy, and only NCIMS members who are State regulators may vote on such proposals. FDA serves on the NCIMS executive board and as a consultant to the organization, and has sole power to veto proposals passed by the voting members (*i.e.*, State regulators).

The Pasteurized Milk Ordinance (PMO) is a model sanitation regulation, including a model milk sampling program, which FDA publishes every two years. The PMO is adopted by States as law. Since 1991, Appendix N of the PMO has required that all bulk-milk pickup tankers delivering milk to a milk plant be tested for residues of beta-lactam antibiotics, which are commonly used in dairy cows. However, other kinds of drugs also are administered to dairy cows. Reports published by the National Milk Drug Residue Database (a third-party system that captures, under contract to FDA, the milk industry's voluntary reporting on results of drug-residue tests) and FDA (Milk Drug Residue Sampling Survey, 2015) confirm the presence of residues from drugs other than beta-lactam antibiotics in some samples from bulk tank or bulk milk pickup tanker in the United States.

FDA developed a multicriteria-based ranking model to rank and prioritize selected animal drugs to assist with re-evaluating which animal drug residues should be considered for inclusion in milk testing programs. The risk assessment provides a science-based, analytical approach to collate and incorporate relevant available data and information.

1.2 Risk Analysis and Process of Risk Assessment

For conducting risk assessment of complex food-safety problems, FDA uses the risk analysis framework recommended by Codex Alimentarius (Codex Alimentarius Commission, 1999). The elements of risk analysis are risk management, risk assessment, and risk communication. The risk analysis approach integrates these three elements to translate scientific knowledge into policy.

At FDA, the risk analysis process begins when the agency's policy-makers or risk managers identify a food-safety problem with potential risk to public health, and charge risk assessors with answering specific, relevant questions (*i.e.,* commission a charge) ultimately intended to inform prevention and mitigation policy. The risk assessment team conducts extensive literature review and data collection, and determines the feasibility of conducting a risk assessment. If the project is determined feasible, the risk assessors develop and implement mathematical models that will respond to the questions with which they have been charged. Once drafted, the model and the report go through review, both internally (*e.g.,* by risk managers) and externally (by external peer reviewers). Such review may result in revision (and re-review and revision, as needed) of various components, to ensure that the model structure, inputs to the model, model assumptions, and the model output will address the charge questions. For example, experts review and comment on the model (*e.g.,* on the criteria for the ranking of the drug residues), which may then be revised accordingly. The draft report is made available for public comment, after which a revised report in which the comments have been considered and incorporated, as appropriate, is issued.

In the broadest terms, the risk-assessment process consists of the following five phases:

Phase I: Commission the risk assessment (including forming the risk-assessment team and defining the scope of the risk assessment).
Phase II: Collect and evaluate data.
Phase III: Develop and validate model. Prepare draft report.
Phase IV: Review (internal and external).
Phase V: Issue final report.

As noted above, these phases are iterative; review (internal and/or external) and public comments may warrant further revision, as needed.

After the risk assessors implement the model and generate the results of the risk assessment, the risk managers use the results to inform their food-safety decisions. The risk-management process involves developing and selecting management options based on the risk-assessment results and other relevant information.

Risk communicators identify stakeholder concerns and consumers' information needs and perceptions of risks, and develop public-health messages based on the results of the risk assessment and subsequent risk-management plans. Engaging in active communication fosters a high level of transparency and encourages stakeholder participation, thereby promoting credibility and scientific accountability. More details about the FDA/CFSAN risk analysis framework are available at http://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/ucm242929.htm

For a graphic depiction of the three elements of risk analysis (*i.e.,* risk management, risk assessment, and risk communication), see Figure 1.1 below:

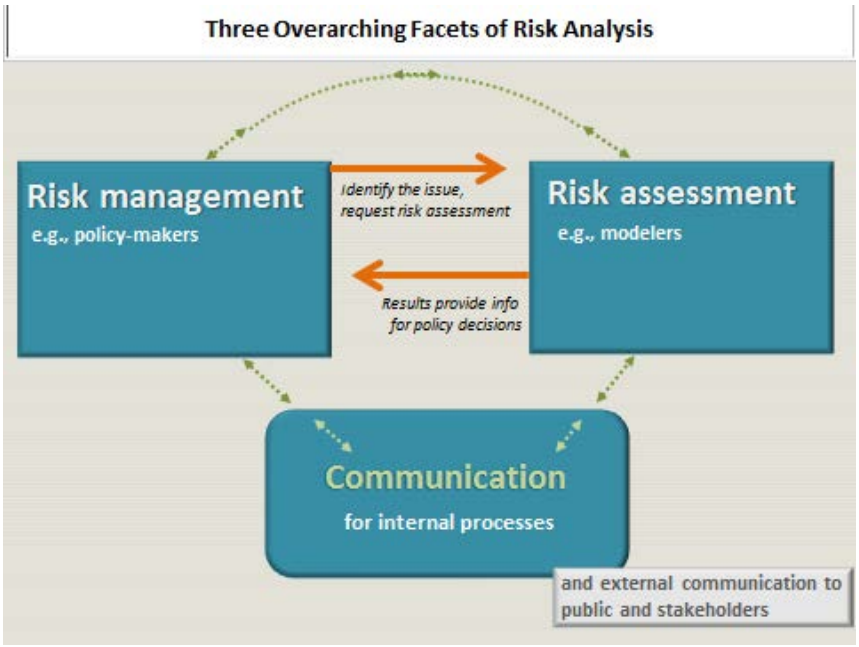

Figure 1.1 Three overarching facets of risk analysis

1.3 Risk Assessment Charge and Scope

As described in the introduction, FDA developed this multicriteria-based ranking of animal drugs in milk and milk products based on scoring of specific criteria. This report also responds to the questions posed by risk managers[1].

- What drugs are most likely to be administered to lactating dairy cows in the United States?
- Which drugs, if administered to lactating dairy cows, are likely to result in drug residues present in milk (bulk-tank or bulk milk pickup tanker)?
- If present in the milk (bulk-tank or bulk milk pickup tanker), what is the fate of these drug residues during processing/manufacturing of various milk products (*i.e.,* in what milk products would these drug residues be found)?
- Of the drug residues present in milk (bulk-tank or bulk milk pickup tanker), which have the potential for concentration in dairy products?
- What is the relative exposure to consumers from drug residue contamination in milk and milk products?
- Which, if any of these drugs, are of particular public health concern and why?
- What is the ranking of the animal drugs under evaluation from a public health perspective?
- What are the critical data gaps or research needs required to more accurately assess the public health impact of drug residues in bulk-tank milk and milk products?

The scope of this ranking report is as follows:

Hazard: Animal drugs with more than a negligible likelihood of being administered to dairy cows

Food products: Milk and milk products made from cow's milk (fluid milk, sour cream, heavy cream, butter, cottage cheese, evaporated milk, non-fat dry milk powder, yogurt, ice cream, mozzarella, cheddar cheese, and processed cheese)

Populations of interest: U.S. population (per-capita lifetime consumption)

Risk-assessment method: Multicriteria-based ranking (semi-quantitative)

Model output: Ranking of animal drug residues

1 These charge questions differ slightly from those NCIMS asked in its charge document (see appendix 1.1).

2. RISK ASSESSMENT APPROACH

2.1 Choice of a Multicriteria-based Ranking Model

We developed a multicriteria-based ranking as the most appropriate type of risk assessment for ranking animal drugs for the purpose of prioritizing drugs to include in a monitoring program. In this section, we provide a description of the multicriteria-based ranking approach, followed by an explanation of why we selected this approach for the ranking model.

2.1.1 Multicriteria-based Ranking, a Semi-quantitative Risk-assessment Approach

In general, risk assessments can be divided into quantitative and qualitative risk assessments (Codex Alimentarius Commission, 1999). Semi-quantitative risk assessments are an intermediate approach between quantitative and qualitative risk assessments. Semi-quantitative risk assessments evaluate risks in terms of rankings, potentially using various decision tools, one of which is multi-criteria decision analysis ("MCDA"). A semi-quantitative ranking that uses MCDA is known as multicriteria-based ranking (FAO/WHO, 2014)

MCDA itself is a sub-discipline of operations research[2], and is a formal mathematical approach that can be employed by individuals or groups to integrate disparate, but important, criteria to inform decisions (Belton and Stewart, 2002). It can be a powerful decision tool, because, as noted above, it allows for explicit consideration of multiple criteria relevant to decision-making that other approaches often consider only implicitly. This mathematical approach is particularly useful in situations in which no single *a priori* "optimal" solution exists and decision-makers need to prioritize among diverse criteria. MCDA allows for the structured integration of multiple objectives and disparate criteria, such as technical data (*e.g.,* molecular weights of chemicals) and subjective preferences of decision-makers, into complex optimization problems (Linkov and Moberg, 2012).

Although MCDA can become quite mathematically involved, to a point where analytical solutions are no longer feasible and complex computer algorithms have to be applied, some forms of MCDA do not require such complex computer algorithms, are relatively straightforward, can be solved analytically, and can be implemented fairly quickly. Such mathematically simple MCDA methods are most suitable for risk assessments (Linkov and Stevens, 2008).

2 Operations research is a rigorous mathematical discipline in which scientific and mathematical methods are applied to complex systems. It is used to study and analyze problems that often involve multiple, diverse, competing factors, to arrive at optimal solutions.

When applied to risk assessment, MCDA typically utilizes criteria to evaluate and compare hazard-commodity pairs with regard to their performance in regard to these criteria (Figueira *et al*., 2005). A criterion's possible evaluations are commonly referred to as scores, which together define the criterion scale (Figueira *et al*., 2005). Hazard-commodity pairs are ultimately ranked based on a single risk score, integrating performance on multiple criteria and sub-criteria related to the associated public-health concerns (and, in some cases, other factors not directly linked to public health, such as economic cost). Individual scores may be combined on additive or multiplicative scales to obtain the final scores. All criteria may obtain equal weights, or certain criteria may obtain greater or lesser weights (Linkov and Stevens, 2008). The selection, scaling, and combination of criteria and sub-criteria can considerably impact the final risk-ranking results and therefore deserve careful attention. For the overview of the criteria and the weights for each drug in this risk-ranking report, see section 5.

Structure and results of multicriteria-based ranking

In terms of the structure and results of the risk assessment, multicriteria-based rankings differ from those of the types of risk assessments traditionally conducted in the food-safety domain, as described in the Codex Alimentarius, for instance. According to the Codex Alimentarius Commission, risk assessments generally have the following structure (Codex Alimentarius Commission, 1999).

- Hazard identification: screens and eliminates hazard-commodity pairs that are of no or limited concern
- Hazard characterization: evaluates the adverse health effects associated with a hazard in a given food, and often incorporates descriptions of the negative health effects associated with a hazard as well as dose-response assessment
- Exposure assessment: characterizes the likely intake of the hazard with food
- Risk characterization: synthesizes the above three steps to generate risk estimates

In comparison, multicriteria-based ranking approaches in the food-safety domain generally have the following structure (FAO/WHO, 2014):

- Identification of key hazards and key commodities of concern
- Description of the model (decision) criteria, scales, scores, and weights
- Results: list of ranking of hazards according to calculated risk scores. (For details about the steps we took in ranking animal drugs in milk and milk products, see section 2.3 of this report)

Accordingly, a multicriteria-based ranking model provides ranking of multiple hazards and commodities based on a set of criteria that may incorporate a wide variety of relevant factors, such as feasibility, disruption of trade relations, and economic cost. Risk, as defined by Codex, is a function of the probability of an adverse event occurring and the expected consequences if

the event indeed occurs, typically expressed in terms of public-health metrics (*e.g.,* morbidity or mortality rates) (Codex Alimentarius Commission, 1999). Therefore, multicriteria-based ranking approaches utilize a somewhat more lenient definition of risk than that typically applied in the food-safety domain, and generally do not generate risk estimates in a metric typical of that generated by a quantitative risk assessment, such as the likelihood of a given adverse effect (*e.g.,* cancer) or the expected number of cases of illness or death among consumers. Instead, the approach generates results that characterize ranking (prioritization) based on potential hazard, but does not directly characterize risk (*e.g.,* illness) to the consumer per se. The approach includes the scoring of criteria that have an impact on risk (the scale of impact), as well as the assigning of weights for the criteria (judgment on the value of impact).

2.2.2 Specific Reasons FDA Selected a Multicriteria-based Ranking Model (Approach)

Although the literature on drug residues in milk and milk products is relatively scant, it did provide us with enough data for *a semi-quantitative approach* to our ranking, to which we applied MCDA. This multicriteria-based ranking allowed us to objectively consider both important subjective information – in essence, to "quantify" it by applying a numeric value – and empiric data; for example, data from results of on-farm inspections. As it allows the ability to numerically consider and compare the diverse criteria (whether subjective or empiric) that influence risk, multicriteria-based ranking provides a more objective ranking than a qualitative risk assessment. More specifically, we selected a multicriteria-based ranking, among many types of risk assessment, to respond to NCIMS's request, based on the following reasons:

- This approach can address the risk management questions posed.
- This approach can accommodate and integrate both quantitative and qualitative data.
- This approach can incorporate multiple, disparate criteria.
- This approach is transparent and reproducible.
- This approach has been successful in address similar types of risk management questions in the past **(**see Appendix 2.1).

For a more detailed discussion, see Appendix 2.2.

2.2 Overall Scheme for Multicriteria-based Ranking Model

The previous section described why we selected multicriteria-based ranking. In this section, we describe the overall scheme we used to rank the animal drugs:

Step 1. Identify drugs for evaluation.
Step 2. Identify milk and milk products for evaluation.
Step 3. Identify and define the criteria and sub-criteria upon which each drug is evaluated.
Step 4. Collect data and develop scoring standards for each criterion and sub-criterion.
Step 5. Assign a weight to each criterion and sub-criterion.
Step 6. Calculate the overall score of each drug, or class of drugs.
Step 7. Rank the drugs (and classes of drugs) according to the multicriteria-based ranking model scores.

These steps were performed by FDA scientists, based on review of the available scientific literature and, where appropriate, expert opinion, peer-review comments, and feedback from FDA risk managers. There is no standard methodology for conducting multicriteria-based ranking. In subsequent sections of this report, we describe each of the steps above in more detail.

3. IDENTIFICATION OF THE DRUGS/DRUG RESIDUES

We selected 54 animal drugs listed in Table 3.1 for evaluation by the multicriteria-based ranking model. Drugs are listed alphabetically by action, then by drug class.

Table 3.1 List of 54 drugs evaluated in the multicriteria-based ranking model, by class

Drug	Action	Class
Acetylsalicylic acid	Anti-inflammatory	NSAID
Flunixin meglumine	Anti-inflammatory	NSAID
Ketoprofen	Anti-inflammatory	NSAID
Meloxicam	Anti-inflammatory	NSAID
Naproxen	Anti-inflammatory	NSAID
Phenylbutazone	Anti-inflammatory	NSAID
Novobiocin	Antimicrobial	Aminocoumarins
Spectinomycin	Antimicrobial	Aminocyclitols
Amikacin	Antimicrobial	Aminoglycosides
Dihydrostreptomycin	Antimicrobial	Aminoglycosides
Gentamycin	Antimicrobial	Aminoglycosides
Kanamycin	Antimicrobial	Aminoglycosides
Neomycin	Antimicrobial	Aminoglycosides
Streptomycin	Antimicrobial	Aminoglycosides
Chloramphenicol	Antimicrobial	Amphenicols
Florfenicol	Antimicrobial	Amphenicols
Ceftiofur	Antimicrobial	Beta lactams: Cephalosporin
Cephapirin	Antimicrobial	Beta lactams: Cephalosporin
Amoxicillin	Antimicrobial	Beta lactams: Non-cephalosporin
Ampicillin	Antimicrobial	Beta lactams: Non-cephalosporin
Cloxacillin	Antimicrobial	Beta lactams: Non-cephalosporin
Hetacillin	Antimicrobial	Beta lactams: Non-cephalosporin
Penicillin	Antimicrobial	Beta lactams: Non-cephalosporin
Danofloxacin	Antimicrobial	Fluoroquinolones
Enrofloxacin	Antimicrobial	Fluoroquinolones
Lincomycin	Antimicrobial	Lincosamides
Pirlimycin	Antimicrobial	Lincosamides
Erythromycin	Antimicrobial	Macrolides
Gamithromycin	Antimicrobial	Macrolides
Tildipirosin	Antimicrobial	Macrolides

Drug	Action	Class
Tilmicosin	Antimicrobial	Macrolides
Tulathromycin	Antimicrobial	Macrolides
Tylosin	Antimicrobial	Macrolides
Furazolidone	Antimicrobial	Nitrofurans
Nitrofurazone	Antimicrobial	Nitrofurans
Sulfabromomethazine	Antimicrobial	Sulfonamides
Sulfachloropyridazine	Antimicrobial	Sulfonamides
Sulfadimethoxine	Antimicrobial	Sulfonamides
Sulfaethoxypyridazine	Antimicrobial	Sulfonamides
Sulfamethazine	Antimicrobial	Sulfonamides
Sulfaquinoxaline	Antimicrobial	Sulfonamides
Oxytetracycline	Antimicrobial	Tetracyclines
Tetracycline	Antimicrobial	Tetracyclines
Albendazole	Antiparasitic	Antiparasitics
Amprolium	Antiparasitic	Antiparasitics
Clorsulon	Antiparasitic	Antiparasitics
Dormectin	Antiparasitic	Antiparasitics
Eprinomectin	Antiparasitic	Antiparasitics
Ivermectin	Antiparasitic	Antiparasitics
Levamisole	Antiparasitic	Antiparasitics
Moxidectin	Antiparasitic	Antiparasitics
Oxfendazole	Antiparasitic	Antiparasitics
Thiabendazole	Antiparasitic	Antiparasitics
Tripelennamine	Histamine Antagonist	Antihistamine

For two of the criteria, it was necessary to consider specific formulations of each drug separately. We included 99 formulations of the 54 drugs (listed in Appendix 3.2) in order to determine the likelihood of administration of drugs, and the likelihood of each drug's presence in milk (bulk-tank or bulk milk pickup tanker). This information was used to determine overall scores for each of the 54 drugs.

Methodology for selecting drugs

We developed a preliminary list of more than 300 drugs using published information indicating any potential for administration to U.S. dairy cows (see Appendix 3.2) (USDA, 2007, USDA, 2008, and USDA, 2009; Moore, 2010; Wren, 2012; NMPF, 2011; Smith, 2005; Haskell, 2003; and USDA, FSIS, 2013).

Drugs in this list that were highly unlikely to be administered to lactating dairy cows in the U.S. were screened out using the following exclusion criteria (see Appendix 3.2 for specific reasons for exclusion of each excluded drug):

- Contra-indicated: The drug is contra-indicated for use in lactating dairy cows (*e.g.,* insulin or drugs specifically approved for euthanasia);
- Route of administration: Formulation makes administration to lactating dairy cows highly impractical and therefore very unlikely (*e.g.,* tablets, capsules, or inhalants approved for use in dogs and cats; medicated feeds approved for use in swine or poultry);
- Species specific: Use of drug is specific to conditions typically treated only in other species (*e.g.,* endocrine, antiemetic, cardiac, oncological, or anticonvulsant drugs used to treat specific conditions in dogs or cats);
- Market status: Drug is no longer marketed in the U.S. (in the absence of data that would indicate their continued use, such as residue-surveillance data);
- Combination drugs: To avoid double-counting of ingredients marketed as stand-alone and combination products;
- Reproductive drugs, hormones, and steroids: High level of similarity between the drug and naturally occurring chemicals in the animal; and
- Expert judgment: FDA subject-matter expert judgment to exclude the drug (*e.g.,* drug judged to be highly unlikely to be chosen for administration due to its vastly inferior effectiveness compared to alternative available drug choices; or mode of application or pharmacodynamic properties render it highly unlikely to enter the milk (bulk-tank or bulk milk pickup tanker).

Using this approach a final list of 54 animal drugs was selected, as shown above in Table 3.1 (also see Appendix 3.1).

4. IDENTIFICATION OF MILK AND MILK PRODUCTS

The milk and milk products included in this multicriteria-based ranking were limited to 12 for practical considerations. We included representative, diverse (liquid, semi-solid, and dry powder) milk and milk products derived from cow's milk for evaluation in the model (see section 5.2.2). We based our selection of the milk and milk products on three general factors: consumption patterns in the U.S., product composition, and dairy processing commonly used in the U.S. The 12 milk and milk products, as shown below, reflect most of the consumption of dairy products in the U.S. and the diversity of dairy products on the market.

- fluid milk
- sour cream
- heavy cream
- butter
- cottage cheese
- evaporated milk
- non-fat dry milk powder
- yogurt
- ice cream
- mozzarella
- cheddar cheese
- processed cheese

(1) Product composition

In addition to milk, we selected products with a wide range of fat, protein, and moisture contents different from those of the "raw" milk from which they originated. Product compositions can vary greatly and can impact drug-residue concentrations in milk products. The 12 categories we selected span the range of dairy-product compositions and allowed us to evaluate the impact of product composition on drug-residue concentrations.

The major components of cow's milk are water, lactose, fat, and proteins (*i.e.,* caseins and whey proteins as well as indigenous enzymes). Milk also contains a range of minor components, including non-protein nitrogen (*e.g.,* urea), minerals (*e.g.,* calcium, magnesium, and potassium), organic acids (*e.g.,* citrate), and vitamins (*e.g.,* riboflavin). The composition of cow's milk can be affected by a variety of factors, such as breed, lactation status, parity, and nutrition. In general, on a weight basis, "raw" cow's milk consists of 3.6-4.5 % milk fat, 3.2-3.5% protein, 4.9 to 5.0% lactose, 0.7% ash (*i.e.,* oxides of milk minerals resulting from combustion), and 86-88% water (Carroll *et al*., 2006; Sol Morales *et al*., 2000; Frelich *et al*., 2009; Fox and McSweeney, 1998; Grieve *et al*., 1986).

The table below summarizes the compositions of the 12 milk and milk products. Note that the table provides values for full-fat version of the products; however, we evaluated consumption of all types of these products (*e.g.,* regular, reduced-fat, low-fat, and non-fat milk).

Table 4.1 Selected dairy products and their compositions

Product	%Moisture	%Fat	%Protein	%Other solids
Fluid milk	87.8[a]	3.3[a]	3.4	5.5
Sour cream	74.5	18	2.9	4.6
Heavy cream	58.2	36	2.2	3.6
Butter	16	80	0.6	3.4
Cottage cheese	79.2	4.3	13.2	3.3
Evaporated milk	77	6.5	7	9.5
Non-fat dry milk powder	5	1.5	36	57.5
Yogurt	88	3.3	3.8	4.9
Mozzarella cheese	52	22	22	4
Cheddar cheese	39	31	25	5
Processed cheese	43	27	24	6
Ice cream	62	10	4	24

Source: USDA Nutrient Database (USDA ARS, 2011); 21 CFR 130-135; McCarthy, 2002; and Roos, 2011.

[a:] The milkfat content in the table has been adjusted down to a milkfat percentage that more closely approximates the Standard of Identity for milk found in 21CFR 131.110. The amount of the adjusted milkfat percentage, the protein percentage, the lactose percentage and the ash percentage was subtracted from 100 to obtain the percent of moisture.

To summarize, the fat content of the milk and milk products selected for this multicriteria-based ranking model ranges from 1.5% or less (*e.g.,* non-fat dry milk powder) to > 80% (*i.e.,* butter); the protein content ranges from <1% (*e.g.,* butter) to > 35% (*i.e.,* non-fat dry milk powder); and the water content ranges from <5% (*i.e.,* non-fat dry milk powder) to nearly 90% (*e.g.,* whole milk).

(2) Dairy processing commonly used in the U.S. market

We selected two processing operations for inclusion in the multicriteria-based ranking model [after initially considering five separate operations; for more detail, see section 5.3 (Impact of processing) and Appendix 5.14)]:

Table 4.2 Processing operations included in model

Processing operation:	Represented in our model by:
Heating	All milk products
Water removal or condensing	Evaporated milk, non-fat dry milk powder

To capture the different time-temperature combinations used for heating different dairy products that may lead to considerably different impacts on drug residue concentrations, we further divided the heating process into five different types, including:

- pasteurization
- higher-impact pasteurization (*e.g.,* manufacture of yogurt): Pasteurization at a higher temperature, for a longer time, or a combination of both (Tamime and Robinson, 1999).
- retorting
- cheese making
- processed-cheese making

All five heating processes are represented among the 12 products selected for evaluation in this multicriteria-based ranking model, as follows:

Table 4.3 Time-temperature combinations – products to which applied

Time-temperature combination	Represented by, e.g.:
pasteurization	fluid milk, non-fat dry milk
higher-impact pasteurization	yogurt
retorting	evaporated milk
cheese making	cheddar cheese, mozzarella
processed-cheese making	processed cheese

Source: 21 CFR 1240.61 and Fox *et al.,* 2000b

The processing model estimates the degree, if any, to which dairy processing increases or decreases drug concentrations, relative to the concentrations in the "raw" milk used for the manufacturing of the dairy products.

(3) Consumption patterns

We used USDA Economic Research Service (ERS) food-availability data (average from 2000-2009) to further refine our product selection for the processing section of the model to arrive at the 12 we chose. For example, under the cheese category, we had available to us a choice of many different kinds of cheeses for the model's cheese category. However, we selected cheddar and mozzarella, because these are the two most commonly eaten cheeses in the U.S., with cheddar representing an aged cheese and mozzarella representing a non-aged cheese (USDA ERS 2011).

Limitations and exclusions

The dairy products selected for this multicriteria-based ranking model necessarily provide a simplified picture of the milk products currently on the U.S. market. Several data limitations complicated the assessment, including the paucity of data of the impact of processing on specific

drug residues. Our strategy to overcome this challenge as to select a set of products that (1) capture the diversity of products with regard to the two factors most likely to impact drug-residue concentrations (*i.e.,* product composition and processing) (Fox and McSweeney, 1998), (2) are very different in composition from "raw" milk and from each other, and (3) are commonly consumed.

In addition, we decided not to evaluate protein-enriched dairy powders, such as whey-protein concentrate and milk-protein concentrate, "special" products such as fortified products or infant formula in the model. These products were excluded mainly because of a lack of information on the importance of drug binding to milk proteins. See Appendix 4.1 for more discussion.

5. MODEL DESCRIPTION

Overview of the model

Criteria:

Based on the charge questions we received from the risk managers and on the available scientific evidence, we selected the following four, distinct criteria to be incorporated in the model:

- Criterion A: Likelihood of the drug's administration to lactating dairy cows.
- Criterion B: Likelihood of the drug's presence in milk (bulk-tank or bulk milk pickup tanker).
- Criterion C: Relative exposure to drug residues from consumption of milk and milk products.
- Criterion D: Potential for human health hazard.

Note that criteria A, B, C, and D have sub-criteria. See the following sections (5.1-5.4) for detailed descriptions of each criterion. Criteria A, B, and C are related to exposure, whereas criterion D is related to hazard.

We ensured that the set of derived criteria and sub-criteria were complete, non-redundant, operational, and mutually independent, to the greatest extent possible (Department for Communities and Local Government, 2009). In this context, "completeness" refers to the consideration of all relevant criteria, objectives, and performance categories, whereas "non-redundancy" indicates that none of the included criteria can be removed without changing the final ranking (Department for Communities and Local Government, 2009). "Operational" refers to the fact that each alternative can be evaluated for each criterion, and "mutual independence" indicates that ranking an alternative's performance on any of the criteria does not depend on knowledge about its performance on any other criterion (Department for Communities and Local Government, 2009).

Notably, while there are dependencies between the data used for criterion A and criterion B (see below), we ascertained that the individual criteria and sub-criteria are value-independent. In particular, while there may be some overlap in the data sources used for criterion A and criterion B, the utilization of the data in the scoring of the criteria and sub-criteria is not redundant. Additionally, we demonstrated, as part of model testing and validation, that omission of any one of the criteria or sub-criteria would change the final ranking. Criterion B is necessarily dependent on a performance of criterion A being above zero (*i.e.,* it is not possible to have drug residues entering the milk (bulk-tank or bulk-milk pickup tanker) without some prior administration of the drug to a cow whose milk eventually enters the bulk-tank milk, given the assumptions of this model). Criteria A and B, as initially defined, are not mutually independent (rather, a non-zero

score for a given drug in criterion B is completely dependent upon a score above zero for each drug in criterion A). However, after initial review of the data and expert elicitation results, it became obvious that none of the evaluated drugs has a likelihood of zero of being administered to cows whose milk may eventually enter the bulk-tank milk. Therefore, the sampling space for criterion A in this model can be re-defined to cover only non-zero probabilities; in that case, criterion B can be defined as the likelihood of drug presence in the milk (bulk-tank or bulk-milk pickup tanker), given that the drug is administered to lactating dairy cows. With these revised definitions, criteria A and B are, in fact, mutually independent and this important assumption of our model is met, even though the same data sources may provide information relevant to criteria A and B.

Data:

The model considers drug residues that may ultimately be present in the milk (bulk-tank or bulk-milk pickup tanker) (criterion B), the relative exposure to drug residues in milk and milk products (through criterion C), and the potential for a human health hazard posed by these drug residues (through criterion D). For criteria A and B, we considered drug administration to lactating dairy cows (assuming that the cow would remain in lactation throughout the withdrawal time) and also considered administration to dry cows or heifers.[3] Data used in our model come from various sources, including, but not limited to, academic journals, scientific books, expert elicitation, and government publications or surveys, as listed below:

Data used for criterion A scoring:

- USDA dairy study [National Health Monitoring System (NAHMS) Dairy, 2007 study]
- Veterinary survey (Sundlof *et al*., 1995)
- External Expert Elicitation (Versar, 2014)[4]
- 21 CFR (Parts 500-599) for drug-approval status and drug-marketing status
- FDA Farm Inspection Data for farms inspected following up on dairy cow tissue residue violations for October 1, 2008 – December 31, 2014 (FDA, 2014).

3 At time points when the cow or heifer may enter the (next) lactation during the withdrawal time, even though in some cases data availability limited our ability to explicitly model such use. For instance, data for drug use to treat heifers was available only in aggregated form, covering the whole period prior to entering the first lactation. Only a small fraction of this period may lead to drug residues at the beginning of the first lactation, and drug use patterns during this period may conceivably differ from those earlier in the heifer's life. Therefore, data on drug administration to heifers was not included in our risk-ranking model.

4 Expert elicitation was performed by Versar, Inc., in collaboration with a team of facilitators from Kearns & West, Inc. A modified Delphi approach, which included two rounds of expert elicitation and one live webinar between rounds, to discuss results from the first round of elicitation, was chosen for this expert elicitation.

Two panels of nine external experts (external to FDA and to the US government entities) each were assembled: one to address drug-specific knowledge gaps related to the likelihood and magnitude of drug administration and the likelihood of drug residue entry into cow's milk and on-farm bulk-tank milk, and the second to address the relative importance of criteria and sub-criteria contained in FDA's risk-ranking model and to inform weighting used in the model. For a short summary of the results from the expert elicitation, see Appendix 5.1. Details of the method for expert identification, the applied selection criteria, and the composition of the two panels are provided in the reference (Versar 2014).

Data used for criterion B scoring:

- FDA Milk Drug Residue Sampling Survey (FDA, 2015a and FDA, 2015b)
- National Milk Drug Residue Data Base for fiscal years 2000-2013 (GLH, Inc.)
- 21 CFR (Parts 500-599) for drug-approval status
- Drug persistence data [21 CFR part 558, FDA/New Animal Drug Application (NADA) , FARAD]
- Expert Elicitation (Versar, 2014)[5]

Data used for criterion C scoring:

- Databases for prediction of drug-partitioning behavior [NCBI PubChem, EMBL CHEMBL (various published journals and database at http://pubchem.ncbi.nlm.nih.gov/))
- Metabolite data (21 CFR part 556, subpart B; FDA/CVM NADA FOIA data, publications from European Medicines Agency (EMA) or FAO; US Pharmacopeia data; peer-reviewed articles, NIH TOXNET data)
- Processing conditions (CFR, Codex Alimentarius Commission, and trade publications)
- Impact-of-processing data for processes such as freezing, heating, culturing (peer-reviewed journal articles; see respective sections for details)
- USDA Economic Research Service (ERS) food availability data to aid in selection of products for analysis (USDA ERS, 2011)
- CDC NHANES Data (CDC, 2011)
- USDA Food and Nutrient Database for Dietary Studies (USDA, 2012a)

Data used for criterion D scoring:

- 21 CFR (Part 556) for ADI values of the drugs for which FDA has established values
- FDA CVM files[6] for our analysis for the purpose of hazard ranking
- Publicly available websites.

For a detailed description of each identified data source in each criterion, see sections 5.1-5.4.

Scoring standards and scales:

We developed a scoring scale that ranged from 1- 9 for each criterion (and, in some cases, its sub-criteria and the sub-criterion's factors and sub-factors). We defined the score assignment by evaluating quantitative data where possible; and, for a criterion that does not allow quantitative evaluation, we constructed a qualitative scale and converted this to a numeric scale that ranged

5 Ibid.

6 Unpublished.

from 1-9. For scoring standards and scales for each criterion, see the following sections (5.1-5.4).

Criterion scores reflect the value the decision maker derived from the performance of an alternative on a given criterion (Belton and Stewart 2002). Accordingly, we ensured that criterion scores in our model (1) are relevant to the objective, which is to rank and prioritize the drug residues; (2) are reliable, so as to ascertain consistency across independent ratings of the same alternatives; and (3) allow for the rating of alternatives that were not used in the definition of the scale (Belton and Stewart, 2002, and Department for Communities and Local Government, 2009). We defined and assigned scores within a scale (1-9) to ensure sufficient spread and separation among the drugs, ultimately to allow for an effective ranking and prioritization among the drugs. For a summary of scoring standards and scales used in each criterion, see Appendix 5.2.

Weighting:

For the weighting of the four criteria, we elicited expert opinion (external experts) and asked them to assign weights to each criterion (Versar, 2014).[7] The external experts assigned certain criteria greater or lesser weight, reflecting their values on the relative importance of individual criteria).

Table 5.1 Weights of criteria by assigned by external experts

Criteria	Weights Assigned by External Experts[8]
A (Likelihood of drug's administration to lactating dairy cows)	0.289
B (Likelihood of the drug's presence in milk (bulk-tank or bulk-milk pickup tanker)	0.262
C (Relative exposure to drug residues in milk and milk products)	0.250
D (Potential for human health hazard)	0.199

A variety of methods are available to determine criterion weights, which are generally based on subjective expert judgment (Yoe, 2002). Our model uses direct weighting and, therefore, decision makers directly assign numerical weights to individual criteria. For a description of

7 Ibid.

8 For description of how we calculated and converted expert elicitation scores from raw data to the assigned weights, see Appendix 5.3.

other commonly used weighting methods (*e.g.*, swing weighting and pair-wise comparison), see Appendix 5.4.

Weighted risk score of each criterion:
For each of the 54 drugs, we determined the ***weighted risk score of each individual criterion*** in our model by multiplying the score of each criterion by its respective weight. When the criterion has sub-criteria, we determined the score of the criterion by summing up the weighted score of each sub-criterion). Note that we determined the weighted score of each sub-criterion by multiplying the score of the sub-criterion by its respective weight.

Final risk score of each drug:
We determined the ***final risk score for each drug*** across all milk products and for all consumer age groups in our model by adding together the weighted score of each criterion divided by the sum of the weights of all criteria. Accordingly, we derived the formula for the final score of each drug as follows:

$$\text{Final Risk Score of Each Drug (F)} = ((A*W_A) + (B*W_B) + (C*W_C) + (D*W_D))/W_{sum}$$

Where:

F = Final risk score for each drug.
A, B, C, D = Criterion scores for each drug with respect to criteria A, B, C, and D.
W_A = Weight assigned to criterion A.
W_B= Weight assigned to criterion B.
W_C = Weight assigned to criterion C.
W_D = Weight assigned to criterion D.
$W_{sum} = W_A + W_B + W_C + W_D$

Figure 5.1 depicts the formula in a graphical manner.

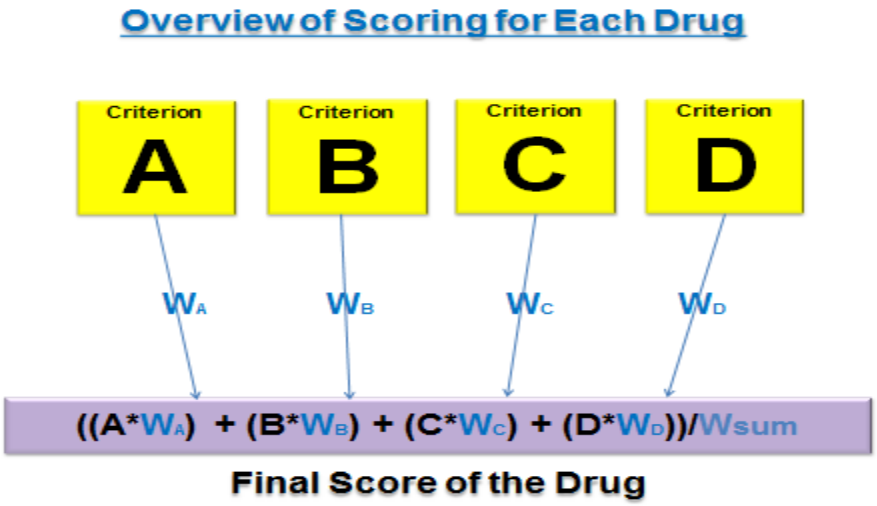

Figure 5.1 Final risk score of each drug

Our multicriteria-based ranking is based on an additive linear aggregation model (ALAM), as we are adding weighted scores of each criterion to derive the final risk score of each drug. Known for its computational ease and the robustness of the method, ALAM is the simplest and among the most widely used models for aggregating value functions for individual criteria (Steward, 1992; Belton and Steward, 2002).

As mentioned earlier, the UK's risk-informed prioritization of surveillance for veterinary drug residues in food (VRC, 2001, 2004, 2005, and 2007) uses a matrix ranking approach. This approach incorporates the following aggregation model that is fundamentally similar to our model, but differs in the aggregation of individual criteria and in the selected criteria, scales, and scores:

The UK model overall substance score = (A + B) x (C + D + E) x F

Where:

A=Scores for criterion A (potential adverse effects from exposure to a substance)
B=Scores for criterion B (potency of the substance)
C=Scores for criterion C (consumption of foods coming from treated animals)
D=Scores for criterion D (frequency of dosing with a particular substance to animals)
E=Scores for criterion E (evidence of high-exposure groups)
F=Scores for criterion F (evidence of detectable residues)
(Substance=veterinary drug)
(Source: VRC, 2008 and VRC, 2010)

The UK model includes criteria that are fundamentally similar to ours. However, we chose ALAM over the UK's approach for two key reasons. First, our weighting system provides increased transparency of both the individual drug score and the assigned weight. The UK's weighting system incorporates a scoring standard (with scales of 0-3, 0-4, 1-4, and 0-6) only, but not the actual weight for each criterion. Separating the scoring from the weighting of each criterion also allows us to conduct sensitivity analysis, using different weighting schemes. Second, ALAM is more suitable in situations where the data are limited, compared to the multiplicative model.

Final ranking of the 54 drugs

The final scores for each 54 drugs were sorted in descending order to generate a rank-order listing. Among the 54 drugs, the one with the highest overall score represents the drug with the highest combined likelihood of drug administration, the likelihood of drug's presence in milk (bulk-tank or bulk-milk pickup tanker), relative exposure to drug residues in milk and milk products, and potential for human health hazard. The ranked list of the 54 drugs (individual and by class) is presented in Section 6 ("Results").

5.1 Likelihood of Drug Administration to Lactating Dairy Cows (Criterion A)

Criterion A evaluates the likelihood of drug administration (LODA) to lactating dairy cows (or dry cows or heifers that enter lactation before the drug can be cleared from their system) in the United States and consists of the following four sub-criteria (and their individual factors):

- Sub-criterion A1. LODA score based on published surveys and formal expert elicitation (section 5.1.1).
    - Factor A1.1: LODA score based on a nationally representative survey of dairy farmers regarding drug administration to dairy cows on U.S. dairy operations (NAHMS Dairy 2007 Study) (section 5.1.1.1).
    - Factor A1.2: LODA score based on a survey of bovine veterinary practitioners in the U.S. regarding drug administration to lactating dairy cows (Sundlof *et al.*,1995) (section 5.1.1.2).
    - Factor A1.3: LODA score based on formal expert elicitation (Versar, 2014) (section 5.1.1.3).
- Sub-criterion A2. LODA score based on drug's marketing status (section 5.1.2).
- Sub-criterion A3. LODA score based on drug's approval status (section 5.1.3).
- Sub-criterion A4. LODA score based on evidence of the drug's presence on dairy farms, based on farm inspection data (section 5.1.4).

For overview of criterion A, its sub-criteria, factors, and sub-factors, see figure below:

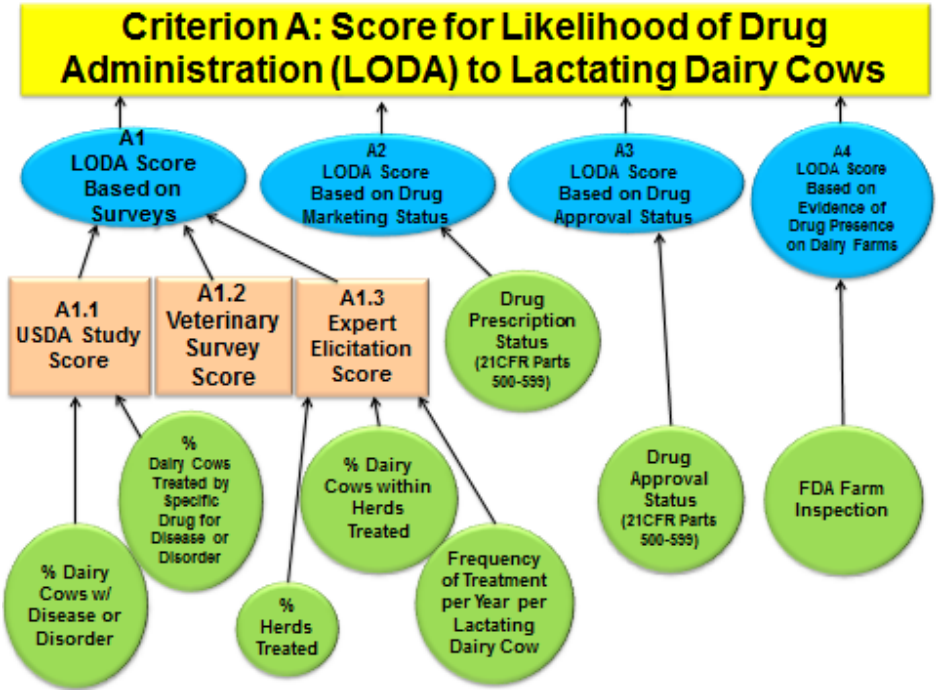

Figure 5.2 Overview of criterion A, its sub-criteria, factors, and sub-factors

About the four sub-criteria (A1-A4):
For criterion A, the LODA score based on published surveys and formal expert elicitation (sub-criterion A1) is most directly relevant to the question at hand. Using these data, we developed a preliminary estimate of the likelihood of use for each drug. However, to provide further granularity for the preliminary estimates and to inform the disaggregation of drug-class data from individual drugs, we developed three additional sub-criteria: drug's marketing status (sub-criterion A2), drug's approval status (sub-criteterion A3), and evidence of drug's presence on dairy farms (sub-criterion A4). These data together (A1-A4), provide relevant and useful information for estimating the LODA to lactating dairy cows.

Summary of scoring for criterion A from its four sub-criteria:
We calculated the overall score for criterion A for each drug as a weighted sum of its four sub-criteria (with all scores normalized to 1).

$$A = ((A1*W_{A1}) + (A2*W_{A2}) + (A3*W_{A3}) + (A4*W_{A4}))/W_{sum}$$

Where:

A = Criterion A score
A1,2,3,4 = Scores from sub-criteria A1, A2, A3, and A4, respectively.
$W_{A1, A2, A3, A4}$ = Weights assigned to A1, A2, A3, and A4, respectively.
$W_{sum} = W_{A1}+W_{A2}+W_{A3}+W_{A4}$

The experts assigned the following weights to the four sub-criteria that define criterion A (see table below):

Table 5.2 Weights of the four sub-criteria that define criterion A

Sub-criteria (A1-A4)	Weights Assigned by External Experts[9]
LODA score based on surveys (A1)	0.273
LODA score based on drug marketing status (A2)	0.273
LODA score based on drug approval status (A3)	0.181
LODA score based on evidence of the drug use on dairy farms (A4)	0.273

9 Ibid.

5.1.1 Likelihood of Drug Administration (LODA) based on Surveys (Sub-criterion A1)

To estimate the LODA for lactating dairy cows (or dry cows or heifers that enter lactation before the drug can be cleared from their system), we used data from surveys and an expert elicitation as represented by the following factors:

- Factor A1.1: LODA score from a survey completed by farmers in the U.S. (NAHMS Dairy 2007 Study) (USDA, 2007, USDA, 2008, and USDA, 2009).
- Factor A1.2: LODA score from a survey completed by veterinarians in the U.S. (Sundlof *et al.*, 1995).
- Factor A1.3: LODA score from results from expert elicitation[10] (Versar, 2014).

We estimated each drug's LODA to lactating dairy cows from rough estimates, using the data in the two surveys combined with information obtained from the expert elicitation. The USDA and Sundlof studies relied on different surveys and covered different points in time. Each study used different methodologies, objectives, and survey sources, which led to some variance in estimated frequency of use. Also, these surveys may have bias, based on geographic location, time-period, or date of the response, and may have under-reported off-label or unapproved use in lactating dairy cows.

Summary of scoring for sub-criterion A1 from factor scores A1.1, A1.2, and A1.3:

We calculated the final score (based on a 1-9 scale) for sub-criterion A1 for each drug as the average (using equal weights for each of the factors) of the three factor scores (A1.1, A1.2, and A1.3).

5.1.1.1 LODA from USDA Survey (Factor A1.1)

We estimated the score for each drug (99 formulations) from a nationally representative survey of dairy farmers completed by USDA in 2007, as part of the data included in the USDA National Animal Health Monitoring System (NAHMS)'s study of the U.S. dairy industry, also known as "NAHMS Dairy 2007"[11] (USDA, 2007, USDA, 2008, and USDA, 2009). USDA conducted its NAHMS Dairy 2007 study in 17 of the nation's major dairy states[12] and thereby collected information from 2,194 dairy operations, which represented 79.5% of U.S. dairy operations and 82.5% of U.S. dairy cows. See appendix 5.5 for data representing the percent of cows affected

10 Expert Elicitation: See Footnote #5 in Section 5. "Model Description" under "Overview of the model."

11 Prior to 2007, USDA has published three dairy studies in 1991-92, 1996, and 2002.

12 California, Idaho, Indiana, Iowa, Kentucky, Michigan, Minnesota, Missouri, New Mexico, New York, Ohio, Pennsylvania, Texas, Vermont, Virginia, Washington, and Wisconsin.

by disease or disorder (respiratory, digestive, reproductive, mastitis, lameness, or others) and data representing the percent of cows (on farms) treated with a particular drug class (primary drug class).

The USDA survey did not collect data specifically on each of the 54 drugs we selected for our evaluation, but rather in aggregated form, on a drug-class level. We assumed that drugs in the same drug class have the same likelihood of being used, if they are used to treat the same conditions. In addition, because the data were on dairy cows, we inferred that LODA to dairy cows is similar to that of lactating dairy cows. The only data available regarding antiparasitic drug administration was for use to de-worm dairy cows; therefore, we presumed all antiparasitic drugs are administered to dairy cows (*i.e.,* lactating dairy cows) as de-worming drugs. Last, USDA data focused on antimicrobial use, whereas our evaluation included a selected number of other drug families as well, such as NSAIDs. Drug use patterns in the "other" category in the USDA data may not be directly applicable to these other types of drugs.

Scoring:
We determined the factor score of each drug by first calculating LODA separately for each disease or disorder for dairy cows, then summed the results across all conditions. We calculated LODA for each disease or disorder as the product of disease prevalence (*i.e.,* percent of cows in herds affected by a disease or disorder) and likelihood of choosing a given drug to treat a cow afflicted by that condition (*i.e.,* percent of cows on farms treated by primary drug class to treat disease or disorder).

For A1.1., the likelihood that a drug is used to treat dairy cows, T(i), is determined by summing the likelihood that the drug is used to treat specific conditions in dairy cows, S1(i, j), across all "j" disease conditions as follows:

$$T(i) = \sum_{j=1}^{6} S1(i,j)$$

Where:

T(i) = LODA for each drug (i)
j = disease or disorder conditions (respiratory, digestive, reproductive, mastitis, lameness, or other)
S1 = likelihood that the drug is used to treat a specific condition (disease prevalence times drug treated to a cow afflicted by that condition).

For more detail on this equation and relevant tables, see Appendix 5.5.

We then assigned a score of 1-9 to the final calculated value as described in the table below:

Table 5.3 Scores for LODA based on USDA study (NAHMS Dairy 2007)

Survey Average-Use Score for each herd size	Score Assigned
if T > 0.08 (8%)	9
if 0.08 ≥ T > 0.04 (4%)	7
if 0.04 ≥ T > 0.02 (2%)	5
if 0.02 ≥ T > 0.005 (0.5%)	3
Else	1

5.1.1.2 LODA from Veterinarian Survey (Factor A1.2)

We estimated the score for each drug formulation from a national veterinarian survey published by Sundlof *et al.* in 1995 (Sundlof *et al.*,1995), who conducted survey of about 4,000 (814 responses) U.S. veterinarians in 1992 on the frequency of drugs administered to lactating dairy cows. The 82 drugs veterinarians administered to lactating dairy cows were the ones reported to be found on farms by the U.S. Government Accountability Office (GAO) in a 1992 report of a 2-year investigation on drug residues in the nation's milk supply (GAO, 1992).

The Sundlof survey calculated an average-use score for each drug and grouped them into the following categories: antibiotics, sulfonamides, anthelminthics, anti-inflammatories and tranquilizers/analgesics, nitrofurans, antifungals, antihistamines, antidotes, estrus regulators, vitamins, and miscellaneous drugs. The survey further divided each of these groups into two status categories: FDA-approved or non-approved for use in lactating dairy cows. The survey included most of the 54 drugs evaluated in this multicriteria-based ranking, with some exceptions, such as the newer drugs not in use at the time of the survey. Also, the data may not be reflective of today's dairy-and animal-management practices and disease-incidence patterns in U.S. dairy cows. However, we compensated for the drugs not included, by considering those drugs as having usage values equivalent to reported usage values for drugs within the same drug group (as defined by Sundlof). We also considered all drug formulations for each drug as having equivalent average-use scores. See Appendix 5.6 for the average-use scores of 54 drugs (99 formulations).

Scoring:
We assigned scores for each drug based on the survey's average-use score, which, in turn, was based on the number of times a veterinarian reported prescribing a drug per week. The average-use scores ranged from 1, which indicated the drug was never used or prescribed, to 9, which indicated that the drug was prescribed or used by all respondents more than 4 times a week. The range of average-use scores and the subsequent scores assigned to drugs in the Sundlof study are described in the table below.

Table 5.4 Scores for LODA based on veterinarian survey (Sundlof *et al.,* 1995)

Survey Average-Use Score	Score Assigned
> 4	9
> 3 and ≤ 4	7
> 2 and ≤ 3	5
> 1.5 and ≤ 2	3
> 1 and ≤ 1.5	1

5.1.1.3 LODA from Expert Elicitation (Factor A1.3)

We convened an expert panel [See Appendix 5.1, Appendix 5.3, and Versar (2014) for details) specifically to support this multicriteria-based ranking (to determine the LODA of the 54 drugs to lactating dairy cows).[13] We asked the experts to consider the three parameters in criterion A:

- The percentage of dairy cows herds administered each drug per year;
- The percentage of dairy cows within a herd (or dry cows or heifers that enter lactation before the drug can be cleared from their system) that have the drug administered per year; and
- The average number of treatments per lactating dairy cow (or dry cow or heifer that enters lactation before the drug can be cleared from its system) per year.

With this expert elicitation, we attempted to reduce the bias introduced from using data from the surveys (USDA and Sundlof) and included recent data on the use of individual drugs, instead of drug classes. However, there may be typical limitations that are associated with any expert elicitation, such as experts' judgments being vulnerable to heuristics and biases (Tversky and Kahneman, 1974). See tables below for the scorings for these three parameters.

Table 5.5 Scores for percentage of dairy cows herds to which the drug is administered, per year ($P_{herds/year}$)

Description	Value	Score Assigned
Very High	>75%	9
High	>50% - 75%	7
Moderate	>25% - 50%	5
Low	>0 – 25%	3
Zero	=0%	1

13 See footnote #7 in section 5 "overview of the model" for a brief description of the expert elicitation.

Table 5.6 Scores for percentage of dairy cows within a herd that have the drug administered per year. ($P_{cows/herd/year}$)

Description	Value	Score Assigned
Very High	>75%	9
High	>50% - 75%	7
Moderate	>25% - 50%	5
Low	>0 – 25%	3
Zero	=0%	1

Table 5.7 Scores for average number of treatments per lactating dairy cow, per year ($F_{tretments/cow/year}$)

Description	Value	Score Assigned
High	>30 times/yr	9
Moderate	6 – 30 times/yr	5
Infrequent	3 – 5 times/yr	3
Negligible	<1 time	1

We determined the overall LODA score for each drug based on expert elicitation by adding and normalizing the three above-mentioned scores as follows:

$$X = (P_{herds/year} + P_{cows/herd/year} + F_{treatments/cow/year})/3$$

Where:

X = The overall LODA based on expert elicitation
$P_{herds/year}$ = Percentage of dairy cows herds to which the drug is administered, per year
$P_{cows/herds\ year}$ = Percentage of dairy cows within a herd that have the drug administered per year
$F_{treatment/cow/year}$ = Average number of treatments per lactating dairy cow per year

5.1.2 LODA Based on Marketing Status (Sub-criterion A2)

We assigned scores based on each drug's marketing status, which we assumed is a measure of a drug's availability and, therefore, the LODA to lactating dairy cows. We acknowledge that external factors, such as a veterinarian-client-patient relationship, may make prescription-only drugs de-facto equally easily available as drugs available over the counter (OTC); however, we considered that a drug available OTC would be slightly more available to dairy farmers and therefore more likely to be administered to lactating dairy cows than would be drugs available only through prescription (Hill *et al.*, 2009). For marketing status of the 54 drugs, see Appendix 3.1.

Scoring:
We used a scale of 5-7, providing a slightly higher score for drugs available OTC. The compressed scale recognizes that marketing status is anticipated to have a small impact on LODA. As illustrated in the table below, if a drug formulation is available OTC, it is assigned a score of 7; if available only via prescription, it is assigned a score of 5; and is assigned a score of 7 if available by both prescription and OTC.

Table 5.8 Scores assigned to LODA based on marketing status of the drug

Marketing Status of Drug	Score Assigned
Drug formulations available by Rx & OTC	7
Drug formulations available over-the-counter (OTC)	7
Drug formulations available by prescription (Rx)	5

5.1.3 LODA Based on Drug-approval Status (Sub-criterion A3)

We assigned scores based on each drug's approval status, which we assumed is a measure of LODA to lactating dairy cows. The ranking score is based on the assumption that drugs approved for a specific use will more likely be used for that purpose than for other purposes. We assumed the following order of preference:

(1) a preference for drugs approved in lactating dairy cows (i.e. farmers and veterinarians would prefer to use drugs approved for a specific use and with established withdrawal times to minimize their risk of residue violation,
(2) a preference for drugs approved for use in non-lactating cows over those approved for other food-producing or companion animals; and
(3) a preference for drugs not approved in food-producing animals (but approved in companion animals) over drugs prohibited from extra-label use by FDA based on its authority under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA)[14].

14 AMDUCA allows veterinarians to prescribe legally extra-label uses (ELU) of certain approved animal or human drugs, under specific conditions (http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ActsRulesRegulations/ucm085377.htm) (21 U.S.C. 360b(a)(4) and (5); 21 CFR part 530). Extra-label administration in lactating dairy cattle that does not specifically follow those conditions is in violation of AMDUCA and can potentially result in violative drug residues in the milk supply (Middleton, 2008). Key conditions that must be met for extra-label use of drugs not approved for lactating dairy cattle include the following:

- the drug must be used for therapeutic purposes only;
- a veterinarian-client-patient relationship must exist;
- there is no animal drug approved for the intended use, and that contains the same active ingredient which is in the required dosage form and concentration, except where a veterinarian has found the approved drug to be clinically ineffective when used as labeled;
- the extra-label drug use will not result in violative drug residues in milk; and
- certain record-keeping requirements are met.

Furthermore, we assumed that drugs prohibited for extra-label use are the least likely to be administered to dairy cows (21 CFR, Part 530.41). Notably, we aggregated across different formulations, indications, administration routes, and dosages, some of which may be approved for lactating dairy cows and others may not be. For approval status of the 54 drugs, see Appendix 3.1.

Scoring:
To bin the scores from 1 to 9, we separated drugs' approval status into five categories: drugs prohibited for extra-label use in food-producing animals; drugs not approved in food-producing animals; drugs approved in food-producing animals; drugs approved in cows, but not in lactating dairy cows; and drugs approved in lactating dairy cows. See table below for the scoring scheme available for drug-approval status.

Table 5.9 Scores assigned to LODA based on drug-approval status

Drug-Approval Status (Based on FDA Approval)	Score Assigned
Drug approved in lactating dairy cows	9
Drug approved in cows, not approved in lactating dairy cows	7
Drug approved in other food-producing animals	5
Drug not approved in food-producing animals	3
Drug prohibited for ELDU in food-producing animals	1

5.1.4 LODA Based on Evidence of the Drug's Presence on Dairy Farms (Sub-criterion A4)

This sub-criterion determines scoring based on FDA inspection reports, with a score assigned based on the number of times each drug was identified on a dairy farm during FDA dairy inspections. We assigned scores for each drug based on FDA inspection reports of dairy farms[15] from October 1, 2008 to December 31, 2014 (FDA, 2014) (see Appendix 5.7), which, in turn, are based on inspection data (for inspections performed in response to dairy cow tissue residue violations in the national monitoring program performed by USDA FSIS). From these reports, we tabulated the number of times the drug was found to be present on dairy farms (here we are referring not to positive milk or tissue samples, but to the presence of the drug; *e.g.*, in storage, etc.) during the inspections. We acknowledge that the inspected farms do not represent all U.S. dairy operations and that drugs present on inspected farms may be used to treat species other than dairy cows on the farm; however, we assume that the presence of the drug on a farm implies a higher likelihood of drug administration to dairy cows on that farm.

15 When dairy cattle are slaughtered at a slaughter plant, USDA FSIS takes drug residue tissue sample and reports positive results to FDA. FDA conducts inspections on the farms identified as the sources of these positive tissue sample results.

Scoring:

A drug is assigned a score of 1- 9 based on the FDA dairy farm inspections (that reported the presence of the drug on the dairy farm) according to the scoring scheme in the table below.

Table 5.10 Scores assigned to LODA based on FDA dairy farm inspection reports

# of FDA Dairy Farm Inspections that Identified the Drug on the Farm	Score Assigned
Drug identified in greater than 45% of farms inspected	9
Drug identified in ≤ 45% and > 30% of farms inspected	7
Drug identified in ≤ 30% and > 10% of farms inspected	5
Drug identified in ≤ 10% and ≥ 1% of farms inspected	3
Drug not identified in < 1% of farms inspected	1

5.2 Likelihood of the Drug's Presence in Milk (Bulk-tank or Bulk Milk Pickup Tanker) (Criterion B)

Criterion B evaluates the likelihood of a drug's presence (LODP) as a residue in milk (bulk-tank or bulk milk pickup tanker), given that the drug is administered to lactating dairy cows (or dry cows or heifers that enter lactation before the drug can be cleared from their system). As with criterion A, we do not have a single study (evaluating all 54 drugs) to estimate the LODP, and, therefore, we considered a range of different sources for this information. This criterion includes the following four sub-criteria (and their individual factors):

- Sub-criterion B1. Score for likelihood of drug presence based on evidence that the drug has been identified in milk (bulk-tank milk or bulk milk pickup tanker (section 5.2.1).
    - Factor B1.1: Score for evidence based on National Milk Drug Residue Database (NMDRD) (2000-2013), which reported on milk testing on samples from bulk milk pickup tankers (section 5.2.1.1).
    - Factor B1.2: Score for evidence based on drug residue sampling (FDA Milk Drug Residue Sampling Survey) (section 5.2.1.2).

- Sub-criterion B2. Score for likelihood of drug presence based on misuse of drugs) (section 5.2.2)
    - Factor B2.1: Likelihood of misuse score (based on drug's approval status) (section 5.2.2.1).
    - Factor B2.2: Consequence of misuse score (based on milk-discard times or estimates of withdrawal calculated by FARAD) (section 5.2.2.2).

- Sub-criterion B3. Score for likelihood of drug presence based on expert elicited information (section 5.2.3).

For overview of criterion B, its sub-criteria, factors, and sub-factors, see figure below:

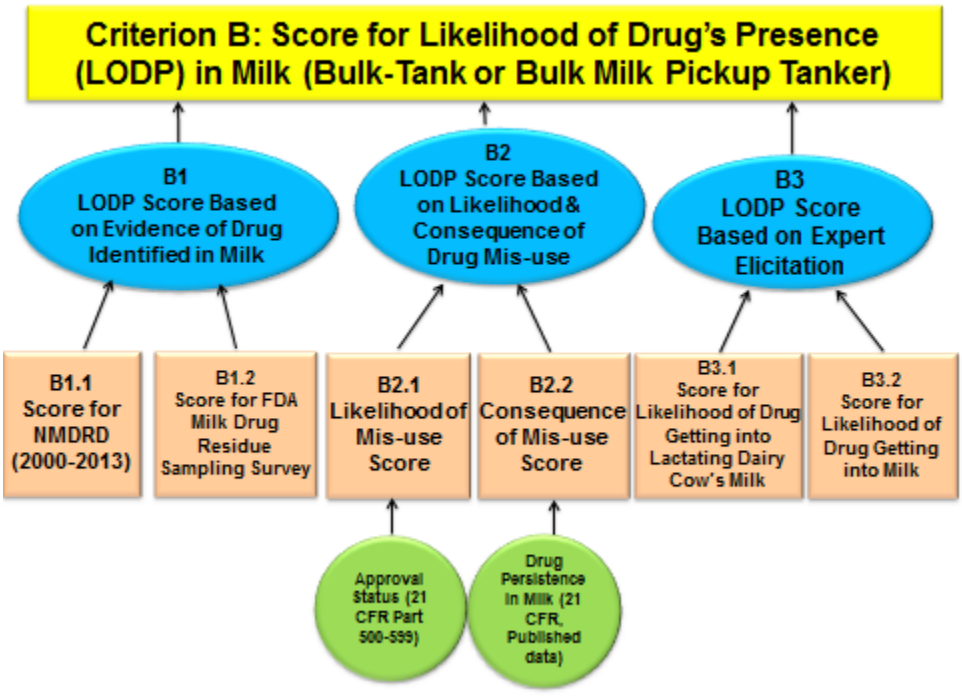

Figure 5.3 Overview of criterion B, its sub-criteria, and factors

About the three sub-criteria (B1-B3):

If drugs are administered to lactating dairy cows (or dry cows or heifers that enter lactation before the drug can be cleared from the cows's system, as previously defined), their residues may, under certain circumstances, enter the bulk milk pickup tanker. Several factors can influence the potential for drug residue presence in the bulk milk pickup tanker, including:

- disease prevalence (*e.g.*, seasons, geographic location, management practices, breed etc.),
- drug concentrations in the udder (*e.g.*, herd management impacting choice of dosage/route of administration), and
- the probability that a cow is milked while the drug residue is present in the cow's milk and that milk enters the bulk-milk tank and subsequently the bulk milk pickup tanker (*e.g.*, management factors, such as separation of sick cows, electronic record management, etc.).

Of the available data, the sampling data provide the most accurate measure for determining the likelihood of drug residue presence (LODP) in bulk-tank milk and bulk milk pickup tanker. However, several drugs have not been routinely sampled in the bulk-tank milk supply. Due to these limitations of the available sampling data, we included two additional sub-criteria: likelihood and consequence of drug misuse (sub-criterion B2), and expert elicitation of the likelihood of each drug resulting in a drug residue in the bulk milk pickup tanker, if administered to lactating or dry dairy cows (sub-criterion B3). In the absence of comprehensive sampling data for drug residue in milk (bulk-tank or bulk milk pickup

tanker), these combined data inform the likelihood of drug residue presence in the milk (bulk-tank or bulk milk pickup tanker).

Summary of scoring for criterion B from its three sub-criteria:
We calculated the score for criterion B for each drug as the weighted sum of the three sub-criteria (with all weights normalized to 1).

$B = ((B1*W_{B1}) + (B2*W_{B2}) + (B3*W_{B3}))/B_{sum}$

Where:

B = Score for criterion B score
B1, 2, 3 = Scores for sub-criteria B1, B2, and B3, respectively.
W_{B1},W_{B2}, W_{B3} = Weights assigned to B1, B2, and B3, respectively.
$B_{sum} = W_{B1}+W_{B2}+W_{B3}$

The experts assigned the following weights to the three sub-criteria that define criterion B (see table below):

Table 5.11 Weights of the three sub-criteria that define criterion B

Sub-criteria (B1-B3)	Weights Assigned by External Experts[16]
LODP based on evidence that the drug has been identified in milk (bulk-tank or bulk milk pickup tanker) (B1)	0.198
LODP based on the likelihood and consequence of drug misuse (based on drug approval status and drug persistence in milk) (B2)	0.319[a]
LODP based on expert elicitation (B3)	0.483[b]

[a] This corresponds to the sum of the following expert elicitation weights: milk persistence (discard) time and approval status.
[b] This corresponds to the sum of the following expert elicitation weights: dosage, mode of administration, and pharmacokinetics.

5.2.1 LODP Based on Evidence That the Drug Has Been Identified in Milk (Bulk Tank or Bulk Milk Pickup Tanker) (Sub-criterion B1)

For this sub-criterion, we ranked the drugs by the presence or absence of evidence that the drug or metabolite of the drug has been found in milk (bulk-tank or bulk milk pickup tanker). The recognized form of evidence is that the drug/metabolite (residue) has been identified in the milk supply via positive milk sample in the NMDRD (GLH, Inc., 2000-2013) or FDA Milk Drug Residue Sampling Survey (FDA, 2015a and FDA, 2015b). The data for both studies are, however, limited by the types of drugs included in the sampling schemes and differences in sampling design and methodology between the two studies. The two studies are:

16 Ibid.

- Factor B1.1: NMDRD for fiscal years 2000-2013, Table 7.1).
- Factor B1.2: FDA Milk Drug Residue Sampling Survey

Scoring for sub-criterion B1 from its two factors:
We calculated the score for sub-criterion B1 by defaulting to the maximum of either of the two factors.

5.2.1.1 LODP Based on Evidence That the Drug has been Identified in Milk (Bulk-milk tanker): NMDRD (Factor B1.1)

We assigned scores for 54 drugs from NMDRD sampling data for fiscal years 2000-2013, Table 7.1 (see Appendix 5.8) (GLH Inc., 2000-2013). NMDRD is a third-party industry program that captures drug residue in milk-testing results, under FDA contract, based on voluntary reporting by the dairy industry. However, mandatory reporting is required by State Regulatory Agencies under NCIMS. State agencies report the extent of the national testing activities, the analytical methods used, the kind and extent of the animal drug residues identified, and the amount of contaminated milk that was removed from the human food supply. The program includes all milk, Grade "A" (about 95% of milk supply in the U.S.) and non-Grade "A" (manufacturing grade).[17] The sampling data is based on well-controlled sampling designs, adequate sample sizes (in particular, given the relatively low expected incidence of drug residue violations in milk (bulk milk pickup tanker), and standardized testing methodologies. However, the current NMDRD report includes only data limited to certain drugs. Therefore, similar to the assumptions we made in criterion A, we considered that there is equal probability across all members of a drug class in the milk (bulk milk pickup tanker), if the drug can be administered to lactating dairy cows (or dry cows or heifers that enter lactation before the drug can be cleared from the cows's system).

Scoring:
We assumed that drugs or metabolites of drugs identified in the milk supply have a greater likelihood of entering the milk (bulk-tank or bulk milk pickup tanker) than drugs not identified in the milk (bulk milk pickup tanker). See table below for a description of drug (or metabolite) identification in NMDRD and assigned scores.

17 Grade "A" milk is regulated through the NCIMS in accordance with the MOU between FDA and the NCIMS, by the State Regulatory Agencies, whereas manufacturing-grade milk is under the direction of the Regulatory Agencies in the States where it is produced and may be subject to the standards recommended by USDA (GLH Inc., 2000-2013).

Table 5.12 Scores assigned based on evidence that a drug (or drug metabolite) has been identified in milk (bulk-milk pickup tanker) as indicated by NMDRD sampling data for fiscal years 2000-2013

Drug identification in the milk supply according to NMDRD (2000-2013)	Score Assigned
Drug is identified in milk	9
Drug class is identified in milk	7
Drug is not identified (drug/drug class was tested but was not identified or drug/drug class was not tested)	3

5.2.1.2 LODP Based on Evidence that the Drug has been Identified in Bulk-tank Milk: FDA Milk Drug Residue Sampling Survey (Factor B1.2)

We assigned this factor score for 54 drugs based on the FDA Milk Drug Residue Sampling Survey (FDA, 2015a and FDA, 2015b) (see Appendix 5.9 for sampling data for drugs tested). This CVM study complemented the NMDRD study by providing data for some of the drugs that are not included the NMDRD study. For example, certain types of drugs, such as NSAIDS, that are not typically tested for as part of NMDRD were included in this study. However, this study was also lacking many of our selected 54 drugs.

Table 5.13 Scores assigned based on evidence that a drug (or drug metabolite) has been identified in bulk-tank milk as indicated by FDA milk drug residue sampling survey

Drug identification in the milk supply according to FDA Milk Drug Residue Sampling Survey (FY 2012-2013)	Score Assigned
Drug tested positive and residue level outside (above) U.S. limit	9
Drug tested positive, but residue level not outside (not above) U.S. limit	5
Drug tested but not positive or drug not tested	3

U.S. limit=U.S. residue tolerances for drugs as specified in 21 CFR 556.
If drugs with no established tolerance tested positive, we considered that the residue level is above the U.S. limit.

We assumed that drugs or metabolites of drugs found in the milk supply (through sampling) have a greater likelihood of entering bulk-tank milk if administered to lactating dairy cows (or dry cows or heifers that enter lactation before the drug can be cleared from the cow's system) than do drugs for which bulk-tank milk samples are not positive. Accordingly, we assigned a score of 9, if a drug test was positive and the drug's residue level was above the established U.S. drug residue tolerance limit. We assigned a score of 5 if a drug test was positive, but the drug's residue level was at or below the established U.S. limit. We assigned a score of 3, if a drug test was not positive, or if no test was done for the drug.

5.2.2 LOPD Based on Misuse of Drugs (Sub-criterion B2)

The potential exists for misadministration of a drug to lactating dairy cows, thus leading to drug residues in milk (bulk-tank or bulk milk pickup tanker). This sub-criterion score was based on the following two factors:

- Factor B2.1. Likelihood of Misuse Score (LMS) based on the drug's approval status
- Factor B2.2. Potential Consequence of Misuse Score (PCMS) based on the drug's potential for long-term persistence in the milk

Scoring for Sub-criterion B2 from its two factors:
To obtain an overall score for sub-criterion #2 (B2) from its two factors [Factor #1 (B2.1) and Factor #2 (B2.2)], we combined these two factors using the following matrix (see table below) to characterize the likelihood and potential consequence of misuse of drugs that may lead to residues in milk (bulk-tank or bulk milk pickup tanker). See sections 5.2.2.1 and 5.2.2.2, respectively for information on the scoring used in factors B2.1 and B2.2.

Table 5.14 Matrix ranking scores for LOPD based on misuse of drugs: scores from Likelihood of Misuse Scores (LMS) and Potential Consequence of Misuse Scores (PCMS)

LMS / PCMS	PCMS=1	PCMS=3	PCMS=5	PCMS=7	PCMS=9
LMS=1	1	3	3	5	5
LMS=3	3	3	5	5	7
LMS=5	3	5	5	7	7
LMS=7	5	5	7	7	9
LMS=9	5	7	7	9	9

LMS=Likelihood of Misuse Score
PCMS=Potential Consequence of Misuse Score

5.2.2.1 Likelihood of Misuse (Based on Drug's Approval Status) (Factor B2.1)

Drugs that are not approved for administration to lactating dairy cows are potentially more likely to be administered in a way that leads to drug residues in the milk (bulk-tank or bulk milk pickup tanker) (*e.g.*, because of the lack of label instructions for administration to lactating dairy cows). FDA approval status of a drug is the best available indicator of whether there are clear

administration instructions (dosing, mode of administration, and official milk-discard time) for a drug on how to treat a specific condition, even though we acknowledge the limitations.[18] Therefore, the potential likelihood of drug misuse resulting in drug residues in the milk (bulk-milk or bulk milk pickup tanker) is related to the approval status. We acknowledge that the likelihood of drug residues in the milk (bulk-tank or bulk milk pickup tanker) (given use of the drug) may not be lower for drugs approved for use in lactating dairy cows than for drugs approved for other species or non-lactating cows only.

Notably, we used drug approval for a factor score in criterion B and also for a sub-criterion score in criterion A (administration based on approval status). However, in criterion B we assumed that drug residues are more likely to occur when the drug is not approved and, therefore, there are no established proper milk-discard times. In criterion A, however, we assumed that farmers and veterinarians are more likely to prefer drugs approved for lactating dairy cows than drugs approved for other species or drugs approved for non-lactating dairy cows. The rationale is that adhering to the required discard time associated with an approved drug for lactating dairy cows reduces the likelihood that the cows' milk will test positive for that drug's residue once the discard time has expired. Therefore, the use of these data in criteria A and B is not redundant.

For factor B2.1, we made the following assumptions:

- if a drug is not approved for use in lactating dairy cows, the drug residue could potentially end up in milk (even though we recognize that certain drugs and administration routes likely pose a negligible risk);
- if the drug is not approved for use in food-producing animals or if the drug is prohibited for ELDU in food-producing animals (AMDUCA), the drug residue would more likely end up in milk; and
- even for drugs that are approved for lactating dairy cows, the drug could still be misused (by not following label instructions, such as dosing, mode of administration, and official milk-discard time).

Scoring:

We assigned the highest score of 9 to drugs not approved in food-producing animals or drugs that are prohibited for ELDU in food-producing animals (AMDUCA). Notably, we did not assign the lowest score of 1 (but instead a 3) to drugs approved in lactating dairy cows, since there would still be a possibility that label instructions may not have been followed (see above assumption). See table below for scoring scheme for the drug's approval status (for the drug's approval status of the 54 drugs, see Appendix 3.1).

18 Intramammary antimicrobial-drug infusion is the most common mode of treatment and is believed to be the source of the majority of drug-residue violations in milk, if administered inappropriately (Kang, *et al.*,2005, Owens, 1988).

Table 5.15 Scores for likelihood of drug misuse based on drug approval status

FDA-Approval Status for Drug	Score Assigned
Drug not approved in food-producing animals	9
Prohibited for ELDU in food-producing animals (AMDUCA)	9
Drug approved in other food-producing animals	7
Drug approved in cows, not approved in lactating dairy cows	5
Drug approved in lactating dairy cows	3

5.2.2.2 Potential Consequence of Misuse (Factor B2.2)

The amount of time required for the cow's system to metabolize each drug to levels low enough to enable residue-free milking varies with each drug and with several other factors related to the cow's metabolism and farm-management practices. The amount of time a drug residue will persist in the milk is an important factor, and is dependent on several different metabolic and drug-administration management issues. Here, we assumed that drugs with longer withdrawal time (either the actual milk-discard times for drugs approved for use in lactating dairy cows or those calculated by FARAD) would pose a higher potential for drug residues to get into the milk (bulk-tank or bulk milk pickup tanker) than would drugs with shorter withdrawal times. We also assumed that cows are more likely to be accidentally milked if the period at risk (milk discard time) is longer. In the absence of other data, we assumed an unknown, but constant, probability of milking during the withdrawal time and independence of the probability, at each milking, from whether the cow was accidentally milked at a preceding milking. While we concede that this is likely an over-simplification (since other factors may impact this probability), in the absence of other data, we made this assumption, as it is the most conservative approach. If a drug is misused (by not following the label instructions on dose, mode of administration, or official milk-discard times), the potential concentration of the drug that gets to the milk (bulk-tank or bulk milk pickup tanker) is directly proportional to the persistence of the drug in milk. However, we acknowledge that drugs with longer withdrawal times may not, in all cases, lead to higher probability of drug residues in the milk (bulk-tank or bulk milk pickup tanker). For a range of milk-discard time, for each of the 54 drugs, see Appendix 5.10.

Table 5.16 Scores for consequence of misuse of administration based on milk-discard time (MDT)

Milk Discard Time (MDT) in Hours	Score Assigned
Drug does not have a MDT	9
MDT $\geq$ 200	9
200 > MDT $\geq$ 100	7
100> MDT $\geq$ 65	5
65> MDT $\geq$ 25	3
MDT < 25	1

Scoring:
With the assumptions made above, we assigned a score of 1 to drugs with milk-discard time less than 25 hours; we assigned a score 9 to drugs with milk-discard times equal or greater than 200 hours. Notably, we assigned a score 9 to drugs without an official milk-discard time since, as discussed previously, as we assumed those drugs to have greater potential to be identified as residues in the milk (bulk-tank or bulk milk pickup tanker).

5.2.3 LODP Based on Expert Elicited Information (Sub-criterion B3)

We elicited expert opinion, because we did not have recent, observational, and comprehensive data on important aspects, such as the probability and root causes of accidental (and potentially intentional) contamination of milk (bulk-tank or bulk milk pickup tanker) with drug residues. We asked the experts to consider the following, because of the limitations as discussed above:

- the Likelihood of the Drug to Enter a Cow's Milk (LDECM) (*i.e.,* getting into udder milk after administration to a cow), and
- the Likelihood of the Drug (in the udder milk) Entering the Milk (bulk-tank or bulk milk pickup tanker) (LDEM)

Details about the expert elicitation are included in Appendix 5.1 and Versar (2014). See Appendix 5.1 and Versar (2014) for more details about the expert elicitation results.

Scoring for sub-criterion B3:
We combined the two factors using the following matrix (see table below) for the expert score for likelihood of a drug getting into the milk (bulk-tank or bulk milk pickup tanker) to characterize the potential for misadministration of drugs to lead to residues in the milk.

Table 5.17 Matrix ranking scores for expert elicited scores for the likelihood of a drug getting into the milk (bulk-tank or bulk milk pickup tanker): scores from the Likelihood of the Drug to Enter Cow's Milk (LDECM) & the Likelihood of the Drug Entering the Milk (LDEM)

LDECM / LDEM	LDEM=1	LDEM=3	LDEM=5	LDEM=7	LDEM=9
LDECM=1	1	3	3	5	5
LDECM=3	3	3	5	5	7
LDECM=5	3	5	5	7	7
LDECM=7	5	5	7	7	9
LDECM=9	5	7	7	9	9

LDECM=The likelihood of the drug to enter cow's milk.
LDEM=The likelihood of the drug entering the milk (bulk-tank or bulk milk pickup tanker).

The scorings for these two parameters are as shown in the tables below:

Table 5.18 Ranking scores for the Likelihood of Drug to Enter Cow's Milk (LDECM) based on expert elicitation

Description	Value	Score Assigned
Very High	>75%	9
High	>50% and ≤ 75%	7
Moderate	>25% and ≤ 50%	5
Low	≥1 and ≤ 25%	3
Negligible	<1%	1

Table 5.19 Ranking scores for the Likelihood of the Drug Entering the Milk (Bulk-Tank or Bulk Milk Pickup Tanker) (LDEM) based on expert elicitation

Description	Value	Score Assigned
Very High	>10%	9
High	>5% and ≤ 10%	7
Moderate	>2% and ≤ 5%	5
Low	≥0.1 and ≤ 2%	3
Negligible	<0.1%	1

5.3 Relative Exposure to Drug Residues in Milk and Milk Products (Criterion C)

Criterion C evaluates the relative exposure to drug residues in milk and milk products by analyzing the impact of processing on drug residues in the selected 12 milk and milk products and the consumption of those products during one's lifetime (*i.e.,* lifetime average daily intake). Assuming that the residues of each of the 54 drugs are present at the same concentration in the bulk-tank milk, this criterion includes the following two sub-criteria (and their individual factors):

- Sub-criterion C1. Impact of processing on drug residue concentrations present in "raw" milk (section 5.3.1).
    - Factor C1.1: Product-composition value (section 5.3.1.1)
    - Factor C1.2: Heat degradation value (section 5.3.1.2)
    - Factor C1.3: Water removal value (section 5.3.1.3)

- Sub-criterion C2. Magnitude of consumption of dairy products (section 5.3.2).
    - Factor C2.1: Mean intake value: intake of dairy products by consumers (g/kg body weight/day) (section 5.3.2.1)
    - Factor C2.2: Percent consumers value: percent of individuals in an age group consuming a dairy product (section 5.3.2.2)
    - Factor C2.3: Proportion of lifetime years in an age group value (section 5.3.2.3)

Notably, C1 and C2 each produce numeric values, not scores for each drug.

For overview of criterion C, its sub-criteria, and factors, see figure below:

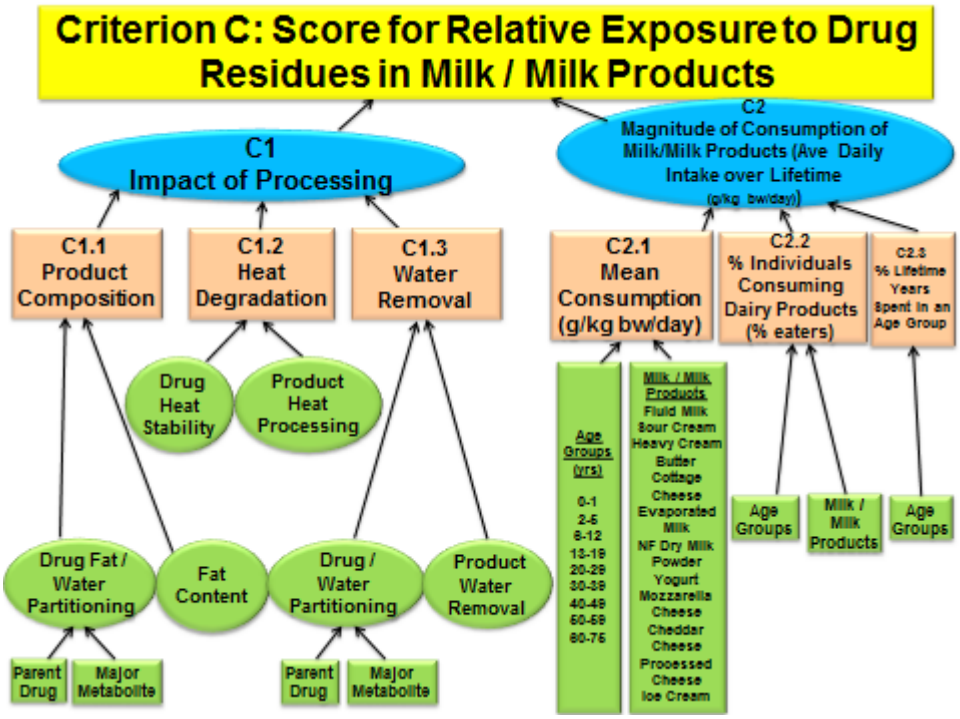

Figure 5.4 Overview of criterion C, its sub-criteria, and factors

About the two sub-criteria (C1-C2):
When multiplied, values from sub-criterion #1 (impact of processing) and sub-criterion #2 (the magnitude of consumption of milk and milk products (g/kg bw/day averaged over a lifetime) provide the relative estimate of exposure of the drug to consumers per day (drug dose/kg bw/day averaged over a lifetime).

Summary of scoring for criterion C:
We assigned an overall score of either a 9 or a 5 for each drug for criterion C based on the relative exposure value (to drug residues in the selected 12 milk and milk products). The cutoff between scores was set at a value that distinguished significant differences in relative exposure predicted among the drugs evaluated.

Scores for criterion C:

Table 5.20 Scoring for criterion C

Relative Exposure Value (C1*C2)	Score Assigned
>6	9
<=6	5

The relative exposure value for each drug, in turn, is a product of values generated from C1 and from C2, and then summed across all products.

C = C1*C2

Where:

C = The relative exposure to drug residue score
C1 = Value from sub-criterion #1 (C1) (Impact of processing)
C2 = Value from sub-criterion #2 (C2) (Consumption of milk and milk products)

5.3.1 Impact of Processing on Drug Residue Concentrations Present in "Raw" Milk (Sub-criterion C1)

Processing steps used to convert "raw" milk into finished milk or milk products may affect the concentration of drug residues in the finished products. The relative impact of processing is generally dependent on the processing conditions, the final milk product composition relative to that of "raw" milk, and the drug characteristics (Moats,1988; Waltner-Toews and McEwen, 1994; Zorraquino *et al.*, 2008b; Zorraquino *et al*., 2009; Whelan *et al*., 2010). This sub-criterion includes the following three factors:

- Factor C1.1: Product-Composition value (section 5.3.1.1)
- Factor C1.2: Heat degradation value (section 5.3.1.2)
- Factor C1.3: Water removal value (section 5.3.1.3)

Before deciding to evaluate the impact of these three types of processing operations, we first considered the great diversity in the manufacturing procedures and technologies used to manufacture dairy products. Next, among those, we identified five relatively common, discrete processing operations used to manufacture common dairy products sold in the U.S. (*i.e.,* heating, culturing, cheese aging, freezing, and water removal or condensing) that reasonably could be expected to impact drug-residue concentrations. Based on our review of the limited available literature, we determined that freezing, culturing, and aging during cheese making would likely have either no impact on drug residue concentrations or lead to only very limited decreases in drug concentration (see Appendix 5.11). This reduced the list of common processing operations to three: product-composition changes, heat treatments, and treatments involving water removal (drying). Since the processing operations employed to manufacturer differ by product, factor values were determined for each drug-product combination. Values from each factor for each drug-product combination reflect the change in drug concentration expected from that processing operation.

Recognizing that residues of a drug administered to dairy cows may include metabolites, the parent drug, or both, we considered both parent and major metabolite(s) when evaluating the impact of processing on the relative concentration of drug residues in milk and milk products. In

many cases, the physio-chemical properties of the drug and major metabolite(s) were sufficiently similar that the impact of processing on the concentration of the drug in the finished product was expected to be approximately the same. In some cases, the properties of parent and metabolite were different enough that differing impacts would be expected. In these cases, we assigned the drug the processing factor value corresponding to the larger concentration in the finished product. See Appendix 5.12 for a detailed description of how we evaluated the metabolites in this multicriteria-based ranking model.

Calculating overall value for sub-criterion C1 (impact of processing) from its three factors: We calculated the final value for sub-criterion #1 (C1) for each drug as a product of the three factors (C1.1, C1.2, and C1.3). The overall processing value for each drug-product combination is the product of the changes expected for each of the three factors.

C1 = C1.1*C1.2*C2.3

Where:

C1 = Value for Sub-criterion #1 (C1)

The value of C1 for a given drug-product is an estimate of the predicted change in drug concentration in the final milk product, as compared to that in "raw" milk, arising from the combination of processing operations applied during the manufacturing of the product. Values for C1 varied from 0.3 (*i.e.,* 3.3-fold decrease) to 10 (*i.e.,* 10-fold increase).

5.3.1.1 Product Composition Value (Factor C1.1)

The product-composition value reflects changes in drug residue concentration arising from drug partitioning during manufacturing of milk products. Partitioning, in this context, refers to the distribution of drug residue originally in the "raw" milk among different components of milk when these are separated during processing, or recombined in proportions different from that of "raw" milk.

The product composition value is dependent on two sub-factors: (1) the fat content of the product and (2) the partitioning behavior of the drug in milk and milk products as predicted by apparent partition coefficient (as ($\log(P_{app})$) (Pandit, 2011). (Water loss during processing is addressed separately, see Section 5.3.1.3). The apparent partition coefficient ($\log(P_{app})$) is an estimate of the ratio of the concentration of a drug in a hydrophobic solvent, such as octanol to that in aqueous solution when a mixture of these two immiscible solvents are at equilibrium. It takes into account the acid-base properties of the drug, which can make a hydrophobic drug significantly more soluble in aqueous solution at pH values at which a significant fraction of the drug will be ionized. Such coefficients have been successfully used to describe the distribution of therapeutic drugs/drug residues within an animal's body (including humans or chemical

contaminants within the environment) (Shargel, *et al.*, 2005 and Hemond and Fechner-Levy, 2000). This coefficient is also commonly referred to as a "distribution" coefficient.

Four levels of the product-composition grade (*i.e.,* C, D, E, and F) express the relative change in drug concentration expected due to changes in product composition from "raw" milk. Expected change and log P_{app} ranges reflect experimental observations.

Table 5.21 Product-composition grade – considers product fat content relative to "raw" milk & P_{app}

Drug partitioning behavior	no change in fat content [0 – 5% fat]	moderate increase in fat content [5.1 – 20% fat]	high increase in fat content [20.1 – 45% fat]	very high increase in fat content [> 45% fat]
all water [log P_{app} < -2]	D	D	C	C
mostly water [-2 < log P_{app}< 2]]	D	D	D	E
essentially all fat [log P_{app} > 2]	D	E	E	F

Table 5.22 Description of product composition and assigned grade and value

Description	Expected Change	Grade	Assigned Value
High increase	6 – 18 x increase	F	9
Moderate increase	>1 – 5 x increase	E	4
No change	no substantive change	D	1
Moderate decrease	2 – 4 x decrease	C	0.3

Rationale:

Experimental data on drug partitioning/distribution among milk components or milk products was obtained for 14 of the drugs evaluated by this multicriteria-based ranking model. See Appendix 5.13 for a review of the relevant literature. Increases in concentration of a factor of 18 were reported for the hydrophobic/lipophilic drug, ivermectin, in 80% milk-fat cream, as compared to 4% milk-fat "raw" milk. Whereas, decreases in concentration of a factor of 0.2 were reported for the hydrophilic drug, oxytetracycline, and were reported in the similar fat cream, as compared with "raw" milk (Hakk, 2015). Smaller increases in concentrations of ivermectin have been reported in soft-pressed cheese and dried/aged cheese, 2.5 to 2.8 and 3 to 9, respectively (Cerkvenik *et al*., 2004; Anastasio *et al*., 2002, Imperiale *et al*., 2004a). Similar data were reported for other avermectins (see Appendix 5.13). Due to the limited nature of the

data available, only broad categories of drug behavior could be distinguished (as defined by three categories of log (P_{app}) values, four categories of product fat content, and the associated grade matrix values). We set a maximum increase in concentration of hydrophobic/lipophilic drugs in high-fat products with a fat-content above 45% to 9 times and in high-fat products with a content between 20 and 45% to 4 times. As more data become available, we will be able to refine this table to more precisely describe the changes in drug residue concentration arising from compositional changes during processing. The concentrations assumed for other dairy products and drugs with other partitioning behavior (as predicted by log (P_{app}) values) are shown in Appendix 5.13.

5.3.1.2 Heat Degradation Value (Factor C1.2)

The heat-degradation value considered the heat treatment history of the dairy product and the heat stability of the drug. The value is determined according to the grade matrix in the table below (for more information, including a comprehensive review of the available literature and the time-temperature conditions considered for the different heat treatment types, see Appendix 5.14). The maximum degradation reported in the literature for heat treatments other than retort processing of animal drugs under consideration in this multicriteria-based ranking model is 30%. Accordingly, not all categories in the matrix presented in the table below are possible. A dash rather than a letter grade indicates categories that are not applicable to the drugs under consideration (see table below).

Table 5.23 Heat-degradation grade – considers heating history & drug heat stability

Heating stability	Pasteurization	Longer Impact Heat Treatment	Retort Processing	Cheese Making	Processed Cheese Making
high [0 – 10 % inactivation]	D	D	D	D	D
moderate [11 – 30% inactivation]	C	C	C	C	C
low [31 – 70% inactivation]	-	-	B	-	-
very low [> 70% inactivation]	-	-	A	-	-

Table 5.24 Description of heat degradation and assigned grade and value

Description	Changes	Grade	Assigned Value
No change	< 1.3 x decrease	D	1
Moderate decrease	1.3 – 1.7 x decrease	C	0.9
High decrease	1.71 – 3.3 x decrease	B	0.7
Very high decrease	> 3.3 x decrease	A	0.3

Rationale:
For a variety of drugs, heat degradation has been experimentally determined, and these data (see Appendix 5.14) have been used in this model where available. We acknowledge that the impact of heat degradation differs across time-temperature combinations. Therefore, we reviewed the range of time-temperature combinations typically used in milk processing, identified five common types of time-temperature combinations during heat processing (see Appendix 5.15), attributed each dairy product in the ranking model to one of the five heat degradation processes, and matched the experimental data to one or more of these time-temperature combinations (see Appendix 5.15). As discussed in detail in the Appendix 5.15, among the data available, we gave greater weight to observations in milk than to those obtained in broth, and we gave even less weight to observations obtained in solid systems. When multiple but differing observations were reported for the same drug and time-temperature category, we assigned the value corresponding to the least amount of degradation. We acknowledge that in this way we may underestimate the true impact of heat processing on drug residue concentrations. Also, we acknowledge that many of the experimental studies measured loss of activity, and that loss of activity may not be perfectly correlated with loss of toxicological concerns. Therefore, the true impact of heat processing on the concentration of the residues in dairy products may be somewhat different from the impact predicted based on experimental heat degradation data. Finally, in some cases, observational data were not available for the drug (see Appendix 5.14). In these cases, we used data for related drugs in the same class, where available. In some other cases, data were neither available for the drug nor for other drugs within the same structural drug class. In these cases, we considered that the drug was not inactivated by heat during processing.

5.3.1.3 Water Removal Value (Factor C1.3)

The water-removal value captures the impact of selective dessication (*i.e.,* selective removal of water through processes such as evaporation) of certain dairy products and is defined as the factor by which the concentration of a drug residue would increase because of water removal. Water removal occurs during the production of evaporated milk and non-fat dry milk powder. Drug residues, when present in the bulk-tank milk, would increase in concentration by approximately a factor of two during evaporated milk production and a factor of ten during non-fat dry milk powder production. These factors were estimated from the relevant compositions of

bulk tank milk and these products, as shown in Table 5.7. Implicit in the assigned water removal value is that the drug present is not volatile, which is generally a good assumption for animal drugs.

Table 5.25 Water removal (drug partitioning behavior) value

Milk Product	Value
Fluid milk (all fat levels)	1
Cottage cheese (Creamed)	1
Non-fat dry milk powder	10
Yogurt	1
Evaporated milk	2
Ice cream	1
Sour cream	1
Mozzarella	1
Processed cheese	1
Cheddar	1
Heavy cream	1
Butter	1

5.3.2 Magnitude of Consumption of Milk and Milk Products (Sub-criterion C2)

Sub-criterion C2 evaluates the magnitude of consumption of the 12 selected milk and milk products, and was quantified by the lifetime average daily intake of dairy products. This sub-criterion includes the following factors:

- Factor C2.1: Mean intake value: mean intake of the 12 selected milk and milk products by consumers in grams per kilogram body weight per day (g/kg body weight/day) (section 5.3.2.1)
- Factor C2.2: Percent consumers value: percent of individuals in an age group consuming a dairy product (section 5.3.2.2)
- Factor C2.3: Proportion of lifetime years in an age group value (section 5.3.2.3)

To accurately capture the magnitude of consumption of milk and milk products in the U.S., we used a database that reflects individual consumption of the food products: What We Eat In America, National Health and Nutrition Examination Survey (WWEIA/NHANES), 2005-2010 (CDC, 2011) (See Appendix 5.17). The lifetime average daily intakes of dairy products (g/kg bw/day) are the product of the mean intake per consumer, the percent consumers, and the

proportion of lifetime in an age group.[19] For this analysis, we considered a "lifetime" to be 76 years. We estimated the mean per capita daily intakes (*i.e.,* intakes of each food averaged over consumers and non-consumers) of the dairy products (g/kg body weight/day) for each age group. For each food, we multiplied each mean per capita intake by the proportion of years represented by each age range (*e.g.,* an individual would be in the 2 – 5 year age range for four years, so the proportion of lifetime in an age group is 4/76, or 0.053). We then totaled the weighted mean per capita intakes for each age range for each food. See table below for the parameters we considered for this sub-criterion: the 12 selected milk and milk products, population groups, and consumption parameters.

Table 5.26 Magnitude of consumption of dairy products: analysis parameters

Analysis Parameters	Description
Milk and milk products (the 12 selected milk and milk products)	Milk, fluid; Processed products: butter, cheese (cheddar, cottage, mozzarella, processed), cream (heavy and sour), ice cream, milk (evaporated and non-fat dried); and yogurt
Population Groups (years)	0-1; 2-5; 6-12; 13-19; 20-29; 30-39; 40-49; 50-59; 60-75
Consumption Parameters	Mean intake of dairy products (g/kg body weight/day) by consumers Percent consumers Lifetime consumption

Calculating value for sub-criterion C2 from its three factors:

We calculated the overall value for this sub-criterion (C2), expressed in lifetime average daily intakes of dairy products, by multiplying all of its three factors: mean intakes of dairy products per consumer (C2.1), percentage of individuals consuming dairy products (C2.2), and proportion of lifetime spent in an age group (C2.3).

$$C2 = (C2.1)*(C2.2)*(C2.3)$$

Where :

C2 = Value for sub-criterion C2.

Again, note that the value for C2 is a numeric value, not a score.

19 While FDA uses consumption of 1.5L of fluid milk for determining ADIs of veterinary drugs, for this risk ranking, we used an accurate description of milk and milk products by using a database that reflects individual consumption of the selected products (not just fluid milk, but also other 11 milk products).

5.3.2.1 Mean Intakes of Dairy Products by Consumers (Factor C2.1)

Mean 2-day average daily intakes (g/kg bw/day) of the 12 selected milk and milk products by age group are presented and shown graphically in the table and figure below. Fluid milk was consumed in the greatest quantities, ranging from 2.19 g/kg bw/day for ages 60-75 y to 40.42 g/kg bw/day for ages 0-1 y. Yogurt was consumed in amounts ranging from 1.21 g/kg bw/day for ages 60-75 y to 6.11 g/kg bw/day for ages 0-1 y. There were some gender-based differences in amounts consumed of certain milk and milk products in certain age groups; however, because we evaluated the lifetime average daily intakes of the 12 selected milk and milk products, we did not incorporate such differences in our analysis. For detailed description of the analysis, see Appendix 5.17.

Table 5.27 Mean intakes of the 12 selected milk and milk products (g/kg bw/day) by consumers

Age range (yr)	Fluid Milk	Butter	Cheddar Cheese	Cottage Cheese	Mozzarella Cheese	Processed Cheese	Heavy cream	Sour Cream	Ice Cream	Evaporated Milk	Non-fat Dried Milk	Yogurt
0 - 1	40.42	0.20	0.83	5.80[a]	0.83	1.05	1.47[a]	0.49[a]	2.32	3.95[a]	0.27[a]	6.11
2 - 5	22.73	0.17	0.75	2.49[a]	0.58	0.90	0.42[a]	0.63	2.70	1.10[a]	0.06[a]	4.27
6 - 12	9.93[b]	0.12	0.38[b]	1.74[a]	0.34	0.54	0.43	0.61	1.97[b]	0.61[a]	0.06	2.20[b]
13 -19	4.39[b]	0.07	0.28	1.17[a]	0.20[b]	0.35[b]	0.24	0.29	1.28[b]	0.34[a]	0.03	1.49
20 -29	2.61	0.06	0.24	1.01[a]	0.18	0.30	0.22	0.29	0.98	0.28[a]	0.06	1.33
30 -39	2.41	0.06	0.20	0.96[a]	0.16	0.25	0.15[a]	0.30	0.83	0.35[a]	0.03	1.18
40- 49	2.40	0.07	0.19[b]	0.96[a]	0.15	0.25	0.15[a]	0.26	0.92	0.47[a]	0.02	1.38
50- 59	2.26	0.08[b]	0.20	0.93[a]	0.15	0.23	0.25[a]	0.26	0.98	0.32[a]	0.02	1.31
60- 75	2.19	0.08	0.16	0.95[b]	0.12	0.21	0.22	0.22	0.89	0.33	0.03	1.21[b]

Data source: What We Eat In America, National Health and Nutrition Examination Survey (WWEIA/NHANES), 2005-2010 (CDC, 2011). Dairy product ingredient percentages were determined using the Food and Nutrient Database for Dietary Surveys (FNDDS) 5.0 (USDA FSIS, 2012a). Intake amounts are two-day averages.

[a] Estimates may be statistically unreliable due to small number of consumers (<68).

[b] The mean amount consumed by males (g/kg bw/day) is significantly different ($p < 0.05$) than the amount consumed by females, for groups with at least 68 consumers.

5.3.2.2 Percentages of Individuals Consuming Dairy Products (Factor C2.2)

The percentages of each age group who reported consuming the selected 12 milk and milk products at least once during the two-day survey period are presented and graphically shown in the table and figure below. Fluid milk was consumed at least once during the two-day survey period by over 50% of individuals in each population group. Processed cheese was consumed by over 50% of individuals in all but two age groups (0-1 y and 60-75 y). Cottage cheese, heavy cream, evaporated milk, and non-fat dried milk were consumed by less than 5% of individuals in most age groups. There were some gender-based differences in percentages of individuals

consuming specific products in certain age groups. Just as in section 5.3.2.1, we did not include such differences in our analysis. For detailed description of the analysis, see Appendix 5.17.

Table 5.28 Percentages of individuals consuming the selected 12 milk and milk products

Age range (yr)	Fluid Milk	Butter	Cheddar Cheese	Cottage Cheese	Mozzarella Cheese	Processed Cheese	Heavy cream	Sour Cream	Ice Cream	Evaporated Milk	Non-fat Dried Milk	Yogurt
0-1	57.5	23.8	22.6	1.8	18.4	31.0	0.2	2.6	11.4	0.8	1.0	20.6
2-5	96.9	39.6	40.1	1.9	38.1	57.8[a]	1.6	7.7	29.7[a]	0.7	2.6	25.1
6-12	95.2	41.1	44.4	1.6[a]	42.7	60.4	3.3	6.9	36.4	0.8	4.0	16.4
13-19	86.5	33.5[a]	52.8	1.6	45.4[a]	58.9	2.7	10.2[a]	27.7	0.7	3.2	7.8
20-29	80.4	32.6	48.3	1.4	41.1	58.6	3.2[a]	12.6	20.9	1.4[a]	5.0	11.3
30-39	83.3[a]	37.5	49.1	2.8	38.1	57.6	2.9	14.4	24.0	1.2	4.1	13.6[a]
40-49	82.0	41.6	44.4[a]	3.0[a]	31.8	54.3	3.1	11.6	24.2[a]	1.6	4.0	14.8[a]
50-59	82.6	41.4	40.2	3.7	29.9	52.1	2.9	11.8	27.0	1.6	5.8	15.7[a]
60-75	86.1	43.8	38.0	5.4	25.4	45.4	2.4	10.3	29.1	2.0	4.1	15.0[a]

Data source: What We Eat In America, National Health and Nutrition Examination Survey (WWEIA/NHANES), 2005-2010 (CDC, 2011). Dairy product ingredient percentages were determined using the Food and Nutrient Database for Dietary Surveys (FNDDS) 5.0 (USDA FSIS, 2012a). Percentages reflect the proportion of survey respondents in each age group reporting intake of the dairy product (or a mixture containing the dairy product) at least once during the two-day survey period.

[a] The proportion of males consuming the product is significantly different ($p < 0.05$) than the proportion of females consuming the product.

5.3.2.3 Proportion of Lifetime Years Spent in an Age Group (Factor C2.3)

For this analysis, we considered a "lifetime" to be 76 years. We determined the proportion of the lifetime years spent in each age group by dividing the years an individual spends in each age group by the total lifetime of 76 years (see table below).

Table 5.29 Proportion of lifetime years in age group

Age Group	Years in Age Group	Proportion of Lifetime Years in Age Group (Years in Age Group / Total Lifetime of 76 years)
0 - 1 y	2	0.026 (2/76)
2 - 5 y	4	0.053 (4/76)
6 - 12 y	7	0.092 (7/76)
13 - 19 y	7	0.092 (7/76)
20 - 29 y	10	0.132 (10/76)
30 - 39 y	10	0.132 (10/76)
40 - 49 y	10	0.132 (10/76)
50 - 59 y	10	0.132 (10/76)
60 - 75 y	16	0.211 (16/76)

Overall value for C2:

The overall value for this sub-criterion is the lifetime average daily intakes of each of the selected 12 milk and milk products, for which we calculated as the product of mean intake per consumer, the percent consumers, and the proportion of lifetime in an age group. As shown in the table below, the lifetime average daily intakes range from <0.01 g/kg bw/day for non-fat dried milk to 4.43 g/kg bw/day for fluid milk.

Table 5.30 Lifetime average daily intakes of the 12 selected milk and milk products (g/kg bw/day)

Dairy Product	Average Daily Intake over Lifetime (g/kg bw/day)
Milk, fluid	4.43
Butter	0.03
Cheese (Cheddar)	0.11
Cheese (Cottage)	0.03
Cheese (Mozzarella)	0.07
Cheese (Processed)	0.18
Cream (Heavy)	0.01
Cream (Sour	0.03
Ice cream	0.32
Milk (Evaporated)	0.01
Milk (Non-fat dried)	<0.01
Yogurt	0.27

Data source: What We Eat In America, National Health and Nutrition Examination Survey (WWEIA/NHANES), 2005-2010 (CDC, 2011). Dairy product ingredient percentages were determined using the Food and Nutrient Database for Dietary Surveys (FNDDS) 5.0 (USDA FSIS, 2012a).

5.4. Potential for Human Health Hazard (Criterion D)

Criterion D evaluates the potential for human health hazard, given exposure to a drug residue. This criterion is based on the hazard-value of each of the 54 selected drugs (including their metabolites).

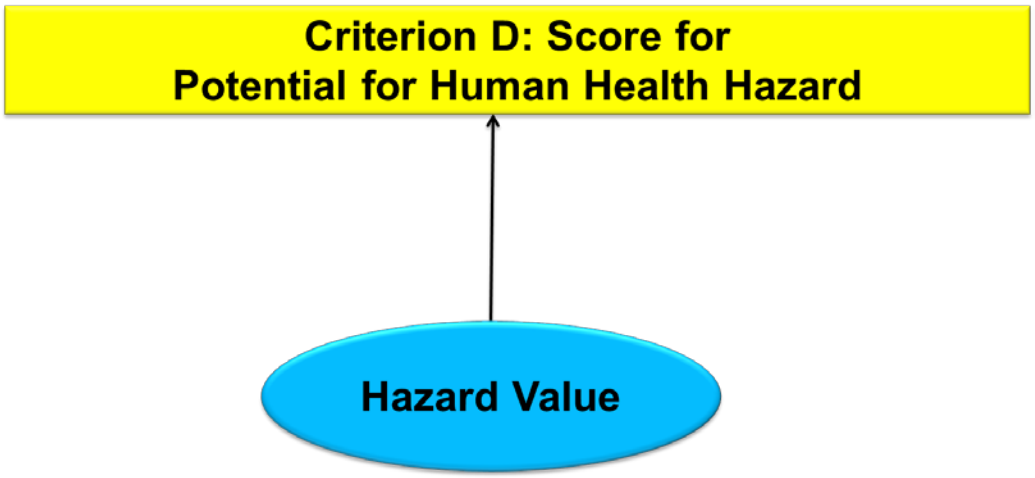

Figure 5.5 Overview of criterion D

The ADI or hazard value establishes a level of drug residue that is not expected to be hazardous to human health. If the exposure to the drug residue exceeds this level, there is concern for potential adverse health effect(s) in humans.

When approved new animal drugs are used in accordance with approved label instructions in lactating dairy cows, we anticipate that the concentration of the drug residue in milk (bulk-tank or bulk-milk pickup tanker) will be at or below the tolerance[20] or, for unapproved drugs, at or below a tolerable level[21]. At this concentration, it is reasonably certain that the residue would not produce adverse health effects when consumed by humans, and thus we do not anticipate any health hazard.

Under some conditions, concentrations of drug residues in milk may exceed the tolerance or tolerable level and subsequently pose a potential human health hazard. Thus, there is a need to address the relative potential for adverse human health effects due to the presence of drug residues in milk above concentrations that exceed the tolerance or tolerable level. This leads to

20 A tolerance is the maximum allowed concentration of a marker residue of the drug (parent drug or metabolite) in the animal tissue, or in this case, the maximum allowed drug residue concentration in milk. Residues at or below the tolerance are considered safe for human consumption.
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207941.pdf

21 For the purpose of this document, tolerable level indicates a concentration of the residues of the drug in the milk that is safe for human consumption. A tolerable level is not an FDA tolerance, does not indicate approval of the drug for this use, and has meaning only within the scope of the current risk assessment.

the question: "Which drug residues in milk and milk products pose the greatest potential hazard to public health?"

Data on observed health effects in humans from direct exposure to or consumption of drug residues in milk/milk products are limited. Thus, the human health hazard potential criterion addresses the above question by estimating the relative potency of each drug to cause adverse health effects when present as drug residue at relatively low concentrations in milk and milk products.

Hazard Value-generated Score for Every Drug or Drug Residue (or Major Metabolite) in Milk

We used the hazard-value score to rank the potential health hazard of each drug relative to other drugs. The score is based on FDA-derived ADIs, where possible, or other science-based information. The hazard value represents the respective dose, in µg/kg bw/day, at which each drug residue (or major metabolite) does not cause an adverse health effect(s) based on toxicological, pharmacological, microbiological (human intestinal microflora disruption) and/or allergenicity endpoints. Hazard values for each drug can thus be used to estimate the potency of the drug residues (or major metabolite).

Drugs approved for use in lactating dairy cows in the United States have an FDA-established ADI in µg/kg bw/day for human exposure to total drug residues in milk and milk products. The hazard value is determined based on an existing ADI, or evaluation of toxicology studies and other relevant information. However, some of the drugs in this study are not approved for use in lactating dairy cows, and do not have an FDA-established ADI. For these drugs without an FDA-established ADI, an equivalent hazard value was estimated based on review of relevant information. Major factors taken into consideration in the determination of the hazard value when an ADI has not been previously established for a drug include one or more of the following:

- ADIs determined by other scientific or regulatory organizations [*e.g.,* Joint FAO/WHO Expert Committee on Food Additives (JECFA)];
- Publicly available or proprietary toxicology information [toxicology information available to FDA, such as toxicological no-observed-adverse effect levels (NOAELs) or lowest-observed adverse effect levels (LOAELs) obtained from repeat-dose oral toxicity studies in laboratory animal species);
- an assessment of the potential impact on the human intestinal flora;
- FDA-established ADIs for the most representative drug of that drug class, as the default hazard value; and
- Safety factors to account for uncertainties associated with extrapolating from animal data to humans, variation in sensitivity among humans, quality of data, severity of response, or other concerns.

A hazard value (tolerance or tolerable level) could not be established for carcinogenic drugs in the study (chloramphenicol, phenylbutazone, furazolidone, and nitrofurazone).[22] The table below lists the hazard values assigned to the 54 drugs we evaluated and the sources of information.

Table 5.31 Hazard values for 54 selected drugs

Drug class	Drug name	Hazard value (µg/kg bw/day), HV[a]	Source of information
Aminocoumarins	Novobiocin	1 ≤ HV < 15	FDA files, the Europe Medicines Agency (EMA) report and our analysis for the purpose of hazard ranking
Aminocyclitols	Spectinomycin	25	FDA ADI (25 µg/kg bw/day; 21 CFR 556.600)
Aminoglycosides	Amikacin	1 ≤ HV < 15	publicly available information and our analysis for the purpose of hazard ranking
Aminoglycosides	dihydro-streptomycin	1 ≤ HV < 15	FDA files
Aminoglycosides	Gentamicin	1 ≤ HV < 15	FDA files and our analysis for the purpose of hazard ranking
Aminoglycosides	Neomycin	6	FDA ADI (6 µg/kg bw/day; 21 CFR 556.430)
Aminoglycosides	Kanamycin	1 ≤ HV < 15	the EMA report and our analysis for the purpose of hazard ranking
Aminoglycosides	Streptomycin	1 ≤ HV < 15	assigned the same hazard value as the one for dihydro-streptomycin
Amphenicols	Chloramphenicol	No HV can be established	FDA websites: a tolerance or tolerable level cannot be established
Amphenicols	Florfenicol	10	FDA ADI (10 µg/kg bw/day; 21 CFR 556.283)
beta lactams	Amoxicillin	HV< 1	FDA files, JECFA, and publicly available information
beta lactams	Ampicillin	HV< 1	FDA files and publicly available information
beta lactams	Cloxacillin	HV< 1	FDA files and publicly available information
beta lactams	Hetacillin	HV< 1	FDA files and publicly available information
beta lactams	Penicillin	HV< 1	FDA files and JECFA (30 µg/person/day)
beta lactams	Cephapirin (or cefaspirin)	1 ≤ HV < 15	FDA files
beta lactams	Ceftiofur	30	FDA ADI (30 µg/kg bw/day; 21 CFR 556.113)
Lincosamides	Lincomycin	25	FDA ADI (25 µg/kg bw/day; 21 CFR 556.360)

22 Chloramphenicol is a human carcinogen as it increases the risk of leukemia, and it may cause an induction of aplastic anemia (NTP, 2014). Furazolidone is mutagenic and carcinogenic in Fischer 344 rats and Swiss MBR/ICR mice, showing an increase in incidence of malignant tumors (increase in incidence of mammary gland adenocarcinomas in female rats, basal cell epithelioma and carcinoma in male rats, mammary adenocarcinomas in female rats and neural astrocytomas in male rats, increase in incidence of bronchial adenocarcinomas in both sexes of mice, and lymphosarcomas in male mice) (FDA, 1991b). Nitrofurazone is mutagenic and is carcinogenic in female F344/N rats, as shown by a markedly increased incidence of fibroadenomas of the mammary gland, and in female B6C3F1 mice as shown by increased incidences of benign mixed tumors and granulosa cell tumors of the ovary (FDA, 1991b and NTP, 1988). Phenylbutazone is an animal carcinogen and genotoxin, and has presented concerns regarding induction of blood dyscrasias (including aplastic anemia, leukopenia, agranulocytosis, and thrombocytopenia); however, it is not classifiable as carcinogenic to humans due to lack of adequate information (International Agency for Research on Cancer, 1977).

Drug class	Drug name	Hazard value (µg/kg bw/day), HV[a]	Source of information
Lincosamides	Pirlimycin	10	FDA ADI (0.01 mg/kg bw/day (10 µg/kg bw/day); 21 CFR 556.515)
Macrolides	Erythromycin	15 ≤ HV < 40	FDA files and our analysis for the purpose of hazard ranking
Macrolides	Tilmicosin	25	FDA ADI (25 µg/kg bw/day; 21 CFR 556.735)
Macrolides	Tulathromycin	15	FDA ADI (15 µg/kg bw/day; 21 CFR 556.745)
Macrolides	Tylosin	15 ≤ HV < 40	FDA files
Macrolides	Tildipirosin	50	FDA ADI (50 µg/kg bw/day; 21 CFR 556.733)
Macrolides	Gamithromycin	10	FDA ADI (10 µg/kg bw/day; 21 CFR 556.292)
Nitrofurans	Furazolidone	No HV value can be established	FDA files and JECFA; a tolerance or tolerable level cannot be established
Nitrofurans	Nitrofurazone	No HV value can be established HV	FDA files, JECFA, and, National Toxicology Program (NTP); a tolerance or tolerable level cannot be established
Fluoroquinolones	enrofloxacin (and metabolite: ciprofloxacin)	3	FDA ADI (3 µg/kg bw/day; 21 CFR 556.226)
Fluoroquinolones	Danofloxacin	2.4	FDA ADI (2.4 µg/kg bw/day; 21 CFR 556.169)
Sulfonamides	sulfachloropyridazine	15 ≤ HV < 40	FDA files
Sulfonamides	sulfadimethoxine	1 ≤ HV < 15	FDA files
Sulfonamides	sulfabromomethazine	HV< 1	no specific data, use the lowest hazard value of this category (0.5 for sulfaquinoxline)
Sulfonamides	Sulfaethoxypyridazine	1 ≤ HV < 15	FDA files
Sulfonamides	Sulfamethazine	1 ≤ HV < 15	FDA files
Sulfonamides	Sulfaquinoxaline	HV< 1	FDA files
NSAIDS	acetylsalicylic acid	1 ≤ HV < 15	EMA and other publicly available information
NSAIDS	flunixin meglumine	0.72	FDA ADI (0.72 µg/kg bw/day; 21 CFR 556.286)
NSAIDS	Ketoprofen	1 ≤ HV < 15	EMA and other publicly available information
NSAIDS	Meloxicam	HV< 1	FDA files
NSAIDS	Naproxen	1 ≤ HV < 15	same as the hazard value for ketoprofen
NSAIDS	Phenylbutazone	No HV value can be established	FDA website/files: a tolerance or tolerable level cannot be established
Antiparasitics	Albendazole	5	FDA ADI (5 µg/kg bw/day; 21 CFR 556.34)
Antiparasitics	Amprolium	1 ≤ HV < 15	FDA files and our analysis for the purpose of hazard ranking
Antiparasitics	Clorsulon	8	FDA ADI (8 µg/kg bw/day; 21 CFR 556.163)
Antiparasitics	Doramectin	0.75	FDA ADI (0.75 µg/kg bw/day; 21 CFR 556.225)
Antiparasitics	Eprinomectin	10	FDA ADI (10 µg/kg bw/day; 21 CFR 556.227)
Antiparasitics	Ivermectin	5	FDA ADI (5 µg/kg bw/day; 21 CFR 556.344)
Antiparasitics	Levamisole	1 ≤ HV < 15	FDA files and our analysis for the purpose of hazard ranking
Antiparasitics	Moxidectin	4	FDA ADI (4 µg/kg bw/day; 21 CFR 556.426)
Antiparasitics	Oxfendazole	1 ≤ HV < 15	FDA files and our analysis for the purpose of hazard ranking

Drug class	Drug name	Hazard value (µg/kg bw/day), HV[a]	Source of information
Antiparasitics	Thiabendazole	1 ≤ HV < 15	FDA files and our analysis for the purpose of hazard ranking
Tetracyclines	Tetracycline	25	FDA ADI (25 µg/kg bw/day; 21 CFR 556.720)
Tetracyclines	Oxytetracycline	25	FDA ADI (25 µg/kg bw/day; 21 CFR 556.500)
Antihistamines	Tripelannamine	HV ≥ 40	NTP and other publicly available information

[a] In the case when the drug has an FDA ADI in Title 21 of the Code of Federal Regulations, we provided the actual ADI value; in other cases, we provided the hazard value (HV) in a range based on FDA experts' judgments.

To rank the potency of each drug residue that can cause an adverse health effect(s) at low-dose exposures, we assigned a score for each drug based on its hazard-value range. As shown in the table below, we chose four scoring bins (no value, 1, 15, and 40 µg/kg bw/day) based on a distribution curve of all available hazard values. The drugs for which no hazard value could be established were assigned the highest score (score of 9).

Table 5.32 Potential for human health hazard score

Hazard value (µg/kg bw/day) (HV) range	Score
A hazard value cannot be established	9
0 <HV < 1	7
1 ≤ HV < 15	5
15 ≤ HV < 40	3
HV ≥ 40	1

Drugs with lower hazard values are considered to be more potent and thus have a greater potential for adverse health effects at a given exposure level than those drugs with higher hazard values. For a given drug, the lower the hazard value, the higher the score it received, indicating its higher potency to cause an adverse health effect(s).

6. RESULTS

6.1 Results: Ranking of the Drugs

6.1.1 Multicriteria-based Ranking Model Results

The multicriteria-based ranking model determines an overall score for each drug evaluated by this model; possible scores derived from the model range from 1 to 9. The scores of the 54 drugs evaluated by this model ranged from 3.2 to 7.0. Figure 6.1 provides the scores, presents the contribution for the weighted score of each criterion, and illustrates the ranking by score for the 54 drugs. In light of the resolution afforded by this multicriteria-based ranking model (small differences in score derived from the model for drugs of adjacent rank) and uncertainties in the data informing the model (discussed in Section 6.2), we focused on drug clusters (by score) or drug classes when analyzing these results.

Table 6.1 Multicriteria-based ranking model results for evaluated drugs in select drug classes

Drug Class	Rank of highest-scoring drug in this class	Ranks of drugs in this class	Number of drugs in this class ranked among the top 20 drugs
Beta-lactams	1	1, 4, 13,16, 24, 24, 28	4
Antiparasitics	2	2, 3, 7, 7, 7, 11, 21, 47, 47, 47	6
Macrolides	5	5, 11, 32, 32, 43, 51	2
Aminoglycosides	6	6, 17, 35, 36, 36, 36	2
NSAID	10	10, 30, 36, 41, 45, 47	1
Sulfonamides	14	14, 17, 17, 22, 24, 34	3
Tetracyclines	15	15, 28	1
Amphenicols	17	17, 30	1

Drugs in a variety of drug classes scored high, with drugs in eight different drug classes ranked among the the top 20 highest-scoring drugs. Table 6.1 lists these eight drug classes and provides the rank of the highest scoring drug in each class, the rank of each drug in the class evaluated in the model, and the number of drugs in each class that were among the top 20 highest-scoring drugs. By all these measures, beta-lactam antibiotics and antiparasitic drugs (especially avermnectins) were the highest ranked drug classes.

The high scores and rank for many of the beta-lactam antibiotics were influenced primarily by the high or higher than average scores for three out of the four criteria (A, B, and D). Penicillin, ampicillin, cloxacillin, and cephapirin ranked among the top 20 highest-scoring drugs (ranking 1st, 4th, 13th, and 16th respectively).

The high scores and rank for many of the antiparasitic drugs (particularly the avermectins) were derived from a combination of high and higher than average scores for all four criteria (A,B,C, and D). Most of the antiparasitic drugs had high scores for criterion C because of drug hydrophobicity or lipophilicity. These hydrophobic or lipohilic drug residue properties increase the potential for drug residues to concentrate in high-fat dairy products. See Appendix 6.2 for more information on the drug residue-dairy product partitioning characteristics of the selected drugs. Dormectin, ivermectin, amprolium, eprinomectin, moxidectin, and oxfendazole ranked among the top 20 highest-scoring drugs (2nd, 3rd, 7th, 7th, 7th, and 11th, respectively) in the overall ranking.

On the other end of the spectrum, the histamine antagonist, tripelennamine, and the aminocoumarin, novobiocin, were the two lowest ranking drugs (ranking 54th and 53rd, respectively). Other drug classes that were not ranked high, when compared to all drug classes, included the lincosamides: pirlimycin and incomycin; and the aminocyclitol: spectinomycin (ranking 45th, 52nd, and 43rd, respectively).

Appendix 6.1 provides a table comparing the top drugs (with scores in the top one-third of all scores) within each criterion (or sub-criterion or factor), by drug class. Appendix 6.2 provides more details comparing each criterion and sub-criterion scores for the top scoring drugs and drug classes.

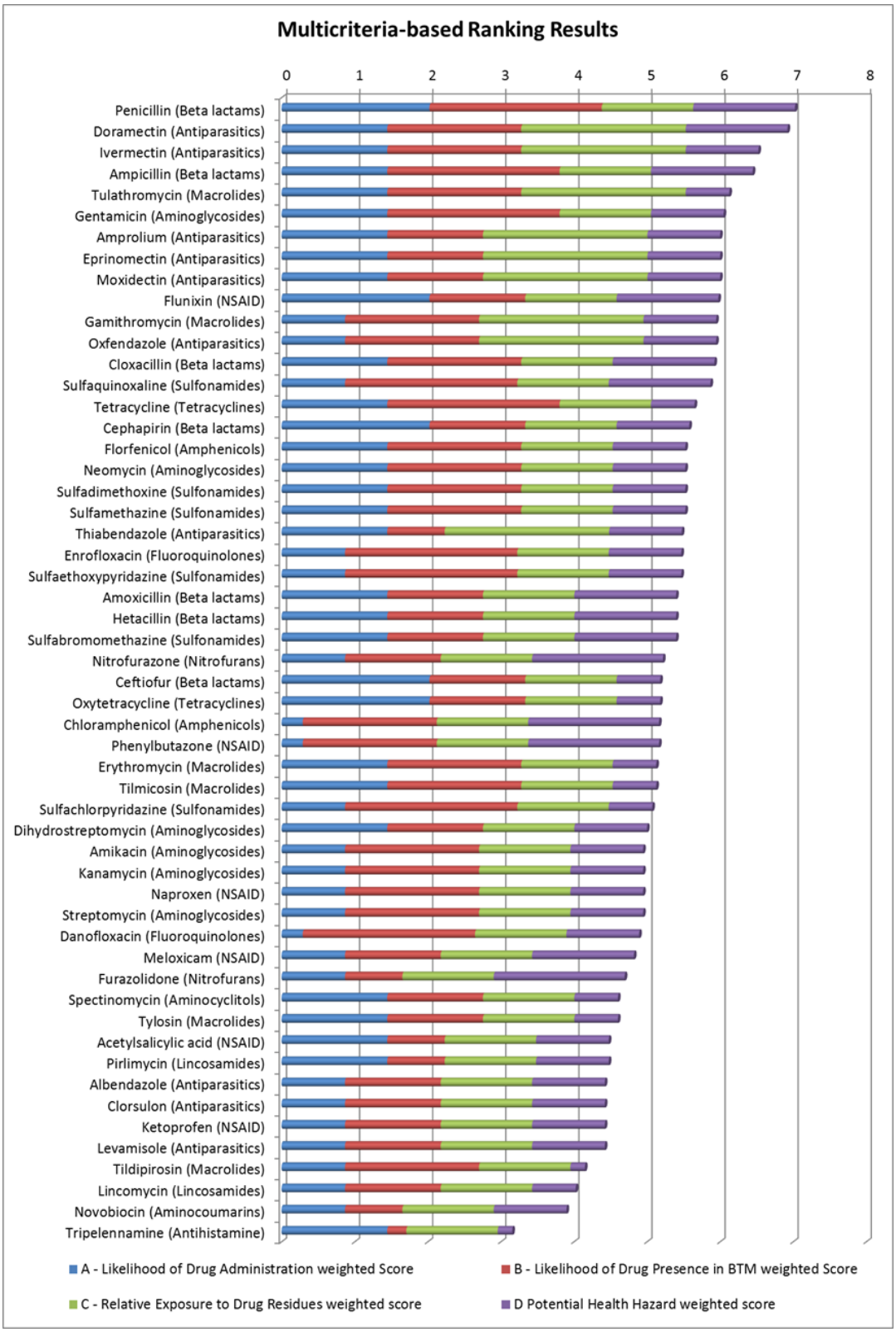

Figure 6.1 Multicriteria-based ranking model results for the 54 drugs evaluated

6.1.2 Results by Each Criterion (A-D)

The score and rank of each of the 54 drugs by criterion is illustrated and discussed below. Additional discussion of specific sub-criterion data and information is provided in Appendix 6.2.

6.1.2.1 Results by Criterion A

The drug scores for criterion A, likelihood of drug administration (LODA), and ranking of the 54 drugs evaluated by this multicriteria-based ranking model, are illustrated in Figure 6.2. The scores for criterion A ranged from 1 to 7, for all drugs evaluated in the study. Drugs in three drug classes ranked highest in terms of LODA, including several beta-lactams (ceftiofur, cephapirin, and penicillin), an NSAID (flunixin), and a tetracycline (oxtetracycline). Drugs in these three classes plus seven additional classes (antiparasitics, aminoglycosides, macrolides, amphenicols, lincosamides, sulfonamides, and antihistamines) were among the drugs with the next highest rank. The most influential sub-criterion for ranking drugs in criterion A was A1 (LODA based on survey data). However, the drug approval status (sub-criterion A3) also played an important role in influencing the final rank order for drug LODA, with approved drugs ranking higher than drugs not approved for use in lactating dairy cows. Drugs with the lowest LODA score included fluoroquinolone, danofloxacin, and the prohibited drugs phenylbutazone and chloramphenicol. The sub-criteria and factor scores for criterion A are illustrated in Appendix 6.2.

6.1.2.2 Results by Criterion B

The drug scores for criterion B, likelihood of presence of the drug in the bulk-tank milk (LODP), and ranking for the 54 drugs evaluated by this multicriteria-based ranking model are illustrated in Figure 6.2. The scores for criterion B ranged from 1 to 9 for all drugs evaluated in the study. Drugs in five drug classes ranked highest in terms of LODP, including beta-lactams (ampicillin and penicillin), fluoroquinolones (danofloxacin and enrofloxacin), aminoglycosides (gentamycin), sulfonamides (sulfachloropyridazine and sulfaethoxypyridazine), and tetracyclines (tetracycline). The most influential sub-criterion for LODP included a combination of the potential for drug residue contamination due to management error and the evidence of drug contamination from milk sampling. Drugs in seven drug classes (beta-lactams, aminoglycosides, sulfonamides, antiparasitics, macrolides, amphenicols, and NSAIDs) were among the drugs with the next highest rank. The antihistamine tripelennamine had the lowest LODP score among the 54 drugs evaluated. The sub-criteria and factor scores for criterion B are illustrated in Appendix 6.2.

6.1.2.3 Results by Criterion C

The drug scores for criterion C, relative exposure to drug residues in milk and milk products, and ranking for the 54 drugs evaluated by this multicriteria-based ranking model are illustrated in Figure 6.3. All drugs evaluated in this study were given a score of 5 or 9 for this criterion. Drugs in two drug classes ranked highest in terms of relative exposure, including six antiparasitics (amprolium, doramectin, eprinomectin, ivermectin, moxidecin, oxfendazole, and thiabendazole) and two macrolides (gamithromycin and tulathromycin). The higher rank of these drugs primarily arose from their hydrophobicity or lipophilicity (See Appendix 6.2 for the partitioning characteristics of all drugs evaluated in this study). These hydrophobic or lipophilic drugs are expected to concentrate in high-fat dairy products, and subsequently are predicted to result in increased exposure to consumers from consumption of high fat milk products. Also, none of these drugs are significantly inactivated by heat during processing, but tetracycline and erythromycin are slightly impacted by pasteurization. Appendix 6.2 provides further illustration of exposure due to consumption.

6.1.2.4 Results by Criterion D

The drug scores for criterion D, the potential for a human health hazard, given exposure, and ranking for the 54 drugs evaluated by this multicriteria-based ranking model are illustrated in Figure 6.3. The scores for criterion D ranged from 1 to 9 for all drugs evaluated in the study. Chloramphenicol, furazolidone, nitrofurazone, and phenylbutazone are the highest-ranked drugs. Drugs with the next highest criterion D scores and rank include the beta-lactams (amoxicillin, ampicillin, cloxacillin, hetacillin, and penicillin), anitparasitics (doramectin), NSAIDs (flunixin and meloxicam), and sulfonamides (sulfabromomethazine and sulfaquinoxaline). Drugs assigned scores of 5 for the potential for a human health hazard, given exposure, included a beta-lactam (ceftiofur), four macrolides (erythromycin, tilmicosin, tulathromycin, and tylosin), an aminocyclitol (spectinmycin), a sulfonamide (sulfachlorpyridazine), a lincosamide (lincomycin), and the tetracyclines (oxytetracycline and tetracycline). The macrolide (tildipirosin) and the antihistamine (tripelennamine) were determined to have the lowest score among all 54 drugs evaluated for the potential for human health hazard (given exposure).

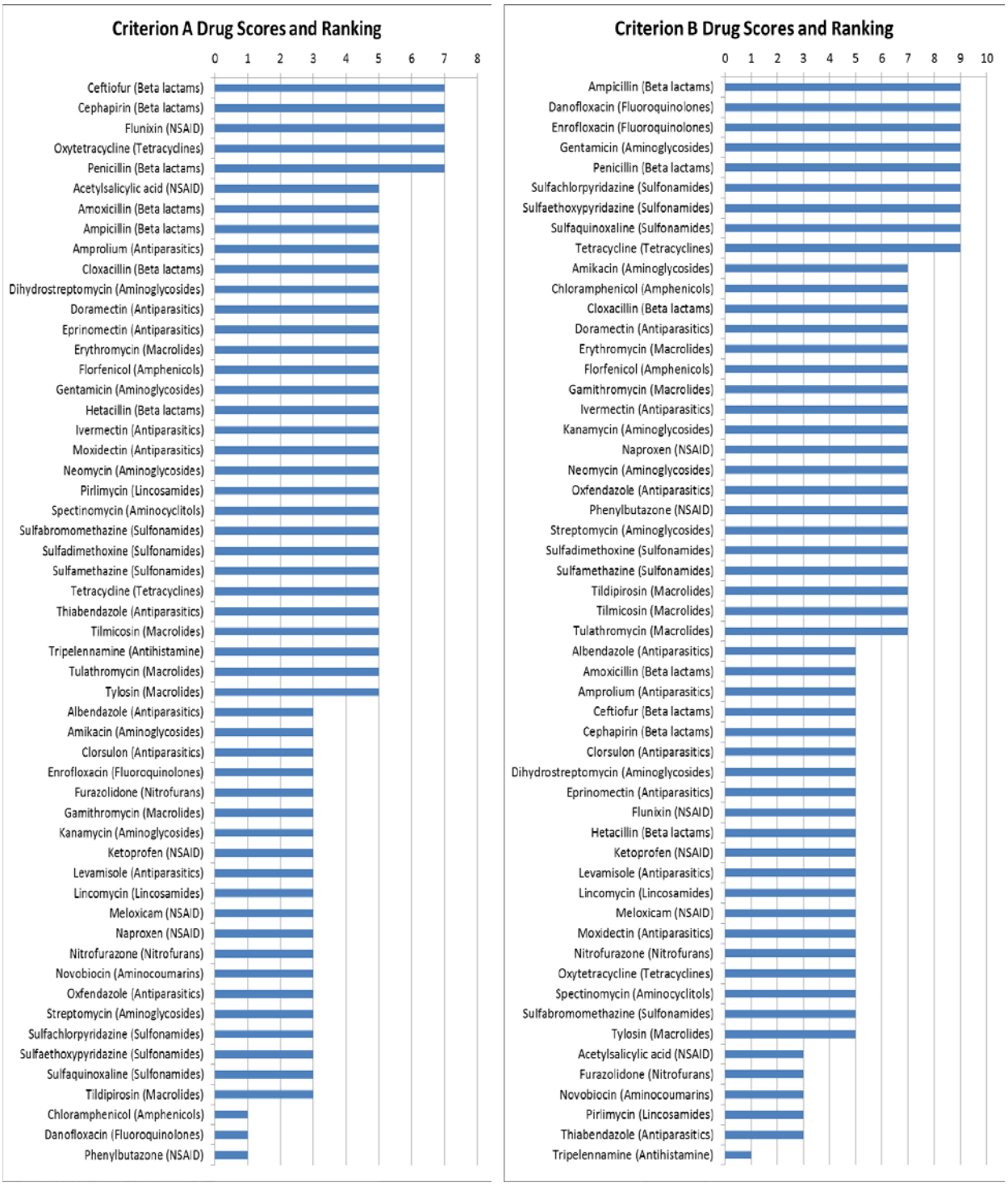

Figure 6.2 Criterion scores and ranking for criterion A and criterion B

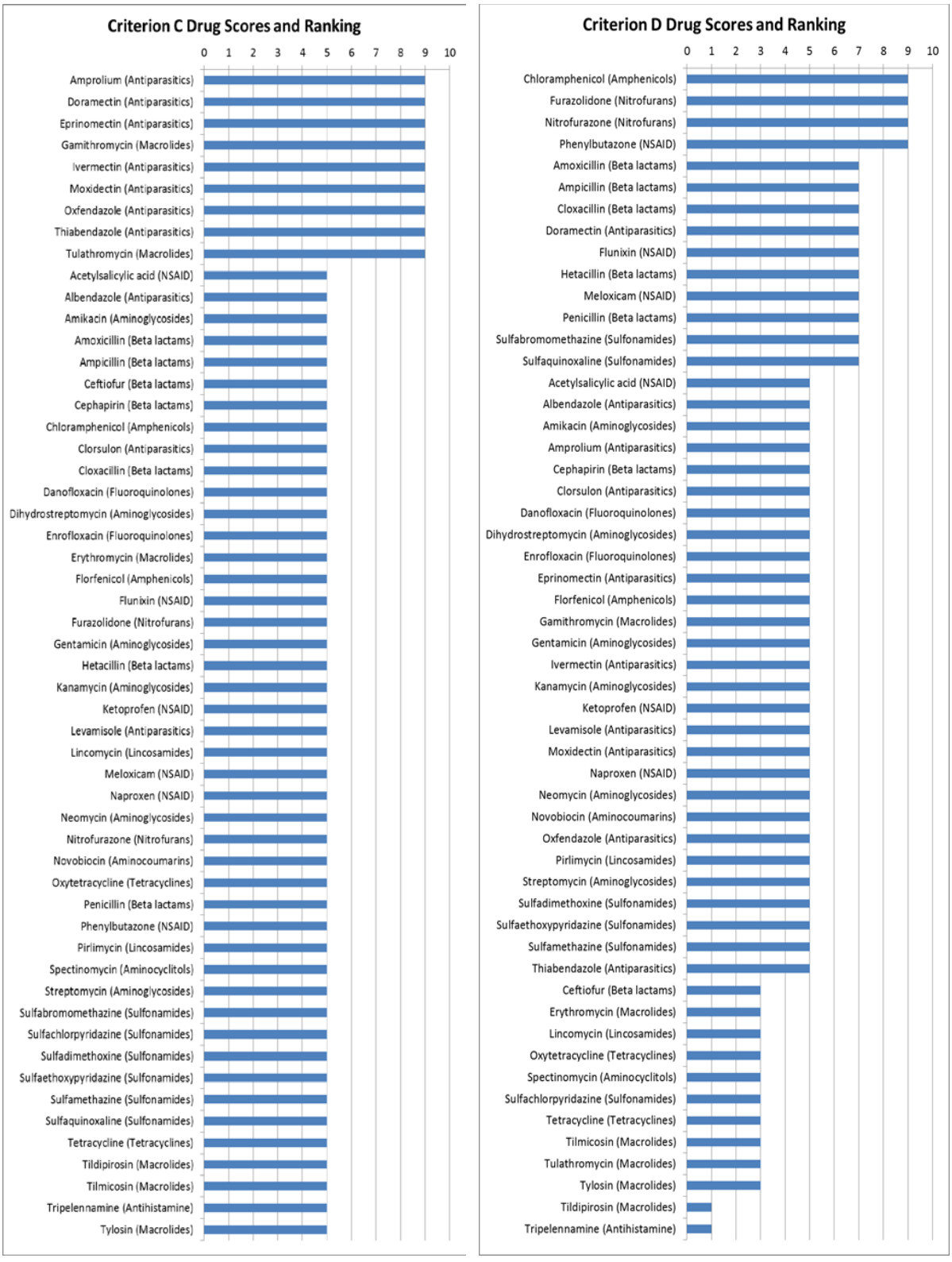

Figure 6.3 Criterion scores and ranking for criterion C and for criterion D

6.2 Uncertainty Analysis

Overview

This section characterizes the uncertainty associated with the multicriteria-based ranking model and results. Uncertainty reflects a lack of perfect knowledge. Uncertainty in the drug ranking produced by this model arose from a combination of uncertainties in the data and the model structure.

Data uncertainty can be characterized by examining the strength and quality of evidence provided by the data. In order to develop a ranking of drugs on the basis of confidence in the data, subject matter experts within the risk assessment team classified their confidence in each datum used in the model. An overall data confidence score for each drug was derived from the assigned datum scores in a manner parallel to the multicriteria-based ranking model. Details are provided in Appendix 6.3.

The companion data confidence ranking of the set of 54 drugs evaluated by this multicriteria-based ranking is shown in the figure below. Data confidence scores for the drugs included in this model ranged from approximately 5 to 9; the lowest ranking drug was amprolium, with a score of 4.95. Among the drugs ranking in the top third on the basis of multicriteria-based ranking model, only three were ranked low for data confidence; oxfendazole (5.90), gamithromycin (5.80), and amprolium (4.95). The lower scores for these drugs (and others not ranked high by the multicriteria-based ranking model) primarily arose from uncertainty associated with data informing criteria A and B. Individual criterion uncertainty scores are provided in Appendix 6.3.

Uncertainty in model structure is more difficult to evaluate. Potential sources of uncertainty can arise from uncertainty in the criteria included, weights assigned, uncertainty in the type of data used to evaluate each criterion, and uncertainty in the scoring scheme and/or aggregation methods used to combine sub-criteria and criteria. Multicriteria-based ranking criteria, type of data used, scoring scheme, and aggregation methods were reviewed by experts during the external peer review, and the present model includes changes to the original model structure arising from feedback from the external peer-review. An expert elicitation was used to determine criterion and sub-criterion weights (where applicable). Model structure uncertainty is discussed and explored further in Appendix 6.4.

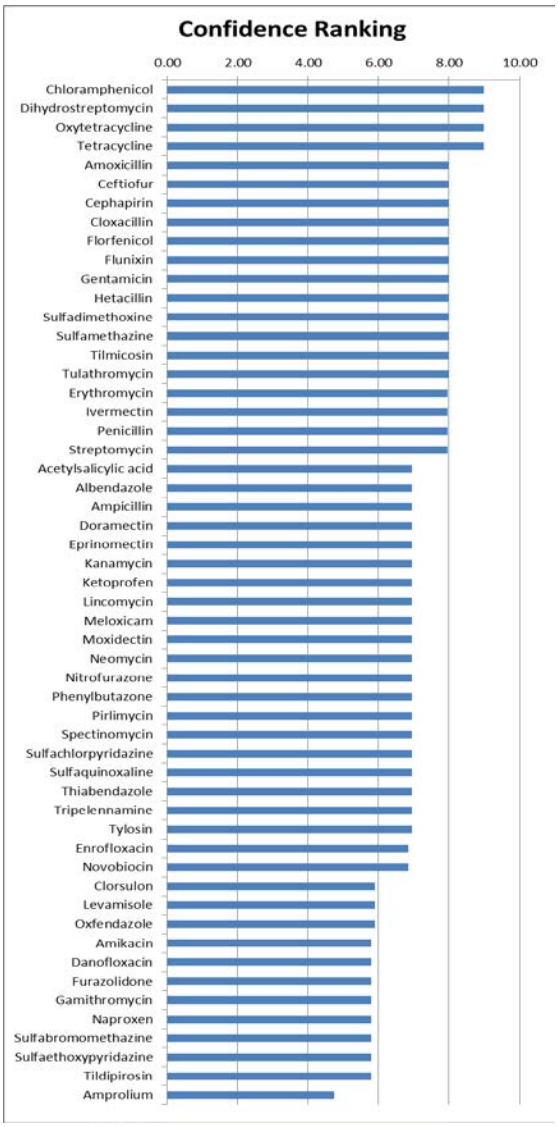

Figure 6.4 Data confidence scores and ranking of the 54 drugs evaluated by the multicriteria-based ranking model

6.3 Answers to the Charge Questions

I. What drugs are most likely to be administered to lactating dairy cows in the U.S?

- The drugs with the highest criterion A scores are expected to be the most likely to be administered to lactating dairy cows in the U.S. These drugs include several beta-lactams (ceftiofur, cephapirin, and penicillin), an NSAID (flunixin), and a tetracycline (oxtetracycline).

II. Which drugs, if administered to lactating dairy cows, are likely to result in drug residues present in milk (bulk-tank or bulk milk pickup tanker)?

- The drugs with the highest criterion B scores are expected to be the drugs (or major metabolites) most likely to persist as drug residues in milk (bulk-milk pickup tanker). These include drugs in five classes: beta-lactams (ampicillin and penicillin), fluoroquinolones (danofloxacin and enrofloxacin), aminoglycosides (gentamycin), sulfonamides (sulfachloropyridazine and sulfaethoxypyridazine), and tetracyclines (tetracycline). Amphenicols (*e.g.,* florfenicol), NSAIDs, and macrolides were the next most likely classes of drugs found to persist in the milk.

III. If present in milk (bulk-tank or bulk milk pickup tanker), what is the fate of these drug residues during processing/manufacturing of various milk products (*i.e.,* in what milk products would these drug residues be found)?

- Generally, residues of all drugs initially present in "raw" milk (bulk-tank or bulk milk pickup tanker) can be expected to be present at some level in finished milk and milk products. A few drugs, including the tetracyclines (tetracycline and oxytetracycline) and erythromycin are slightly impacted by heat and may be slightly reduced in concentration, relative to "raw" milk (bulk-tank or bulk milk pickup tanker) in some types of finished milk and milk products (see Appendix 6.2). Lipophilic drugs are expected to become more highly concentrated in high-fat milk products, relative to the initial concentration in "raw" milk (bulk-tank or bulk milk pickup tanker), while hydrophilic drugs are expected to be less concentrated in these high-fat products.

IV. Of the drug residues present in milk (bulk-tank or bulk milk pickup tanker), which have the potential for concentration in dairy products?

- As mentioned in response to charge question III, hydrophobic/lipophilic drugs are expected to become more highly concentrated in high-fat milk products, relative to the initial concentration in "raw" milk (bulk-tank or bulk milk pickup tanker).

V. What is the relative exposure to consumers from drug residue contamination in milk and milk products?

- Criterion C drug scores provide a measure of the relative exposure to consumers from drug residue contamination in milk and milk products, based on the lifetime average daily intake of the 12 selected milk and milk products considered in this multicriteria-based ranking and assuming all drugs are initially present in the bulk-tank milk at the same concentration.

VI. Which, if any of these drugs, are of particular public health concern and why?

- This risk assessment was not designed to estimate absolute risk associated with the selected drugs. Instead, it was designed to rank the drugs from a food safety perspective to assist in re-evaluating which animal drug residues should be considered for inclusion in milk testing programs.

VII. What is the ranking of the animal drugs under evaluation from a public health perspective?

- The multicriteria-based ranking model results are presented in Section 6.1.1. The multicriteria-based ranking model was based on four overarching criteria that collectively contribute to a drug's score and rank within the group: (1) the likelihood that it would be administered to lactating dairy cows; (2) the likelihood that, following administration, drug residues would be present in milk (bulk tank or bulk milk pickup tanker); (3) the relative extent to which consumers could be exposed to drug residues via consumption of milk and milk products; and (4) the potential for a human health hazard given exposure to the drug residue. Drugs in the following eight different drug classes ranked among the top 20 highest-scoring drugs: beta-lactams, avermectins, macrolides, aminoglycosides, NSAIDs, sulfonamides, tetracyclines, and amphenicols.

VIII. What are the critical data gaps or research needs required to more accurately assess the public health impact of drug residues in bulk-tank milk and milk products?

- These are described in section 6.4 Data gaps & Research Needs

6.4 Data Gaps and Research Needs

Data gaps and research needs:

- Current scientific data identifying the drug formulations used in lactating dairy cows in the United States on an annual basis and quantitative data on the frequency and magnitude of administration.
- Additional milk testing data to more comprehensively and quantitatively estimate the prevalence and level of each of the 54 drugs and related metabolites in bulk tank milk.
- Experimental data characterizing the relative concentration of each of the 54 drugs in milk and milk products when each is initially present in "raw" milk at levels typical of the U. S. milk supply.
- Toxicological data to better characterize the hazard of residues of drugs in milk for all drugs (including microbiological data to characterize the hazard presented to human gut flora), especially for older drugs, for which comprehensive data are not available, and drugs not approved or for use in dairy cows.
- Characterization of the low-dose-response relationship for each drug and relevant human health endpoints.
- Experimental data characterizing drug residue or major metabolite protein-binding characteristics in milk and milk products, as well as heat stability and the effect of heat processing on the levels of residue of each of the 54 drugs.

7. CONCLUSION

In conducting the risk assessment, we developed a multicriteria-based ranking model for risk management of animal drug residues in milk and milk products. This risk assessment provides a science-based analytical approach to collate and incorporate relevant available data and information, and serves as a decision-support tool to assist with re-evaluating which animal drug residues should be considered for inclusion in milk testing programs. The multicriteria-based model evaluated an overall score for each of the selected animal drugs based on four criteria. The four overarching criteria that collectively contributed to a drug's score and rank (within the group evaluated) included: (1) the likelihood that it would be administered to lactating dairy cows; (2) the likelihood that, following administration, drug residues would be present in milk (bulk tank or bulk milk pickup tanker); (3) the relative extent to which consumers could be exposed to drug residues via consumption of milk and milk products; and (4) the potential for a human health hazard given exposure to the drug residue.

Beta-lactams were not the only drug class that scored highly. Drugs in a variety of drug classes scored highly, with drugs in eight different drug classes ranked among the top 20 highest-scoring drugs. These eight classes include beta-lactam antibiotics, antiparasitics, macrolides, aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonamides, tetracyclines, and amphenicols. Based on three different analytics (the rank of the highest scoring drug in each class, the rank of each drug in the class evaluated in the model, and the number of drugs in each class that were among the top 20 highest-scoring drugs), beta-lactam antibiotics and antiparasitic drugs (especially avermectins) were the two most highly ranked drug classes.

The results of the risk assessment provide information for FDA, the NCIMS, and other stakeholders, regarding potential changes to the Pasteurized Milk Ordinance (PMO). The risk assessment report documents the methodology used to develop the model, the model structure, and model results. The report also collects, provides, and analyzes all the currently available data and information for each of 54 animal drugs that were in this risk assessment. The risk assessment also may be used to identify and prioritize research needs.

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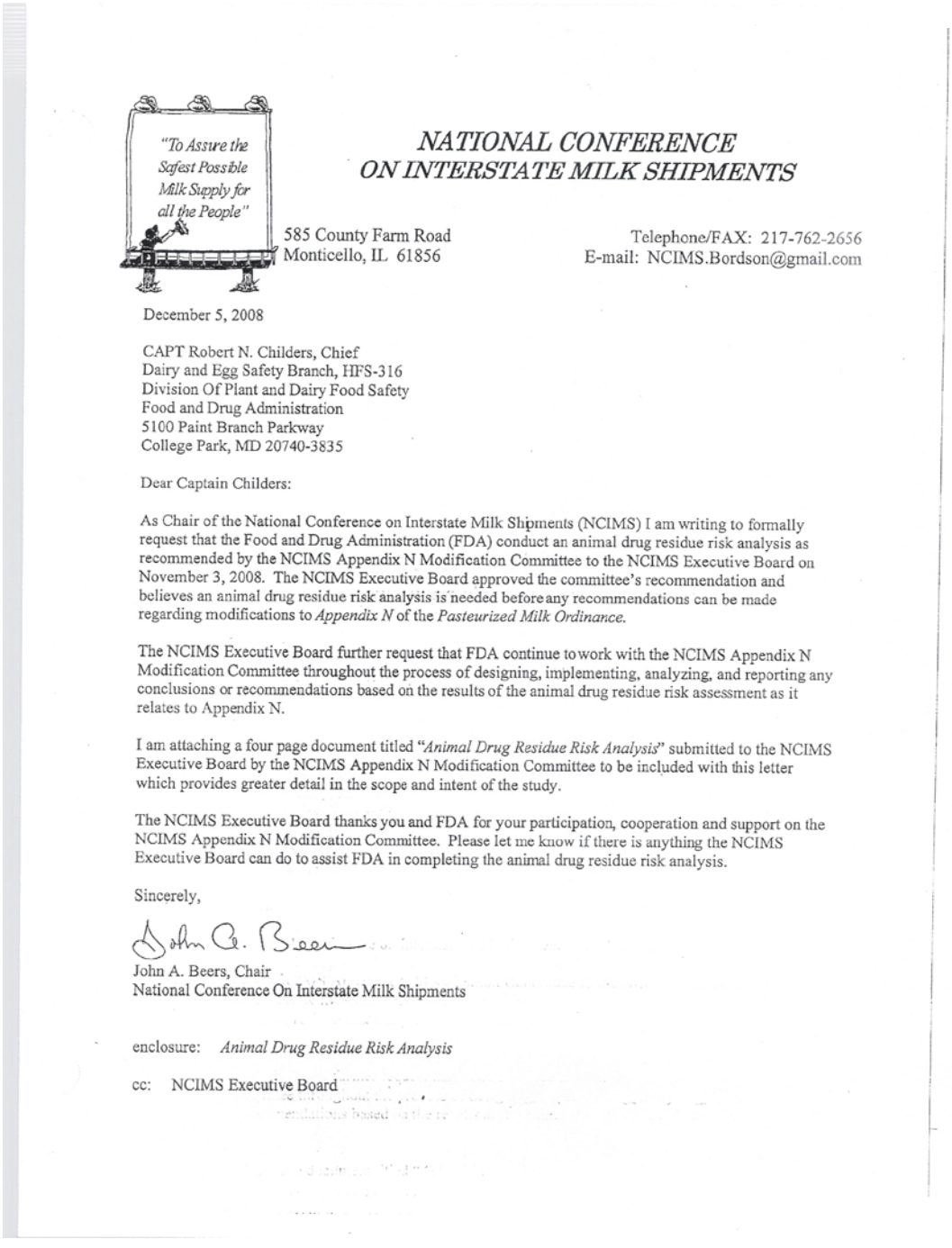
APPENDIX 1.1: NCIMS REQUEST TO FDA



"To Assure the Safest Possible Milk Supply for all the People"

NATIONAL CONFERENCE ON INTERSTATE MILK SHIPMENTS

585 County Farm Road
Monticello, IL 61856

Telephone/FAX: 217-762-2656
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December 5, 2008

CAPT Robert N. Childers, Chief
Dairy and Egg Safety Branch, HFS-316
Division Of Plant and Dairy Food Safety
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Captain Childers:

As Chair of the National Conference on Interstate Milk Shipments (NCIMS) I am writing to formally request that the Food and Drug Administration (FDA) conduct an animal drug residue risk analysis as recommended by the NCIMS Appendix N Modification Committee to the NCIMS Executive Board on November 3, 2008. The NCIMS Executive Board approved the committee's recommendation and believes an animal drug residue risk analysis is needed before any recommendations can be made regarding modifications to *Appendix N* of the *Pasteurized Milk Ordinance.*

The NCIMS Executive Board further request that FDA continue to work with the NCIMS Appendix N Modification Committee throughout the process of designing, implementing, analyzing, and reporting any conclusions or recommendations based on the results of the animal drug residue risk assessment as it relates to Appendix N.

I am attaching a four page document titled "*Animal Drug Residue Risk Analysis*" submitted to the NCIMS Executive Board by the NCIMS Appendix N Modification Committee to be included with this letter which provides greater detail in the scope and intent of the study.

The NCIMS Executive Board thanks you and FDA for your participation, cooperation and support on the NCIMS Appendix N Modification Committee. Please let me know if there is anything the NCIMS Executive Board can do to assist FDA in completing the animal drug residue risk analysis.

Sincerely,

John A. Beers

John A. Beers, Chair
National Conference On Interstate Milk Shipments

enclosure: *Animal Drug Residue Risk Analysis*

cc: NCIMS Executive Board

Animal Drug Residue Risk Analysis
July 21, 2008

Background Information
PMO Appendix N

History
Since 1924 the Grade "A" Pasteurized Milk Ordinance (PMO), a model document published by the Food and Drug Administration (FDA) and adopted by the States to enforce the national Grade "A" milk safety program, has contained a requirement for testing for animal drug residues. Until 1991, this was limited to a requirement that raw milk and finished products be sampled and tested for penicillin at least four times each six months using only the Bacillus subtilis and later the Bacillus stearothermophilus test methods and that the milk producer's permit be suspended after a positive test until a negative test result could be obtained.

In May 1988, in response to published papers and researcher's warnings, FDA, in cooperation with the Executive Board of the National Conference on Interstate Milk Shipments (NCIMS), issued a Memorandum of Information (M-I)[i] (Note: the NCIMS is a voluntary coalition of States, who with FDA administer the national Grade "A" milk Safety Program). This memorandum provided three documents. The **first** was an FDA accepted "High Pressure Liquid Chromatography (HPLC) Analysis of Sulfamethazine in Milk" test method for determining if there were sulfamethazine residues in milk. The **second** was an article from the FDA Consumer, "Sulfa residues in milk," that described a small survey in which 36 of 49 samples (73%) tested in 10 metropolitan areas contained detectable levels of sulfa drug residue. The **third** was an NCIMS Information Bulletin, which reminded farmers that sulfamethazine is prohibited from use in lactating dairy cattle. As a part of this same effort, in June 1988 FDA issued an M-I transmitting a letter to the NCIMS Conference Chair in which FDA stated their position that extra-label use of sulfamethazine in lactating dairy cattle was prohibited[ii]. In November 1988, FDA issued and in January 1989, FDA updated, an M-I providing more recent survey information to the States that indicated a dramatic drop in the findings of drug residues in milk[iii]. The January 1989 report ended with the words: "In conclusion, the results contained in this report demonstrate the effectiveness of the prevention efforts of FDA, States, and industry working together to achieve product safety."

In December 1989, the Wall Street Journal reported the results of two surveys of animal drug residues in milk, one sponsored by the newspaper and one sponsored by the Center for Science and the Public Interest, a consumer food safety and nutritional organization. The two surveys indicated that 20 and 38 percent, respectively, of the retail milk samples tested may have contained animal drug residues, possibly including sulfamethazine and other drugs that were not approved by the FDA for use in dairy cattle. Congressional hearings were held to explore a General Accounting Office (GAO) report that was issued in November 1990. This GAO report, "FDA Surveys Not Adequate to Demonstrate Safety of Milk Supply" [iv] disagreed with the January 1989 FDA report and conclusion. The GAO report cited limitations in the FDA survey methods that precluded any overall conclusions. The GAO report also noted that FDA did not have analytical methods to detect and confirm some drugs that GAO believed to be used in milk producing animals.

Animal Drug Residue Risk Analysis
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In November 1990, FDA issued a National Drug Residue Milk Monitoring Program (NDRMMP).[v] This program went into effect in February 1991 and was conducted until 2004. The NDRMMP was designed to provide an indication of animal drug residues that may be present in milk and to determine the extent that farmers, distributors, and veterinarians complied with the Federal Food, Drug, and Cosmetic Act (FFDCA), and its implementing regulations and applicable policies. When the program began, samples were analyzed for sulfonamides, tetracyclines and chloramphenicol. The program expanded over time from 500 to 5,000 annual samples being "quick-screened" by States and 750 annual samples being analyzed in FDA laboratories for chloramphenicol, florfenicol, chlortetracycline, oxytetracycline, tetracycline, sulfachloropyridazine, sulfadiazine, sulfadimethoxine, sulfamerazine, sulfamethazine, sulfapyridine, sulfaquinoxaline, sulfathiazole, novobiocin, ivermectin, and clorsulon. The sampling was designed to represent at least 10% of the milk tank trucks received on a daily basis at each milk plant sampled. Under this program, positive test results were traced back to the producer and forward to finished product.

At the April 1991 meeting of the NCIMS, FDA, the States, and industry revised the PMO to include a definition for the term "drug", amended several PMO sections regarding drug storage and use on farms and drug residue sampling and regulatory response to positive drug residue findings, and mandated State reporting to a third party database. At this meeting, Appendix N of the PMO, "Drug Residue Testing and Farm Surveillance" was adopted (NCIMS 1991 Proposal 232)[vi]. Appendix N provisions were intended to increase the number of milk samples analyzed, drug residues tested for, and test methods the States and industry could use for milk monitoring and regulatory purposes. For the first time, industry was required to sample and test raw milk for Beta lactam drugs from all bulk milk tank trucks as they entered a dairy plant. This family of drugs was selected because information available to FDA at the time indicated that Beta lactam drugs were the drugs most commonly used to treat lactating dairy cattle and so were considered most likely to result in a residue in milk. Also, validated screening tests for this family of animal drugs were readily available. In addition, the industry was (and is) required to keep, and make available, records on all tests conducted. Milk found positive was (and is) required to be disposed of in a manner that removes it from the human food chain. No milk from the farm responsible for a drug residue positive test result was (or is) allowed to be shipped until after a negative test for the drug residue in question.

In 1992, GAO again evaluated FDA's efforts to eliminate drug residues in milk[vii]. In this report, GAO questioned FDA's extra-label use policy, acknowledged several of the steps that FDA and the NCIMS had taken, and stated that the problem was not yet resolved. They noted that under the FFDCA and FDA policy, at the time, "…food items containing unapproved and/or harmful animal drug residues are considered to be adulterated and subject to enforcement action", and that while "…some international studies have concluded that the small amounts of animal drug residues in foods are not likely to cause a serious health hazard to humans... some scientists believe that the potential health risks of even minute exposures to low levels of some animal drug residues over several years are unknown."

Animal Drug Residue Risk Analysis
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FDA has provided a significant amount of information to States and the dairy industry regarding the effort to eliminate animal drug residues from the milk supply. Since 1988, FDA has issued 69 M-Is dedicated to subjects related to animal drug residue avoidance. Twenty of these M-Is remain active. FDA has also issued 29 Memoranda of Interpretation (M-a). Three of these M-a, which address test methods that can be used, remain active. Some of the inactive M-Is and M-as have been incorporated into NCIMS documents. Appendix N has been modified to include the information contained in several of these memoranda. Other remaining inactive memoranda are outdated and are no longer valid. FDA has also issued numerous general M-Is in question and answer format. Most of these contain questions and answers regarding animal drug storage, use and residue testing. Over the years, there have been other NCIMS conference changes to Appendix N and other PMO sections dealing with inspection and testing requirements related to animal drugs. The effective dates and wording of these changes can be found in the Memoranda of Conference Actions (IMS-a), which document such NCIMS actions.[viii] Since 1991, training for States and the dairy industry in all aspects of this program dealing with eliminating animal drug residues from the milk supply has been, and continues to be, a major focus for FDA. The States and the dairy industry now have available screening and confirmation tests for many more of the animal drugs that are currently found on dairy farms in the United States.

Current Status

Milk from Grade "A" dairy farms represents over 90% of the national farm milk supply. Milk from these Grade "A" dairy farms is sold as Class I (38%) and Class II (12%) and Class III (50%). Class I milk is universally manufactured into Grade "A" finished products such as fluid milk. A portion of Class II milk is also manufactured into Grade "A" products such as yogurt.[ix] Current Grade "A" and analogous USDA rules[x] require that every bulk milk pick-up tanker delivering milk to a milk plant must be tested for Beta lactam drugs regardless of its intended use. Milk from each individual Grade "A" dairy farm must be tested for Beta lactam drugs at least four times each six months. Pasteurized milk and milk products, for which there are validated Beta lactam test methods, must also be tested at least four times each six months. Some individual purchasers of milk require testing for other types of drugs. FDA evaluates and validates test methods. Dairy farms are routinely inspected for drug storage and use as well as for the presence of illegal or mislabeled drugs. Milk plants are audited regularly to be sure they are testing every incoming tanker and properly disposing of any milk that tests positive. Milk plants found not in substantial compliance with Appendix N will have their acceptable listings immediately removed from the list of shippers, titled "IMS Sanitation Compliance and Enforcement Ratings of Interstate Milk Shippers". Because receiving jurisdictions will not accept milk from an unlisted source, this effectively precludes the plant from shipping milk or milk products in interstate commerce.

The third party National Milk Drug Residue Data Base, which was begun in 1991, produces annual fiscal year reports. This data collection and reporting system includes reported data for all milk, Grade "A" and non-Grade "A", commonly known as manufacturing grade milk. The latest of these reports, for fiscal year 2007[xi], documents

Animal Drug Residue Risk Analysis
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that drug residue findings in milk are now relatively uncommon. Test results from 4,002,185 samples collected in 48 states were provided. A total of 4,026,485 tests were performed on these samples Only two of 43,851 pasteurized fluid milk samples tested were found to be positive (0.005%) resulting in 40,000 pounds of milk being disposed of as required (see table below).

Sample Results

Source of Sample	Total Samples	Number Positive	Percent Positive	Milk Disposed of (Pounds)
Bulk Milk Pick-Up Tanker	3,303,479	1,052	0.032%	83,121,000
Pasteurized Fluid Milk and Milk Products	43,851	2	0.005%	40,000
Producer	570,011	616	0.108%	2,752,000
Other	84,844	11	0.013%	307,000
TOTALS	4,002,185	1,681	*	86,220,000

Types of Drug Residue Testing Preformed

Type Of Drug Residue Tested for	Number of Tests	Number of Positive Tests	Percent Positive
Beta-Lactam	3,963,569	1,677	0.042%
Aminoglycosides	36	0	0.0%
Neomycin	604	2	0.331%
Amphenicols	34	0	0.0%
Enrofloxin	1,579	0	0.0%
Macrolides	860	1	0.116%
Spectinomycin	14	0	0.0%
Sulfonamides (Generic)	33,377	3	0.009%
Sulfamethazine	14,538	2	0.014%
Tetracyclines	11,847	2	0.017%

The NCIMS Drug Residue Committee is addressing whether the public health needs of this country are best served by the current testing protocol which requires States and the regulated industry to perform so many Beta lactam drug residue tests (3,963,569 of 4,026,485 tests performed in 2007). This represents over 98% of the samples tested. The National Milk Drug Residue Database data shows that the total number of samples tested for non-Beta lactam drug residues is much less (see table above). For example the Beta-lactam positive findings were 0.042% (1,677 positive results found in the testing of 3,963,569 samples). Comparatively, the findings for Neomycin were 0.331% (2 positive results found out of 604 tests), Macrolides were 0.116% (1 positive result found out of 860 tests), and Sulfamethazine were 0.014% (2 positive results found out

of 14,538 tests). It is important to note that the numbers of positive test results for these other residues are too limited to draw any meaningful conclusions[xii] but they do suggest that a re-evaluation and possible refocusing of this effort may be in order. Further, other drugs used in dairy cattle, such as flunixin, were not tested in fluid milk.

This increased focus on prevention of animal drug residues in milk and milk products began almost 20 years ago. Over the intervening years this effort has evolved based partly on science and partly on inertia. There has been some re-examination of this effort during this intervening time. Some years ago the need for the National Drug Residue Milk Monitoring Program was re-examined at the request of the States and, after examination by this agency, this program was suspended.

The NCIMS Drug Residue Committee is requesting that FDA perform a risk analysis. This risk analysis might include but not be limited to:

I. *Which drug residues might be expected to be present in milk based on their usage on the farm?*
II. *Which, if any of these, is of particular public health concern and why? Issues to consider:*
   - *Of the drugs that are used in dairy cattle and could be present in bulk tank milk, what is the frequency and levels of specific drug residues?*
   - *Of the drug residues found in bulk tank milk, what is the fate of these residues during processing/ manufacturing of various milk products (that is where and at what concentrations would these residues be found in milk products)?*
   - *Of the drug residues found in bulk tank milk and milk products, what is the level that would not cause adverse reactions in humans (i.e., what is the "safe" level)?*
   - *Of the available literature, what data gaps or research needs exist in addressing the public health context of drug residues in bulk tank milk and milk products?*
III. *What risk management options are available to minimize or eliminate risk (on a per residue basis)?*
IV. *Which risk management options are recommended on a per residue basis and why?*
V. *Needs Analysis: What methods are available for screening and confirmatory purposes and what additional methods are needed?*

The risk analysis suggested by the NCIMS Drug Residue Committee seems a prudent and reasonable way to begin is this re-evaluation. With the results of this risk analysis, FDA should be better equipped to identify practices or issues that would trigger a risk management question or risk assessment, identify and state the specific concerns, and formulate appropriate risk management questions. These will allow FDA to examine what this agency, their State partners, and the regulated dairy industry are now doing with the intent of making this vital State/federal public health effort more focused on minimizing current risk as identified by this FDA risk management process. It is important to note that due to the limited amount of information regarding milk residues involving drugs other than beta-lactams, additional surveillance sampling may need to

be conducted prior to evaluating the risk. It is also important to note that the results of the risk assessment will need to be balanced with legal considerations of what may constitute adulterated milk (raw or retail) under the Federal Food, Drug and Cosmetic Act, especially at the time of interstate movement.

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[i] M-I-88-5 Sulfamethazine And Other Animal Drugs – Use and Storage on Dairy farms May 4, 1988.
[ii] M-I-88-9 Extra-Label Use of Sulfamethazine June 22, 1988.
[iii] M-I-88-13 FDA Status Report – Sulfamethazine in Milk November 10, 1988 and M-I-89-1 FDA Status Report – Sulfamethazine in Milk January 25, 1989.
[iv] Food Safety and Quality: FDA Surveys Not Adequate to Demonstrate Safety of Milk Supply (GAO/RCED-91-26, Nov.1, 1990).
[v] M-I 90-8 National Drug Residue Milk Monitoring Program, November 9, 1990.
[vi] IMS-a 30 Actions of the 1991 National Conference on Interstate Milk Shipments, August 22, 1991
[vii] Food Safety and Quality: FDA Strategy Needed to Address Animal Drug Residues in Milk (GAO/RCED-92-209, August 5, 1992).
[viii] http://www.cfsan.fda.gov/~ear/ims-a-in.html
[ix] 2008 Dairy producer Highlights, November 2007, National Milk Producer's Federation, Arlington, VA.
[x] Code of Federal Regulations (CFR) Title 7 Part 133(c)
[xi] National Milk Drug Residue Data Base Fiscal Year 2007 Annual Report
[xii] NCIMS Appendix N sub-committee report January 9, 2008

RHWS2008

APPENDIX 2.1: LITERATURE REVIEW

To determine which other risk-assessment studies have been performed on drug residues in milk and milk products, we conducted a study of the available literature, using the Google search engine and the keywords listed in Table 2.1.

Search strategy

To determine which other risk-assessment studies have been performed on drug residues in milk and milk products, we conducted a systematic review[23] of the available literature, using the Google search engine and the keywords listed in Table 1. We reviewed the first 20 pages of search results for each of 18 separate searches. This search strategy generated 152 articles meriting further study, which we subsequently screened to identify duplicates and determine whether they met the following inclusion criteria:

- risk-ranking or risk-assessment study or risk-based surveillance study;
- study that evaluated animal drug residues in milk or milk products; or
- quantitative or qualitative evaluation of the public-health risks associated with presence of drug residues in milk and milk products or results of risk-based inspections.

Exclusion criteria

Studies were excluded if they:

- evaluated the safety or toxicological risks of drug residues or aimed to set maximum residue limits (MRL) or tolerance levels or only evaluated a single drug;
- evaluated only the risks of drug residue violations on farms and to producers;
- only discussed general risk-assessment approaches or policy considerations;
- focused on pesticides, heavy metals, or other contaminants that are not animal drug residues;
- evaluated drug residues in meat or other non-dairy foods (or that broadly compared hazards in different foods, including, but not limited to, dairy products);
- evaluated only environmental risks associated with drug use;
- were general guidance documents for avoiding drug-residue violations;
- evaluated supply-chain risks;

23 The PRISMA report (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) defines systematic reviews as: " a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review." We followed PRISMA recommendations (available at http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.1000097&representation=PDF) and the prisma checklist when conducting this systematic review.

- evaluated antimicrobial resistance risks only;
- provided survey results for drug residues in milk, dairy products, and / or other foods, without describing risk-based inspections;
- evaluated economic risks only;
- only reviewed existing risk rankings, risk assessments, or surveillance plans;
- reported epidemiologic or expert elicitation studies related to drug-residue risks;
- evaluated exposure assessments only;
- ranked risks according to human-health impacts only;
- evaluated residues and contaminants associated with feed; or
- evaluated the risks associated with potential presence of microbial pathogens in "raw" milk.

Results

The literature review approach generated ten unique studies for the final analysis, which are summarized below. Of these, four documents represented annual reports on surveillance for veterinary drug residues in food in the United Kingdom (UK), which were included because they were based on risk-informed prioritization of surveillance (Veterinary Residues Committee (VRC), 2001, 2004, 2005, and 2007). In these four studies, milk was analyzed for substances for which no MRL can be set and thus are banned (European Commission Regulation 37/2010 Table 2), antimicrobials (*i.e.,* general screening as well as sulfonamides, tetracyclines, etc.), anthelmintic, and NSAIDS as well as non-therapeutic residue, all based on EU legislation, Council Directive 96/23/EC.

The fifth document described the national program for monitoring and surveillance of chemical residues in "raw" milk developed by New Zealand's Ministry of Agriculture and Forestry, and was included because it relied on targeted surveillance and considered several compounds with importance as veterinary drugs (Ministry of Agriculture and Forestry, 2012). The program considers a number of factors including toxicity, good agricultural practices, extent and pattern of use, exposure routes, potential for misuse or abuse, persistence in the environment, previous monitoring frequencies and findings, availability of a practical regulatory analytical method, international concerns about residues of the compound, and regulatory requirements of international markets). The document stated that the following substances were not deemed to present a risk in New Zealand: stilbenes, their derivatives, salts and esters; anhydroid agents; steroids, resorcyclic acid lactones; beta-agonists. Of the veterinary drugs for which the document concluded that an MRL cannot be set, chloramphenicol, chloropromazine, colchicine, dapsone, dimetridazole, metronidazole, nitrofurans, ronidazole, and aristolochia species were either included in the sampling plan or, even though currently not included, their future inclusion in subsequent years was not ruled out. For veterinary drugs for which an MRL can be set, the document provides justification for the inclusion or exclusion of antibacterial substances (including sulfonamides and quinolones), anthelmintic, anticoccidials, carbamates and

pyrethoids, sedatives, nonsteroidal anti-inflammatory drugs (NSAIDs), and other pharmacologically active substances, based on regulatory approval status in New Zealand and considerations regarding likelihood of use.

The sixth document describes the approach the Food Safety Authority of Ireland took to develop a risk-based approach to developing the national residue-sampling plan for veterinary medicinal products and medicated feed additives in domestic animal production (Food Safety Authority of Ireland, 2014). The document discusses a risk ranking of substances, based on the nature of a substance (*i.e.,* nature, potency/Acceptable Daily Intake (ADI)), the usage of a substance (*i.e.,* number of animals treated and number of treatments per animal), the residue occurrence (*i.e.,* evidence for detectable residues), and dietary exposure (*i.e.,* contribution of food to diet, and consumer groups subjected to higher exposure, due to diet). The document then goes on to discuss each of these factors and discusses the development of a risk-ranking system. Finally, the document concludes that substances can be grouped into five distinct groups, for each species, depending on risk of occurrence as residues in food, and provides a risk ranking for veterinary drugs in beef cows, sheep and goats, pigs, poultry, and dairy cows. For dairy cows, the following drugs were identified as the two drug residues with highest rank: triclabendazole and amoxicillin, with albendazole, fenbendazole, and oxytetracycline tied for third rank.

The seventh document, published by two Canadian authors employed as professors at academic institutions, reviews residues of antibacterial and antiparasitic drugs in food, and was included because it provides a pragmatic approach for risk assessment (Walter-Toews and McEwen 1994). In the dose-response and hazard-identification section, this document discusses numerous veterinary drugs, including tetracyclines, beta-lactams, chloramphenicol, sulfonamides, aminoglycosides, and antiparasitic drugs. The exposure assessment discusses the results of surveillance studies as well as the limitations of such data. The risk-characterization and risk-avoidance sections discuss potential mitigation options, and the paper goes on to discuss the results of drug-residue surveys in final products (*e.g.,* dairy, meat, eggs) as well as the limitations of such data.

The eighth study conducted a risk assessment of streptomycin and tetracycline residues in meat and milk on the Croatian market, based on sampling data and food consumption data (Vragović *et al*., 2011). Similarly, the ninth study evaluated the risk of consuming marketed milk with antimicrobial residues in Kenya, based on surveillance data and exposure data (Kang'ethe *et al*., 2005). The final study evaluated the risk of beta-lactam residues in Kosovo's milk, based on ELISA[24]-based surveillance data and drug- administration data (Ibraimi *et al*., 2013).

24 Enzyme-linked immunosorbant assay (ELISA).

Table A2.1 List of keyword searches

Key Words
ranking, priority, surveillance, veterinary drugs, dairy products (milk and milk products)
risk ranking veterinary drug residues
surveillance veterinary drug residues
surveillance veterinary drug residues milk
milk surveillance testing veterinary residues
risk assessment veterinary residues milk
risk ranking veterinary drug residues milk
risk prioritization veterinary residues milk
surveillance veterinary residues milk
risk assessment veterinary drugs
risk assessment veterinary drugs McEwan
application of risk assessment and management principles to the extra-label use of drugs in food-producing animals
development and evaluation of a risk assessment tool for control of antimicrobial drug residues in milk
residues of antibacterial and antiparasitic drugs in foods of animal origin: a risk assessment
milk sampling residues
multi criteria decision analysis veterinary residues
drug residues dairy products
risk assessment dairy products residues

APPENDIX 2.2: RISK ASSESSMENT APPROACH

Synopsis:

Fully quantitative risk assessments generally involve development of models that mathematically simulate a given food/contaminant combination, or a small number of such combinations, in considerable depth and detail, to generate numeric estimates of risk and changes in risk. Our reasons for not adopting this approach for this risk assessment are as follows. First, the scarcity, in the scientific literature, of much of the quantitative evidence we would have needed to develop and populate a fully quantitative risk assessment model prohibited us from taking this approach.[25] Had the data been available, the approach still would have proven highly impractical; *i.e.,* it would have involved conducting a quantitative risk assessment on each of the 54 drugs selected for the project and comparing the result (*i.e.,* the estimated risk level) generated for each drug – a labor- and resource-intensive approach in excess of what was needed to achieve our objectives. Second, a key utility of fully quantitative risk assessments is that they can numerically estimate increases or decreases in numbers of illnesses that would occur if various mathematically simulated changes (*e.g.,* foods' manufacturing processes) were applied, but this risk assessment was not intended to evaluate or compare the effectiveness of interventions. Third, we needed to simultaneously consider multiple hazards (large number of different animal drugs) and commodities (milk and various milk products) for this multicriteria-based ranking, and this potentially large number of hazard-commodity pairs would likely have rendered a full quantitative analysis prohibitively complex.

Note that a quantitative risk assessment incorporating a Bayesian Network model[26] may have been considered appropriate for a situation similar to ours; however, we concluded that such a method would not be feasible, due to limited data; the large number of drugs, formulations, and dairy products to be considered; and, again, the possibility of our quantitative model becoming too complex.

Qualitative risk assessments, on the other hand, can be done to generate broader, descriptive results, such as ranking risk as "low," "medium," or "high," rather than numerically; for example, when a dearth of data prohibits a quantitative assessment. The results of qualitative risk assessments are based largely on an implicit understanding of the issues, as from subjective expert opinion, for example, rather than on clearly stated, quantifiable data. This approach may

25 To date, large-scale, representative surveys of drug-residue levels in milk and milk products in the U.S. and comprehensive surveys of drug-residue levels in bulk-tank milk that test for all drugs of interest are not available. Thus, it is not *a priori* obvious which drugs and foods do or do not pose public-health concern, and we do not have reliable estimates of the levels of different drug residues in milk and milk products. In addition, the public-health consequences associated with different drugs, products, and population subgroups may not be clearly quantifiable in all cases.

26 A graphical model based on probability and statistics that represents a set of random variables and their conditional dependencies.

have been somewhat useful for very broadly categorizing the 54 drugs evaluated in this project in this manner. A key reason we did not choose this approach is that it could not generate a more precise, objective ranking of each of the drugs in a documented and repeatable form, to better inform prioritization decisions.

Why we selected multicriteria-based ranking approach:

- Risk management questions

The risk-management questions (as posed by FDA risk managers) asked for the ranking of animal drug residues, rather than estimates of absolute risk associated with exposure to different drug residues through milk and milk products. The MCDA risk- ranking approach fulfills that objective. As stated in the "Risk Assessment Charge and Scope" (see section 1.4), one of the charge questions is "What is the ranking of the drug residues under evaluation, in terms of their potential for risk?" This question is particularly relevant to the purpose of our study, since NCIMS intends to use the results of this report to re-evaluate current milk-sampling requirements, regarding the kinds of animal drugs to be included for testing (see section 1.2). As such, our goal was to produce a ranked list of animal drugs that are important for NCIMS to include in its milk-sampling requirements. The MCDA risk-ranking provided us with a prioritized list of animal drugs that may pose concerns for consumers, if the drugs (or their metabolites) are present in milk and milk products.

- Availability and integration of various types of evidence (*e.g.,* quantitative and qualitative)

MCDA accommodates different types of scientific evidence that are qualitative or quantitative in nature. Although we lacked the fully quantitative information to conduct a traditional risk assessment, we had a mixture of qualitative and quantitative data sufficient to conduct a semi-quantitative assessment. For a list of scientific evidence used in this multicriteria-based ranking, see section 5 of this report. By combining the relevant quantitative and qualitative information, we could postulate criteria that together informed our efforts (*i.e.,* related to health risks associated with drug residues in milk and milk products) sufficiently to allow for a ranking. Specifically, we were able to obtain data that allowed us to evaluate the likelihood and frequency of drug presence in bulk-tank milk qualitatively, by considering drug use on U.S. dairy farms and the specific pharmacodynamics and pharmacokinetic properties of the respective drugs. We could also estimate the impact of dairy processing on drug-residue concentration in milk and milk products and quantify the magnitude of consumption of dairy products. We could also characterize semi-quantitatively the human health hazard estimates for human exposure (ADI or similar values). Therefore, by taking into account both quantifiable and non-quantifiable factors in an objective manner, we could develop and integrate the following four criteria to prioritize

animal drugs that could conceivably pose concerns to consumers if the drugs (or their metabolites) are present in milk or milk products:

- the likelihood of the drug's administration to lactating dairy cows;
- the likelihood of the drug's presence in milk (bulk-tank or bulk-milk pickup tanker);
- the relative exposure of drug residue in milk and milk products; and
- the potential for a human health hazard.

- Multicriteria-based ranking includes multiple, disparate criteria

As mentioned earlier, based on a mixture of qualitative and quantitative data, we selected four disparate criteria, which we included in this MCDA risk-ranking.

- Multicriteria-based ranking is transparent and reproducible

An added benefit of multicriteria-based ranking we used is that because we documented the weights and scores assigned to the various criteria, our ranking is transparent and reproducible. Notably, we can explore the impact of the weights and scores in additional scenarios or "what-if" scenarios. For example, when more scientific information becomes available, we could revise the existing criteria by further refining their weights or scales/scores or add more criteria; or, we could add more drugs or milk products for evaluation.

- Literature Review

Our literature review (see Appendix 2.1) revealed that semi-quantitative risk rankings based on multiple criteria have been used successfully by other agencies that tried to address similar risk-management questions, such as developing a prioritized list of drugs to include in national or international sampling plans. The successful implementation of matrix ranking, a similar approach by others (*e.g.,* the UK) suggested the appropriateness of multicriteria-based ranking for the problem at hand. In addition, the multicriteria-based ranking we used is consistent with approaches used by others to address risk-assessment questions other than those related to sampling plans; for example, a risk ranking to prioritize combinations of fresh produce and pathogens (Anderson *et al*., 2011), foodborne parasites (FAO/WHO 2014), and exotic diseases in pigs (Brookes 2014), again illustrating the practical utility of multicriteria-based ranking approaches.

APPENDIX 3.1: LISTING OF DRUGS

Table A3.1 Listing of antibiotics

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
1.1	Amoxicillin trihydrate-1	Abx	IM/SC	BRD, foot rot	-
1.2	Amoxicillin trihydrate-2	Abx	oral drench	bacterial enteritis	-
1.3	Amoxicillin trihydrate-3	Abx	IMAM	mastitis/lactating dairy	-
2.1	Ampicillin trihydrate-1	Abx	IM, SC	BRD, bacterial enteritis	-
2.2	Ampicillin Sodium	Abx	IV, IM	BRD	-
2.3	Ampicillin trihydrate-2	Abx	oral drench	bacterial enteritis	-
2.4	Ampicillin trihydrate-3	Abx	IM	bacterial enteritis, resp. tract infections (pneumonia)	-
3.1	Bacitracin	Abx (Polypeptide)	Medicated feed	-	RA
3.2	Bacitracin methylene disalycylate (BMD)	Abx (Polypeptide)	Medicated feed	-	RA
3.3	Bacitracin zinc	Abx (Polypeptide)	Medicated feed	-	RA
4	Bambermycins	Abx	Medicated feed	-	RA
5.1	ceftiofur crystalline free acid	Abx (cephalosporin) Beta-lactam	IM, SC	BRD, foot rot, acute metritis	-
5.2	ceftiofur hydrochloride-1	Abx	IM/SC	BRD. foot rot, acute metritis	-
5.3	ceftiofur hydrochloride-2	Abx	IMAM	mastitis/ lactating dairy; mastitis/ dry cow	-
5.4	ceftiofur sodium	Abx	IM/ SC	BRD, foot rot	-
6.1	cephapirin benzathine	Abx (cephalosporin) Beta-lactam	IMAM	mastitis/ dry cow	-
6.2	cephapirin sodium	Abx	IMAM	mastitis/ lactating dairy	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
7.1	Chlortetracycline	Abx (Tetracycline)	Medicated feed, soluble powder	-	RA
7.2	Chlortetracycline hydrochloride	(Tetracycline)	Tablet, bolus	-	RA
7.3	Chlortetracycline sulfamethazine	Abx (Tetracycline)	Medicated feed	-	C, RA
8.1	cloxacillin benzathine	Abx Beta-lactam	IMAM	mastitis/ dry cow	-
8.2	cloxacillin sodium	Abx	IMAM	Mastitis/ lactating dairy	-
9.1	Erythromycin-1	Abx	IM	BRD	-
9.2	Erythromycin-2	Abx	IMAM	subclinical mastitis due to streptococcus A	-
9.3	Erythromycin thiocyanate	Abx	oral	stimulating growth and improving feed efficiency	RA
10	Gamithromycin	Abx (macrolide)	Intrauterine, IM, Intrasynovval	Respiratory infection	-
11.1	gentamicin sulfate-1	Abx	ophthalmic	Treatment of pink eye	-
11.2	Gentamycin sulfate-2	Abx	Intrauterine injection	metritis	-
12	hetacillin potassium	Abx, Beta-lactam	IMAM	Mastitis/ lactating dairy	-
13	Laidlomycin	Abx (ionophore)	Medicated feed	-	-
14	Lasalocid	Abx (ionophore)	Medicated feed	-	-
15	Monensin	Abx (ionophore)	Medicated feed	Increased milk production efficiency	RA
16	novobiocin sodium	Abx	IMAM	Mastitis/ lactating dairy; mastitis/ dry cows	-
17.1	Oxytetracycline hydrochloride-1	Abx	oral	bacterial enteritis, resp. tract infections (pneumonia), colibacillosis	-
17.2	Oxytetracycline hydrochloride-2	Abx	Intravenous, IM, or SC	resp. infection, foot rot, anthrax, anaplasmosis, bacc leptosporosis, acute metritis	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
17.3	Oxytetracycline-3	Abx	IV, IM, or SC	resp. infection, foot rot, anthrax, anaplasmosis, diptheria, bacc leptosporosis, acute metritis, wooden tongue	-
17.4	oxytetracycline, polymixin	Abx	topical	Treatment of ocular infections	C
18.1	penicillin G procaine, novobiocin	Abx, betalactam	IMAM	mastitis/dry cows; mastitis/lactating dairy	C
18.2	penicillin G procaine, dihydrostreptomycin	Abx, betalactam	IMAM	mastitis/dry cows	C
18.3	penicillin G procaine-1	Abx, betalactam	IM	BRD	-
18.4	penicillin G procaine-2	Abx, betalactam	IMAM	mastitis/lactating dairy and dry cows	-
18.5	penicillin G procaine-3	Abx, betalactam	IM	strangles in horses	-
19	Pirlimycin hydrochloride	Abx (lincosamide)	IMAM	clinical and subclinical mastitis/lactating dairy cows	-
20	Sulfabromomethazine sodium	Abx (Sulfonamide)	bolus	foot rot, scours, mastitis, and metritis	-
21.1	Sulfadimethoxine-1	Abx, sulfonamide	oral, bolus	resp. infect.,(pneumonia, shipping fever) foot rot, calf diptheria, colibacillosis,	-
21.2	Sulfadimethoxine-2	Abx, sulfonamide	Intravenous	resp. infect. (pneumonia, shipping fever), foot rot, calf diptheria, acute mastitis, acute metritis	-
21.3	Sulfadimethoxine-3	Abx, sulfonamide	oral, bolus	resp. infect. , foot rot, calf diptheria	-
22	Sulfaethoxypyridazine	Abx (Sulfonamide)	oral, tablet, IV	BRD, foot rot, scours, septicemia assoc w/mastitis and metritis	-
22.1	Sulfaethoxypyridazine-1	Abx (Sulfonamide)	oral	resp. infect. , foot rot, calf diptheria	-
22.2	Sulfaethoxypyridazine-2	Abx (Sulfonamide)	Intravenous	Resp. infect., foot rot, acute metritis,	-
22.3	Sulfaethoxypyridazine-3	Abx (Sulfonamide)	oral	foot rot and infections, shipping fever	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
23	Bacitracin	Abx (Polypeptide)	Medicated feed	Feedlot beef cows; reduction in the number of liver condemnations due to abscesses.; growing cows: weight gain/feed efficiency (WG/FE)	RA
23.1	bacitracin methylene disalycylate (BMD)	Abx	Medicated feed	Feedlot beef cows; reduction in the number of liver condemnations due to abscesses.	RA
23.2	bacitracin zinc	Abx	Medicated feed	growing cows: weight gain/feed efficiency (WG/FE	RA
24	Bambermycins	Abx	Medicated feed	cows (fed for slaughter, pasture cows, and replacement heifers): WG/FE	RA
25	Chlortetracycline-1	Abx (Tetracycline)	Medicated feed, soluble powder, tablet, bolus	cows (calves, beef/NLD): E. coli scours in calves; wt gain/feed efficiency, anaplasmosis, pneumonia; salmonella; maintenance of wt gain in presence of respiratory disease	RA
25.1	Chlortetracycline-2	Abx	Medicated feed, soluble powder	cows (calves, beef/NLD): E. coli scours in calves; wt gain/feed efficiency, anaplasmosis, pneumonia	RA
25.2	chlortetracycline hydrochloride	Abx	Tablet, bolus	cows (calves): E. coli scours, pneumonia, salmonella	RA
25.3	chlortetracycline, sulfamethazine	Abx	Medicated feed	cows (beef): maintenance of wt gain in presence of respiratory disease	C, RA
26	Danofloxacin mesylate	Abx	SC	cows (beef/NLD): treatment of respiratory disease	-
27	dihydrostreptomycin sulfate	Abx (aminoglycoside)	IM, oral suspension, tablet	cows (beef/NLD): treatment of leptospirosis, bacterial scours in calves	-
28	Enrofloxacin	Abx (fluoroquinolone)	SC	cows (beef/NLD): treatment of respiratory disease	-
29.1	florfenicol-1	Abx (amphenicol)	IM/SC	cows (beef/NLD): treatment/control of respiratory disease/BRD, treatment of foot rot and control of associated pyrexia	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
29.2	florfenicol-2	Abx	oral	BRD	-
29.3	florfenicol-3	Abx	SC	-	-
29.4	florfenicol, flunixin	Abx	IM/SC	cows (beef/NLD): treatment of respiratory disease/BRD and control of associated pyrexia	C
30	Laidlomycin	Abx (ionophore)	Medicated feed	cows (fed for slaughter): WG/FE	RA
31	Lasalocid	abx (ionophore)	Medicated feed	cows (beef, dairy heifers, calves): WG/FE, coccidiostat	RA
32	Neomycin	Abx (aminoglycoside)	oral powder, ophthalmic	cows: colibacillosis; treatment of pink eye	-
32.1	neomycin sulfate	Abx	oral powder,	cows: colibacillosis (bacterial enteritis)	-
32.2	neomycin, nystatin, thiostrepton, triamcinolone	Abx	ophthalmic	cows: treatment of pink eye	C
33	spectinomycin sulfate	Abx	SC	cows (beef/NLD): treatment of BRD	-
33.1	spectinomycin hydrochloride	Abx	IM, SC, or oral	Rep. infect. (pneumonia), bacterial enteritis, weight gain	-
34	Streptomycin sulfate	Abx, aminoglycoside	Oral solution	cows (calves): bacterial enteritis, scours of calves, leptospirosis, actinomycosis, mastitis, calf pneumonia	-
35.1	Sulfachlorpyridazine	Abx (sulfonamide)	soluble powder, IV	cows (calves): colibacillosis	-
35.2	Sulfachlorpyridazine	Abx, sulfonamide	oral	colibacillosis in calves	-
36.1	sulfamethazine-1	Abx, sulfonamide	IV	BRD, foot rot, collibacillosis, acute metritis	-
36.2	sulfamethazine-2	Abx, sulfonamide	oral-SR bolus	BRD, foot rot, bacterial enteritis, calf diptheria, acute mastitis, acute metritis	-
36.3	sulfamethazine-3	Abx, sulfonamide	oral solution	BRD, foot rot, bacterial enteritis, calf diptheria, coccidiosis, acute mastitis, acute metritis	-
37	sulfaquinoxaline	Abx. Sulfonamide	soluble powder, oral solution	cows (calves, beef, NLD): coccidiosis	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
38.1	tetracycline hydrochloride-1	Abx, tetracycline	bolus, soluble powder	cows (calves): bacterial enteritis (scours), bacterial pneumonia	-
38.2	tetracycline hydrochloride-2	Abx, tetracycline	topical	Unspecified	-
39	tilmicosin phosphate	Abx, macrolide	SC / IMAM	cows (beef/NLD): BRD	-
40	Tildipirosin	Abx macrolide	SC	Cows (beef/NLD)	-
41	Tulathromycin	Abx (macrolide)	SC	cows (beef, NLD): BRD, pinkeye, foot rot	-
42.1	tylosin phosphate-1	abx	medicated feed	beef cows: reduction of liver abscesses;	RA
42.2	tylosin phosphate-2	abx	IM	beef/NLD: BRD, foot rot, diphtheria, metritis	-
43	Virginiamycin	Abx (streptogramin)	Medicated feed	cows (fed for slaughter): WG/FE, reduction of liver abscesses	RA
44	apramycin sulfate	abx (aminoglycoside)	soluble powder, medicated feed	swine - colibacillosis	RA
45	arsanilic acid	abx (arsenical)	Medicated feed	swine: WG/FE, swine dysentery; chkn, turkey: WG/FE, improved pigmentation	RA
46	Carbadox	abx	Medicated feed	swine -WG/FE, swine dysentery, enteritis	RA
47	colistimethate sodium	abx	injectable	chkn - E. coli mortality	SS
48	Efrotomycin	abx	Medicated feed	swine - WG/FE	RA
49	hygromycin B	abx (aminoglycosid e)	Medicated feed	chkn, swine - control of intestinal parasites	RA
50.1	lincomycin hydrochloride	Abx (lincosamide)	medicated feed, soluble powder, injectable	swine: swine dystentery, enteritis; chkn: necrotic enteritis arthritis, mycoplasmal pneumonia	-
50.2	lincomycin hydrochloride monohydrate	abx	injectable	swine - arthritis, mycoplasmal pneumonia	-
51	maduramicin ammonium	abx (ionophore)	Medicated feed	chkn - coccidiostat	RA, SS
52	Narasin	abx (ionophore)	Medicated feed	chkn - coccidiostat	RA, SS

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
53	Nitarsone	abx (arsenical)	Medicated feed	chkn, turkey - prevention of blackhead	RA, SS
54	oleandomycin	abx (macrolide)	Medicated feed	swine, chkn, turkey: WG/FE	RA, SS
55	Robenidine	abx	Medicated feed	chkn - coccidiostat	RA, SS
56	Roxarsone	abx (arsenical)	medicated feed, soluble powder, tablet, oral solution	swine - (feed) WG/FE, (SP, tablet) swine dysentery; chkn, turkey - WG/FE, improved pigmentation, (tablet [chkn]) coccidiosis	RA, SS
57	Salinomycin	abx (ionophore)	Medicated feed	chkn, quail - coccidiostat	RA, SS
58	semduramicin	abx (ionophore)	Medicated feed	chkn - coccidiostat	RA, SS
59.1	sulfamerazine	abx (sulfonamide)	Medicated feed	fish - control of furunculosis	RA, SS
59.2	sulfamerazine, sulfamethazine, sulfaquinoxaline	abx (sulfonamide)	Soluble powder	chkn, turkey - coccidiosis, fowl cholera	C, RA, SS
60	Sulfomyxin	abx (sulfonamide)	injectable	chkn, turkey - colibacillosis, chronic respiratory disease	SS
61	Tiamulin	abx (pleuromutilin)	medicated feed, soluble powder	swine - (feed) WG/FE, swine dysentery, enteritis; (SP) - swine dysentery, SRD	RA, SS
62.1	amikacin sulfate-1	Abx (aminoglycoside)	intrauterine	genital tract infect in horse mares	-
62.2	amikacin sulfate-2	abx	IM, SC	genitourinary tract infections (cystitis)	-
63	Cefadroxil	abx (cephalosporin)	tablet	Dog, cat	RA, SS
64	Cefovecin	abx (cephalosporin)	injectable	Dog, cat	RA, SS
65	Cefpodoxime	abx (cephalosporin)	tablet	Dog	RA, SS
66.1	Chloramphenicol-1	abx (amphenicol)	tablet, capsule, injectable, ophthalmic	Dog, cat	-
66.2	chloramphenicol palmitate	abx	oral suspension	dog, resp. infect., bacterial enteritis, urinary tract infections.	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
66.3	chloramphenicol -3	abx	IV, IM	resp. infect., bacterial enteritis, urinary tract infections	-
66.4	chloramphenicol, prednisolone	abx	ophthalmic	Dog, cat	S, ST
67	Clindamycin	abx (lincosamide)	tablet, capsule, oral solution	Dog, cat	RA, SS
68	Cuprimyxin	abx, antifungal	topical	Horse, dog, cat	RA
69	dicloxacillin sodium monohydrate	abx (beta-lactam)	capsule	Dog	C, RA, SS
70	Difloxacin	abx (fluoroquinolone)	tablet	Dog	RA, SS
71	doxycycline hyclate	abx (tetracycline)	injectable	Dog	SS
72	Furazolidone	abx (nitrofuran)	topical	Horse, dog	-
73	Iodochlorhydroxyquin	abx	bolus	Horse	SS
74.1	Kanamycin	abx (aminoglycoside)	ophthalmic	Dog	-
74.2	kanamycin sulfate	abx (aminoglycoside)	injectable	Dog, cat	-
74.3	kanamycin sulfate, calcium amphomycin, hydrocortisone acetate	abx (aminoglycoside)	Topical	Dog	C
74.4	kanamycin, bismuth subcarbonate, activated attapulgite	abx (aminoglycoside)	Oral suspension	Dog	C
75	marbofloxacin	abx (fluoroquinolone)	tablet	Dog, cat	RA
76	Mupirocin	abx	topical	Dog	RA, SS
77.1	nitrofurazone	Abx (nitrofuran)	topical	Horse, dog, cat	-
77.2	nitrofurazone, butacaine sulfate	-	Topical	Horse, dog, cat	C
78.1	Orbifloxacin	abx (fluoroquinolone)	Oral suspension, tablet	Dog, cat	RA,

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
78.2	orbifloxacin, mometasone furoate monohydrate, posaconazole	-	topical	Dog	C, RA
79	sulfadiazine/pyrimethamine	abx (sulfonamide)	oral suspension	Horse	C
80	sulfamethizole, methenamine mandelate	abx (sulfonamide)	tablets	Dog	C, RA, SS
81	Sulfisoxazole	abx (sulfonamide)	tablet	Dog, cat	RA
82	Ticarcillin	abx (beta-lactam)	intrauterine infusion	Horse	SS
83	trimethoprim, sulfadiazine	abx (sulfonamide)	injectable, paste, oral powder, tablet, oral suspension	Horse, dog	C
84	benzathine penicillin G	abx (beta lactam)	injectable	Beef cows	C
85	demeclocycline	abx, (tetracycline)	tablet	Dog	RA, SS
86	dimetridazole	abx, (nitroimidazole)	feed and drinking water	treatment of enterohepatitis in turkeys and swine	RA,SS
87	Ipronidazole	abx, (nitroimidazole)	feed	Treatment of histomoniasis in turkeys and swine	RA, SS
88	Methacycline	abx (nitroimidazole)	capsule, oral suspension	used in companion animals	NM
89	Minocycline	abx (tetracycline)	capsule, tablet, oral suspension	dogs, cats, horse	RA, SS
90	Sarafloxacin	abx (fluoroquinolone)	-	-	NM
91	sulfamethoxazole	abx (sulfonamide)	-	-	NM
92	sulfanilamide	abx (sulfonamide)	-	-	NM
93	Sulfapyridine	abx (sulfonamide)	-	-	NM
94	Sulfathiazole	abx (sulfonamide)	-	-	RA
95	Vancomycin	abx (glycopeptide)	-	-	NM

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
96	ceftin, cefuroxime	abx, cephalosporin	-	-	C

Table A3.2 Listing of antifungals

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
97	bicyclohexylammonium fumagillin	antifungal	Soluble powder	bees - prevention of nosema	SS
98	Clotrimazole	antifungal	topical	Dog, cat	RA, SS
99	copper naphthenate	antifungal	topical	Horse	RA, SS
100	Griseofulvin	antifungal	oral powder	Horse, dog, cat	SS
101.1	Miconazole	antifungal	topical	Dog, cat	RA, SS
101.2	miconazole, polymixin B, prednisolone	antifungal, abx, steroid	topical	Dog	C, RA, SS
102	Tolnaftate	antifungal	topical	Dog, cat	RA, SS

Table A3.3 Listing of antihistamines

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
103	trimeprazine tartrate, prednisolone	Antihistamine, steroid	Tablet, capsule	Dog	C, RA, ST, SS
104	doxylamine succinate	antihistamine	tablet, injectable	Horse, dog, cat	Cl, SS
105	chlorpheniramine	antihistamine	-	-	Cl
106	pyrilamine maleate	antihistamine	injectable	Horse	Cl, SS

Table A3.4 Listing of anti-inflamants

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
107.1	dexamethasone	Anti-inflamatory/ Steroid	IM,IV, oral powder, bolus	ketosis, supportive therapy for inflammatory conditions, shock, and stressful conditions	ST
107.2	dexamethasone, trichlormethiazide	Anti-inflamatory/ Steroid, diuretic	oral bolus	Udder edema	C, ST
108.1	flunixin meglumine-1	Antiinflammant /NSAID	IV	pyexia, associated w/ respiratory tract, control of inflammation; endotoxemia and mastitis; for control of inflammation in endotoxemia	-
108.2	flunixin meglumine-2	Antiinflammant /NSAID	IM, IV, or oral	control inflamation & pain w/musculoskeletal pain	-
109	isoflupredone acetate	Anti-inflamatory/ Steroid	IM	bovine ketosis, alleviation of pain/lameness assoc with arthritis etc, tx of hypersensitivity reactions, supprotive therapy in severe infections	ST
110	tripelennamine hydrochloride	Anti-inflamatory/ Antihisamine	IM/IV	tx of conditions in which antihistaminic therapy may be expected to lead to alleviation of some signs of disease.	-
111	gelatin solution	Shock therapy, anti-inflamatory	IV	restore circluatory volume in animals treated for shock	O
112	trenbolone acetate	steroid	implant	cows (steers and heifers only): WG/FE	ST
113	Zeranol	steroid	implant	cows (beef): WG/FE	ST
114	Albuterol	Steroid	inhaler	Horse	Cl, ST
115.1	betamethasone acetate, betamethasone disodium phosphate	Steroid	injectable	Horse	C, Cl, ST
115.2	betamethasone dipropionate, betamethasone disodium phosphate	Steroid	injectable	Horse, dog	C, Cl, ST
116	Boldenone	Steroid	injectable	Horse	Cl, ST

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
117	Carprofen	NSAID	Tablet, injectable	Dog	SS
118	chlorphenesin carbamate	anti-inflam	tablet	Dog	RA, SS
119	Clenbuterol	steroid	Oral syrup	Horse	Cl
120	Deracoxib	NSAID	tablet	Dog	RA
121	Diclofenac	NSAID	topical	Horse	SS
122	dimethyl sulfoxide	anti-inflam	topical	Horse, dog	SS
123	Etodolac	NSAID	Tablet, injectable	Dog	SS
124	Firocoxib	NSAID	Tablet, injectable, paste	Horse, dog	SS
125	flumethasone	steroid	Injectable, tablet	Horse, dog, cat	ST
126	flumethasone, neomycin sulfate, polymixin B sulfate	steroid, abx	topical	Dog, cat	C, RA
127.1	fluocinolone acetonide	steroid	topical	Dog, cat	RA, ST, SS
127.2	fluocinolone acetonide, dimethyl sulfoxide	Steroid, anti-inflam.	topical	Dog	C, RA
127.3	fluocinolone acetonide, neomycin sulfate	Steroid, abx	topical	Dog, cat	C, RA, ST, SS
128	Ketoprofen	NSAID	IV	Horse	-
129	meclofenamic acid	Ant-inflam.	oral granules, tablet	Horse, dog	RA, SS
130	Meloxicam	NSAID	oral suspension, injectable	Horse, dog	-
131.1	Methylprednisolone	Steroid	Injectable, tablet	Horse, dog, cat	ST, SS
131.2	methylprednisolone, aspirin	Steroid, NSAID	tablet	Dog	C, O
132	Naproxen	NSAID	IV, or oral granules	Horse	-

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
133	Orgotein	anti-inflam	injectable	Horse	SS
134.1	phenylbutazone-1	NSAID	IV	Relief of inflam. Conditions assoc. w/ musculoskeletal	-
134.2	phenylbutazone-2	NSAID	Oral	Relief of inflam. Conditions assoc. w/ musculoskeletal	-
135.1	Prednisolone	steroid	tablet	Dog	ST, SS
135.2	prednisolone acetate	steroid	injectable	horse, dog, cat	RA, ST, SS
135.3	prednisolone acetate, neomycin sulfate	steroid, abx	topical	Dog, cat	C, RA, ST, SS
135.4	prednisolone sodium phosphate	steroid	injectable	Dog	ST, SS
135.5	prednisolone sodium phosphate, neomycin sulfate	steroid, abx	ophthalmic	Dog, cat	C, ST, SS
135.6	prednisolone sodium succinate	steroid	injectable	Horse, dog, cat	ST, SS
135.7	prednisolone tertiary butylacetate	steroid	injectable	Horse, dog, cat	ST, SS
135.8	prednisolone, neomycin sulfate	Steroid, abx	ophthalmic	Dog, cat	C, ST, SS
136	Prednisone	steroid	injectable	Horse, dog, cat	ST, SS
137	Stanzolol	steroid	injectable, tablet	Horse, dog, cat	Cl
138	Tepoxalin	NSAID	tablet	Horse, dog, cat	RA
139	triamcinolone	steroid	Oral powder, injectable, topical	Horse, dog, cat	ST, SS
140	Mibolerone	steroid	oral solution, medicated feed	Dog	RA, SS
141	Aspirin (salicylic acid)	NSAID	Oral	management of inflammation	-
142	sodium salicylate	NSAID	-	-	O

Table A3.5 Listing of antiparasitics

	Drug	Drug Type	Dosage Form	Indications	Why Removed
143	Coumaphos	Antiparasitic	Medicated feed	Control of gastrointestinal roundworms	RA
144.1	Eprinomectin-1	Antiparasitic	topical	control of internal and external parasites; gastrointestinal roundworms, lungworms, mites	-
144.2	Eprinomectin-2	Antiparasitic	SC	control of internal and external parasites; gastrointestinal roundworms, lungworms, mites	-
145	Fenbendazole	Antiparasitic	Medicated feed	control/removal of internal parasites	RA
146	Morantel tartrate	Antiparasitic	Medicated feed, bolus	control of internal parasites	RA
147.1	Moxidectin-1	Antiparasitc	topical	treatment and control of external parasites	-
147.2	Moxidectin-2	Antiparasitc	SC	treatment and control of external parasites	-
148	Thiabendazole	Antiparasitc	oral	gastrointestinal parasites	-
149	Albendazole	antiparasitic	Oral suspension, paste	cows: (beef/NLD): control of internal parasites	-
150.1	Amprolium	Antiparasitic/ coccidiostat	oral solution	Cows (calves): treatment/ prevention of coccidiosis	-
150.2	Amprolium	Antipaaitic/cocc idiostat	medicated feed	Cows (calves): treatment/ prevention of coccidiosis	RA
151	Clorsulon	Antiparasitic	Oral drench	cows (beef/NLD): fluke infestation	-
152	decoquinate	Antiparasitic/ coccidiostat	Medicated feed, soluble powder	cows (beef, NLD, calves): coccidiostat	RA
153	doramectin	antiparasitic	IM, SC, topical	cows (beef/NLD): treatment of roundworms; control of internal/external parasites	-
154	famphur	antiparasitic	Medicated feed, topical	beef/NLD: control of external parasites (lice/grubs)	RA

	Drug	Drug Type	Dosage Form	Indications	Why Removed
155	fenthion	antiparasitic	topical	cows (beef/NLD): control of external parasites (lice/grubs)	RA
156	haloxon	antiparasitic	Oral drench, bolus	cows (beef, NLD): control/removal of internal parasites	RA
157.1	ivermectin-1	antiparasitic	IM	gastrointestinal and external parasites	-
157.2	ivermectin-2	antiparasitic	Oral	gastrointestinal and external parasites	-
157.3	ivermectin-3	antiparasitic	SC	gastrointestinal and external parasites	-
157.4	ivermectin-4	antiparasitic	oral	gastrointestinal and external parasites	-
157.5	ivermectin-5	antiparasitic	topical	gastrointestinal and external parasites	-
157.6	ivermectin-6	antiparasitic	oral	gastrointestinal and external parasites	-
157.7	ivermectin, clorsulon	antiparasitic	SC	cows (beef/NLD): control of internal/external parasites	C
158.1	levamisole	antiparasitic	SC, oral powder, topical, bolus, oral gel	cows (beef/NLD): control of internal parasites	-
158.2	levamisole hydrochloride	antiparasitic	oral	gastrointestinal parasites, anthelmintic	-
158.3	levamisole phosphate	antiparasitic	SC	gastrointestinal parasites, anthelmintic	-
158.4	levamisole resinate, famphur	antiparasitic	paste	cows (beef/NLD): control of internal/external parasites	C
159	N-(mercaptomethyl) phthalimide S-(O,O-dimethyl phosphorodithioate)	antiparasitic	topical	cows (beef): control of external parasites	C, RA
160	Oxfendazole-1	antiparasitic	Oral suspension, paste	cows (beef/NLD): control of internal parasites	-
160.1	Oxfendazole-2	antiparasitic	Oral	control of internal parasites	-

	Drug	Drug Type	Dosage Form	Indications	Why Removed
161	clopidol	antiparasitic	Medicated feed	chkn: coccidiostat; turkey: prevention of leucocytozoonosis	RA, SS
162	dichlorvos	antiparasitic	Medicated feed	swine - control of internal parasites	RA, SS
163	diclazuril	antiparasitic	Medicated feed	chkn, turkey - coccidiostat	RA, SS
164	nequinate	coccidiostat	Medicated feed	chkn - coccidiostat	RA, SS
165	halofuginone hydrobromide	anitparasitic	Medicated feed	chkn, turkey - coccidiostat	RA, SS
166	nicarbazin	coccidiostat	Medicated feed	chkn - coccidiostat	RA, SS
167	piperazine	antiparasitic	soluble powder, oral suspension	swine, chkn, turkey - control of internal parasites	RA, SS
168	pyrantel tartrate	antiparasitic	medicated feed, oral powder, pellets	swine - control of internal parasites	RA, SS
169	amitraz	antiparasitic	topical	Dog	RA, SS
170	arsenamide sodium	antiparasitic	injectable	Dog	SS
171	bunamidine hydrochloride	antiparasitic	tablet	Dog, cat	RA, SS
172	butamisole hydrochloride	antiparasitic	injectable	Dog	SS
173	cambendazole	antiparasitic	oral suspension, oral pellets, paste	Horse	RA, SS
174	carnidazole	antiparasitic	tablet	pigeon	RA, SS
175	cythioate	antiparasitic	oral liquid, tablet	Dog	RA, SS
176.1	dichlorophene	antiparasitic	capsule	Dog	RA, SS
176.2	dichlorophene, toluene	antiparasitic	capsule	Dog	C, RA, SS
177.1	diethylcarbamazine citrate	antiparasitic	tablet, syrup, capsule	Dog, cat	RA, SS

	Drug	Drug Type	Dosage Form	Indications	Why Removed
177.2	diethylcarbamazine citrate, oxibendazole	antiparasitic	tablet	Dog	C, RA, SS
178.1	dithiazanine iodide	antiparasitic	tablet, oral powder	Dog	RA, SS
178.2	dithiazanine iodide, piperazine citrate	antiparasitic	oral suspension	Horse	C, RA, SS
179	emodepside, praziquantel	antiparasitic	Topical	Cat	C, RA, SS
180	epsiprantel	antiparasitic	tablet	Dog, cat	RA, SS
181.1	febantel	antiparasitic	paste, oral suspension, tablet	Horse, dog, cat	RA, SS
181.2	febantel, praziquantel	-	paste	Dog, cat	C, RA, SS
182.1	imidacloprid, ivermectin	antiparasitic	topical	Dog	C, RA, SS
182.2	imidacloprid, moxidectin	antiparasitic	topical	Dog, cat	C, RA, SS
183	imidocarb dipropionate	antiparasitic	injectable	Dog, cat	C, SS,
184	lufenuron	antiparasitic	oral suspension, injectable, tablet	Dog, cat	SS
185.1	mebendazole	antiparasitic	oral powder, paste	Horse, dog	RA
185.2	mebendazole, trichlorfon	antiparasitic	oral powder, paste	Horse	C, RA
186	melarsomine dihydrochloride	antiparasitic	injectable	Dog	RA, SS
187.1	milbemycin oxime	antiparasitic	Tablet, topical	Dog, cat	RA, SS
187.2	milbemycin oxime, lufenuron	antiparasitic	Tablet	Dog	C, RA, SS
188	n-butyl chloride	antiparasitic	capsule	Dog, cat	RA, SS

	Drug	Drug Type	Dosage Form	Indications	Why Removed
189	nitenpyram	antiparasitic	tablet	Dog, cat	RA, SS
190	oxibendazole	antiparasitic	oral suspension, paste	horse	RA
191	ponazuril	antiparasitic	paste	horse	RA
192.1	praziquantel	antiparasitic	Injectable, tablet	Dog, cat	RA, SS
192.2	praziquantel, pyrantel pamoate	antiparasitic	tablet	Dog, cat	C, RA, SS
192.2	praziquantel, pyrantel pamoate, febantel	antiparasitic	tablet	Dog, cat	RA, SS
193	selamectin	antiparasitic	topical	Dog, cat	RA, SS
194	spinosad	antiparasitic	tablet	Dog	RA, SS
195	thenium closylate	antiparasitic	tablet	dog	RA, SS
196	tioxidazole	antiparasitic	oral granules, paste	horse	RA
197.1	trichlorfon	antiparasitic	oral granules, bolus	horse	RA
197.2	trichlorfon, atropine	antiparasitic	Oral	Lab mice	RA, SS
197.3	trichlorfon, phenothiazine, piperazine dihydrochloride	antiparasitic	Soluble powder	horse	C, RA

Table A3.6 Listing of antiseptics

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
198	balsam peru oil, castor oil, trypsin	Antiseptic etc.	topical	Wound care	C, RA
199	chlorhexidine	Antiseptic	intrauterine infusion	Metritis, vaginitis	O

Table A3.7 Listing of anesthetic/SED

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
200	sodium thiamylal	Anesthetic	IV	Anesthesia	O
201	thialbarbitone sodium	Anesthetic	IV	Anesthesia	O
202	azaperone	sedative	injectable	swine - control of aggressiveness	SS
203	metoserpate hydrochloride	Sedative	Oral powder	chkn - tranquilizer, control of hysteria	SS
204	tricaine methanesulfonate	anesthetic	Water tx	fish - temporary immobilization	C, SS,
205	acepromazine	tranquilizer	injectable, tablet	horse, dog, cat	RA, SS
206	butorphanol tartrate	analgesic	injectable, tablet	Horse, dog, cat	RA, SS
207	carfentanil citrate	tranquilizer	injectable	cervidae	Cl
208	detomidine	analgesic, sedation	oral, injectable	horse	RA, SS
209	dexmedetomidine	analgesic, sedation	injectable	Dog, cat	RA, SS
210	chloral hydrate, pentobarbital, magnesium sulfate	Anesthetic, sedative	IV	general anethesia, sedative-relaxant	C, O
211	doxapram	anesthetic (resp stim)	injectable	Horse, dog, cat	RA, SS
212	droperidol, fentanyl citrate	anesthesia	injectable	dog	C, RA, SS
213	ethylisobutrazine hydrochloride	tranquilizer	tablet, injectable	dog	RA, SS
214	etorphine hydrochloride	tranquilizer	injectable	Wild/exotic	RA, SS
215	glycopyrrolate	anesthetic	injectable	Dog, cat	RA, SS
216	halothane	anesthesia	inhalant	Non-food animals	RA
217	isoflurane	anesthesia	inhalant	Horse, dog	RA
218.1	ketamine hydrochloride	anesthesia	injectable	cat, subhuman primate	RA, SS

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
218.2	ketamine hydrochloride, promazine hydrochloride, aminopentamide hydrogen sulfate	anesthesia	injectable	cat	C, RA, SS
219	medetomidine hydrochloride	analgesic, sedation	injectable	Dog	RA, SS
220	mepivacaine	anesthesia	injectable	horse	SS
221	methoxyflurane	anesthesia	inhalant	dog	RA, SS
222	oxymorphone hydrochloride	analgesic/anesthesia	injectable	Dog, cat	SS
223	pentazocine lactate	analgesia	injectable	horse	SS
224	promazine hydrochloride	tranquilizer	injectable	horse, dog, cat	SS
226	propiopromazine hydrochloride	tranquilizer	injectable, tablet	Dog, cat	RA, SS
227	propofol	anesthesia	injectable	Dog, cat	RA, SS
228	romifidine	analges/anesth	injectable	horse, dog	RA, SS
229	sevoflurane	anesthesia	inhalant	dog	RA
230	sodium pentobarbital	anesthesia	injectable, capsule, tablet	Horse, dog, cat	NM
231.1	sodium thiopental	anesthesia	injectable	Dog, cat	RA, SS
231.2	sodium thiopental, sodium pentobarbital	anesthesia	injectable	Dog, cat	C, RA
232	tiletamine hydrochloride, zolazepam hydrochloride	anesthesia	injectable	Dog, cat	C, RA, SS
233	trifluprom azine hydrochloride	tranquilizer	injectable, tablet, oral suspension	horse, dog, cat	NM
234	xylaxine	tranquilizer	injectable	horse, dog, cat, elk, deer	RA, SS
235	dipyrone	analgesic/ antipyretic	-	-	Cl

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
236	chlorbutanol	local anesthetic/ Sedative	topical	dog	NM

Table A3.8 Listing of anesth. reversal

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
237	nalorphine hydrochloride	narcotic antagonist	injectable	dog	RA, SS
238	naloxone hydrochloride	narcotic antagonist,	injectable	dog	RA, SS
239	naltrexone hydrochloride	tranquilizer reversal	injectable	Elk, moose	RA
240	diprenorphine hydrochloride	sedation reversal	injectable	Wild/ exotic	RA, SS
241	atipamezole	sedation reversal	injectable	Dogs, Reversal agent used to reversal sedative effects of xylazine	RA, SS,
242	tolazoline hydrochloride	anesth reversal	injectable	horse	SS
243	yohimbine	anesth reversal	injectable	dog, elk, deer	SS

Table A3.9 Listing of diuretics

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
244	furosemide	diuretic	IM, IV, bolus, oral powder	Udder edema	O
245	hydrochlorothiazide	diuretic	IM, IV	Udder edema	O
246	acetazolamide sodium	diuretic	soluble powder, injectable	dog	RA, SS

Table A3.10 Listing of electrolytes

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
247	dextrose/glycine/electrolyte	electrolyte	Soluble powder	cows (calves): dehydration (assoc with scours)	Cl

Table A3.11 Listing of hormones/repro

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
248	Chorionic gonadotropin	Reproductive/ Hormone	IM	treatment of nymphomania (frequent or constant heat) due to cystic ovaries	RGH
249	Cloprostenol sodium	Reproductive/ Hormone	IM	To induce luteolysis; scheduling estrus and ovulation; terminating unwanted pregnancies; tx pyometra	RGH
250	Corticotropin	Endocrine/ Hormone	IM/ SC	Bovine ketosis	RGH
251	dinoprost	Reproductive/ Hormone	IM	To induce luteolysis; scheduling estrus and ovulation; terminating unwanted pregnancies; tx pyometra	RGH
252	follicle stimulating hormone	Reporductive/ Hormone	IM/SC/IV	For induction of superovulation in cows; used as a supplemental source of FSH	RGH
253	gonadorelin	Reproductive/ Hormone	IM/IV	cystic ovaries	RGH
254	iodinated casein	Endocrine/ Hormone	Medicated feed	Increasing milk production	RGH
255	oxytocin	Endocrine/ Hormone	IM/SC/IV	uterine contraction (induction of parturition or postpartum uterine evacuation), milk letdown	RGH
256	pituitary luteinizing hormone	Reproductive/ Hormone	SC/IV	tx of breeding disorders assoc with pituitary hypofunction	RGH
257	progesterone	Reproductive/ Hormone	intravaginal	estrus synchronization	RGH
258	Sometribove zinc	Endocrine/ Hormone	SC	increase milk production	RGH
259.1	estradiol	horomone	implant, SC	cows (steers and heifers only): WG/FE	RGH
259.2	estradiol valerate, norgestomet	reproductive	Implant, IM, SC	For synchronization of estrus/ovulation in cycling beef cows and non-lactating dairy heifers.	RGH

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
260	fenprostalene sodium	reproductive	SC	For feedlot heifers to induce abortion when pregnant 150 days or less. For beef or nonlactating dairy cows for estrus synchronization.	RGH
261	melengestrol	hormone	Medicated feed	cows (beef heifers): WG/FE, suppression of estrus	RA, RGH
262	altrenogest	reproductive	Oral topdress	swine - estrus synchronization	RGH
263	flurogestone acetate	reproductive	intravaginal	sheep - estrus synchronization	RGH
264	alfaprostol	reproductive	injectable	horse	RA
265	deslorelin	reproductive	implant	horse	RA
266	fluprostenol sodium	reproductive	injectable	horse	RA
267	luprostiol	reproductive	injectable	horse	RA
268	prostalene	reproductive	injectable	horse	RA
269	ractopamine	Beta agonist	Medicated feed	cows (fed for slaughter): WG/FE, carcass leanness	RA
270	zilpaterol	Beta agonist	Medicated feed	cows (fed for slaughter): WG/FE	RA
271	diethylstilbestrol (DES)	non-steroidal estrogen	-	historically used in cows rations for WG/FE	Cl
272	melatonin	hormone	injectable	mink	Cl, RGH, SS

Table A3.12 Listing of other drugs

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
273	poloxalene	Surfactant	medicated feed, oral drench, block	treatment and control of bloat	RA
274	cupric glycinate	mineral	SC	cows (beef): copper deficiency/ molybdenum toxicity	Cl

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
275	polyoxyethylene laurel ether	surfactant	block	cows (beef, NLD): reduction of incidence of bloat	Cl
276	selenium, vitamin E	mineral	IM, SC	cows (beef cows, calves): white muscle disease, selenium deficiency	Cl
277	formalin	disinfectant	Water tx	fish - control of parasites and fungi infection	SS
278.1	iron dextran	mineral	Oral solution	swine - iron deficiency	SS
278.2	iron for injection	mineral	Oral solution	swine - iron deficiency	SS
279	neostigmine	anticholinesterase	SC	cows (beef/NLD): rumen atony; initiating peristalsis which causes evacuation of the bowel; emptying the urinary bladder; and stimulating skeletal muscle contractions.	Cl
280	Bc6 recombinant deoxyribonucleic acid (rDNA) construct	recombinant	NA	goat - directing the expression of the human gene for antithrombin (which is intended for the treatment of humans) in the mammary gland of goats derived from lineage progenitor 155–92.	C
281	2-mercaptobenzothiazole	wound care	topical	dog	RA, SS
282	aminopentamide hydrogen sulfate	antispasmotic	tablet, injectable	Dog, cat	RA, SS
283.1	aminopropazine fumarate	antispasmotic	injectable, tablet	horse	Cl, SS
283.2	aminopropazine fumarate, neomycin sulfate	antispasmotic	tablet	Dog, cat	C, Cl, ST, ST
284	beta-aminopropionitrile fumarate	tendonitis tx	injectable	horse	SS
285	caramiphen ethanedisulfonate, ammonium chloride	cough suppressant	tablet	dog	RA, SS
286	clomipramine	anti-depressant	tablet	dog	RA, SS

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
287	cyclosporine	immunosuppressant	capsule, ophthalmic	dog	Cl, RA
288	desoxycorticosterone pivalate	endocrine	injectable	dog	Cl, SS
289	diatrizoate meglumine, diatrizoate sodium	contrast agent	oral solution, injectable	Dog, cat	C, Cl, SS
290	dirlotapide	weight loss	oral solution	Dog, cat	Cl, SS
291	domperidone	tx of fescue toxicosis	oral gel	dog	Cl, SS
292	embutramide, chloroquine, and lidocaine solution	euthanasia	injectable	dog	C, Cl, SS
293	enalapril	cardiac	tablet	dog	RA, SS
294	euthanasia solution (pentobarbitol, phenytoin sodium, secobarbitol, dibucaine hydrochloride)	euthanasia	injectable	dog	Cl, SS
295	fluoxetine	anti-depressant	tablet	dog	Cl, RA, SS
296	fomepizole	antidote (ethylene glycol tox)	injectable	dog	Cl, SS
297	guaifenesin	muscle relaxant	injectable	horse	SS
298	hemoglobin glutamer-200 (bovine)	anemia tx	injectable	dog	SS
299	hyaluronate sodium	osteoarthritis tx	injectable	horse	SS
300	insulin	endocrine	injectable	Dog, cat	Cl, SS
301	liothyronine sodium	endocrine	tablet	dog	RA, SS
302	maropitant	antiemetic	Tablet, injectable	dog	Cl, SS
303	methimazole	endocrine	tablet	cat	RA, RGH, SS
304	methocarbamol	antispasmotic	injectable, tablet	horse, dog, cat	Cl, SS

#	Drug	Drug Type	Dosage Form	Indications	Why Removed
305	N-butylscopolammonium bromide	antispasmotic	injectable	horse	SS
306	oleate sodium		injectable	horse	SS
307	omeprazole	enzyme inhibitor (GI dz)	paste	horse	RA
308	pimobendan	cardiac	tablet	dog	RA, SS
309	polysulfated glycosaminoglycan	osteoarthritis tx	injectable	Horse, dog	SS
310	pralidoxime chloride	antidote	injectable	Horse, dog	RA, SS
311	primidone	anticonvulsant	tablet	dog	RA, SS
312	Prochlorprazine, isopropamide	antiemetic	capsule, injectable	dog	C, Cl, SS
312.1	prochlorperazine, isopropamide, neomycin	antiemetic	capsule	dog	C, Cl, SS
313	selegiline hydrochloride	endocrine	Tablet	dog	RA, SS
314	toceranib	mast cell tumor tx	Tablet	dog	RA, SS
315	trilostane	endocrine	Capsule	dog	RA, RGH, SS
316	zinc gluconate	chemical castration	Injectable	dog	Cl, SS
317	adenosine monophosphate	nucleotide	-	-	NM
318	ammonium sulfate	chemical	-	used in cows rations	NM
319	carbamolcholine chloride	cholinomimetic	-	-	NM
320	D-panthenol (dexpanthenol)	cholinergic	-	-	NM
321	methylene blue	bacteriologic stain, antidote in cyanide poisoning	topical	Bacteriological stain, antidote for cyanide poisoning	RA

C=combination drug; RA=route of administration; CI=contra-indicated; SS=species specific; RGH=reproductive drug/hormone ST=steroid; NM=not marketed in U.S; O=other (no discard time, no tolerance)
NLD: Non-lactating dairy cows

APPENDIX 3.2: SELECTED 54 DRUGS (INCLUDING 99 FORMULATIONS, APPROVAL STATUS, MARKETING STATUS, AND ROUTE OF ADMINISTRATION)

Table A3.13 The selected 54 drugs (including various formulations (total 99), approval status, marketing status, and route of administration)

#	54 Drugs	Drug Formulation	Approval Status [1]	Market Status [2]	Route of Administration [3]
1	**Acetylsalicylic acid**	Acetylsalicylic acid	Not approved in food-producing animals	OTC	Oral
2	**Albendazole**	Albendazole	Approved in cows, not approved in lactating dairy cows	OTC	Oral
3	**Amikacin**	Amikacin sulfate-1	Not approved in food-producing animals	Rx	Intrauterine
	Amikacin	Amikacin sulfate-2	Not approved in food-producing animals	Rx	Intramuscular or subcutaneous
4.1	**Amoxicillin**	Amoxicillin trihydratetrihydrate-1	Approved in lactating dairy cows	Rx	Intramuscular or subcutaneous
4.2	**Amoxicillin**	Amoxicillin trihydrate-2	Approved in cows, not approved in lactating dairy cows	Rx	Oral, drench
4.3	**Amoxicillin**	Amoxicillin trihydrate-3	Approved in lactating dairy cows	Rx	Intramammary
5.1	**Ampicillin**	Ampicillin sodium	Not approved in food-producing animals	Rx	Intravenous or intramuscular
5.2	**Ampicillin**	Ampicillin trihydrate-1	Approved in Cows (no use class stated)	Rx	Intramuscular, subcutaneous
5.3	**Ampicillin**	Ampicillin trihydrate-2	Approved in cows, not approved in lactating dairy cows	Rx	Oral
5.4	**Ampicillin**	Ampicillin trihydrate-3	Approved in cows, not approved in lactating dairy cows	Rx	Intramuscular
6	**Amprolium**	Amprolium	Approved in cows, not approved in lactating dairy cows	OTC	Oral
7.1	**Ceftiofur**	Ceftiofur crystalline free acid	Approved in lactating dairy cows	Rx	Intramuscular or subcutaneous
7.2	**Ceftiofur**	Ceftiofur hydrochloride-1	Approved in lactating dairy cows	Rx	Intramuscular or subcutaneous
7.3	**Ceftiofur**	Ceftiofur hydrochloride-2	Approved in lactating dairy cows	Rx	Intramammary
7.4	**Ceftiofur**	Ceftiofur sodium	Approved in lactating dairy cows	Rx	Intramuscular or subcutaneous
8.1	**Cephapirin**	Cephapirin benzathine	Approved in cows (dry cows)	OTC	Intramammary
8.2	**Cephapirin**	Cephapirin sodium	Approved in lactating dairy	OTC	Intramammary

Appendix 3.2: Selected 54 Drugs (Including 99 Formulations, approval status, marketing status, and route of administration) |

#	54 Drugs	Drug Formulation	Approval Status [1]	Market Status [2]	Route of Administration [3]
			cows		
9.1	**Chloram-phenicol**	Chloramphenicol -1	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Oral
9.2	**Chloram-phenicol**	Chloramphenicol -2	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Intravenous or intramuscular
9.3	**Chloram-phenicol**	Choramphenicol-3	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Ophthalmo-logic
10	**Clorsulon**	Clorsulon	Approved in cows, not approved in lactating dairy cows	OTC	Oral, drench
11.1	**Cloxacillin**	Cloxacillin benzathine	Approved in lactating dairy cows	Rx	Intramammary
11.2	**Cloxacillin**	Cloxacillin sodium	Approved in lactating dairy cows	Rx	Intramammary
12	**Danofloxacin**	Danofloxacin mesylate	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Subcutaneous
13	**Dihydrostrepto-mycin**	Dihydrostreptomycin sulfate	Approved in cows, not approved in lactating dairy cows	OTC, Rx	Intramuscular
14	**Doramectin**	Doramectin	Approved in cows, not approved in lactating dairy cows	OTC	Subcutaneous, intramuscular, or topical
15	**Enrofloxacin**	Enrofloxacin	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Subcutaneous
16.1	**Eprinomectin**	Eprinomectin-1	Approved in lactating dairy cows	OTC	Topical
16.2	**Eprinomectin**	Eprinomectin-2	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous
17.1	**Erythromycin**	Erythromycin-1	Approved in cows, not approved in lactating dairy cows	OTC	Intramuscular
17.2	**Erythromycin**	Erythromycin-2	Approved in lactating dairy cows	OTC	Intramammary
18.1	**Florfenicol**	Florfenicol-1	Approved in cows, not approved in lactating dairy cows	Rx	Intramuscular or subcutaneous
18.2	**Florfenicol**	Florfenicol-2	Approved in other food producing animals	Rx	Oral
18.3	**Florfenicol**	Florfenicol-3	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous
19.1	**Flunixin**	Flunixin meglumine-1	Approved in lactating dairy cows	Rx	Intravenous

Appendix 3.2: Selected 54 Drugs (Including 99 Formulations, approval status, marketing status, and route of administration) |

#	54 Drugs	Drug Formulation	Approval Status [1]	Market Status [2]	Route of Administration [3]
19.2	**Flunixin**	Flunixin meglumine-2	Not approved in food-producing animals	Rx	Intramuscular/ intravenous or oral
20	**Furazolidone**	Furazolidone	Prohibited for ELDU in food-producing animals (AMDUCA)	OTC	Topical
21	**Gamithromycin**	Gamithromycin	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous, in neck
22.1	**Gentamicin**	Gentamicin sulfate-1	Approved in lactating dairy cows	OTC	Ophthalmo-logic
22.2	**Gentamicin**	Gentamicin sulfate-2	Not approved in food-producing animals	Rx	Intrauterine, intramuscular, intrasynovial
23	**Hetacillin**	Hetacillin potassium	Approved in lactating dairy cows	Rx	Intramammary
24.1	**Ivermectin**	Ivermectin-1	Approved in cows, not approved in lactating dairy cows	Rx	Intramuscular
24.2	**Ivermectin**	Ivermectin-2	Not approved in food-producing animals	Rx, OTC	Oral
24.3	**Ivermectin**	Ivermectin-3	Approved in cows, not approved in lactating dairy cows	OTC, Rx	Subcutaneous
24.4	**Ivermectin**	Ivermectin-4	Approved in cows, not approved in lactating dairy cows	OTC	Oral
24.5	**Ivermectin**	Ivermectin-5	Approved in cows, not approved in lactating dairy cows	OTC	Topical
24.6	**Ivermectin**	Ivermectin-6	Approved in cows, not approved in lactating dairy cows	OTC	Oral
25.1	**Kanamycin**	Kanamycin	Not approved in food-producing animals	Rx	Ophthalmo-logic
25.2	**Kanamycin**	Kanamycin sulfate	Not approved in food-producing animals	Rx	Subcutaneous or intramuscular
26	**Ketoprofen**	Ketoprofen	Not approved in food-producing animals	Rx	Intravenous
27.1	**Levamisole**	Levamisole	Approved in cows, not approved in lactating dairy cows	OTC	Topical
27.2	**Levamisole**	Levamisole hydrochloride	Approved in cows, not approved in lactating dairy cows	OTC	Oral
27.3	**Levamisole**	Levamisole phosphate	Approved in cows, not approved in lactating dairy cows	OTC	Subcutaneous
28.1	**Lincomycin**	Lincomycin	Approved in other food	OTC	Oral

Appendix 3.2: Selected 54 Drugs (Including 99 Formulations, approval status, marketing status, and route of administration) |

#	54 Drugs	Drug Formulation	Approval Status [1]	Market Status [2]	Route of Administration [3]
		hydrochloride	producing animals		
28.2	**Lincomycin**	Lincomycin hydrochloride monohydrate	Approved in other food producing animals	Rx, OTC	Intramuscular, intravenous
29	**Meloxicam**	Meloxicam	Not approved in food-producing animals	Rx	Oral, intravenous, subcutaneous
30.1	**Moxidectin**	Moxidectin-1	Approved in lactating dairy cows	OTC	Topical
30.2	**Moxidectin**	Moxidectin-2	Approved in cows, not approved in lactating dairy cows	OTC	Subcutaneous
31	**Naproxen**	Naproxen	Not approved in food-producing animals	Rx	Oral or intravenous
32	**Neomycin**	Neomycin sulfate	Approved in cows, not approved in lactating dairy cows	OTC	Oral
33	**Nitrofurazone**	Nitrofurazone	Prohibited for ELDU in food-producing animals (AMDUCA)	OTC	Topical
34	**Novobiocin**	Novobiocin sodium	Approved in cows (dry cows), not approved in lactating dairy cows	Rx, OTC	Intramammary
35.1	**Oxfendazole**	Oxfendazole-1	Not approved in food-producing animals	Rx, OTC	Oral
35.2	**Oxfendazole**	Oxfendazole-2	Approved in cows, not approved in lactating dairy cows	Rx, OTC	Oral
36.1	**Oxytetracycline**	Oxytetracycline hydrochloride-1	Approved in cows, not approved in lactating dairy cows	OTC	Oral
36.2	**Oxytetracycline**	Oxytetracycline hydrochloride-2	Approved in cows, not approved in lactating dairy cows	OTC, Rx	Intravenous, intramuscular, or subcutaneous
36.3	**Oxytetracycline**	Oxytetracycline-3	Approved in lactating dairy cows	Rx, OTC	Intravenous, intramuscular, or subcutaneous
37.1	**Penicillin**	Penicillin g procaine-1	Approved in lactating dairy cows	OTC, Rx	Intramuscular
37.2	**Penicillin**	Penicillin g procaine-2	Approved in lactating dairy cows	OTC	Intramammary
37.3	**Penicillin**	Penicillin g procaine-3	Not approved in food-producing animals	OTC	Intramuscular
37.4	**Penicillin**	Penicillin G benzathine & Penicillin G Procaine	Approved in cows, not approved in lactating dairy cows	Rx, OTC	Subcutaneous or intramuscular
38.1	**Phenylbuta-zone**	Phenylbutazone-1	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Intravenous

Appendix 3.2: Selected 54 Drugs (Including 99 Formulations, approval status, marketing status, and route of administration) |

#	54 Drugs	Drug Formulation	Approval Status [1]	Market Status [2]	Route of Administration [3]
38.2	**Phenylbuta-zone**	Phenylbutazone-2	Prohibited for ELDU in food-producing animals	Rx	Oral
39	**Pirlimycin**	Pirlimycin hydrochloride	Approved in lactating dairy cows	Rx	Intramammary
40.1	**Spectinomycin**	Spectinomycin hydrochloride	Approved in other food producing animals	Rx, OTC	Intramuscular, subcutaneous, or oral
40.2	**Spectinomycin**	Spectinomycin sulfate	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous, in neck
41	**Streptomycin sulfate**	Streptomycin sulfate	Approved in cows, not approved in lactating dairy cows	OTC	Oral
42	**Sulfabromo-methazine**	Sulfabromomethazine sodium	Approved in lactating dairy cows	OTC	Oral, bolus
43.1	**Sulfachlor-pyridazine**	Sulfachlorpyridazine-1	Prohibited for ELDU in food-producing animals (AMDUCA)	OTC	Oral
43.2	**Sulfachlor-pyridazine**	Sulfachlorpyridazine-2	Prohibited for ELDU in food-producing animals (AMDUCA)	OTC	Intravenous
44.1	**Sulfa-dimethoxine**	Sulfadimethoxine-1	Approved in lactating dairy cows	OTC	Oral, bolus
44.2	**Sulfa-dimethoxine**	Sulfadimethoxine-2	Approved in lactating dairy cows	OTC	Intravenous and subcutaneous
44.3	**Sulfa-dimethoxine**	Sulfadimethoxine-3	Approved in cows, not approved in lactating dairy cows	Rx	Oral, bolus
45.1	**Sulfaethoxy-pyridazine**	Sulfaethoxypyridazine -1	Approved in lactating dairy cows	Rx	Oral
45.2	**Sulfaethoxy-pyridazine**	Sulfaethoxypyridazine -2	Approved in lactating dairy cows	Rx	Intravenous
45.3	**Sulfaethoxy-pyridazine**	Sulfaethoxypyridazine -3	Prohibited for ELDU in food-producing animals (AMDUCA)	Rx	Oral
46.1	**Sulfamethazine**	Sulfamethazine-1	Approved in cows, not approved in lactating dairy cows	OTC	Intravenous
46.2	**Sulfamethazine**	Sulfamethazine-2	Approved in cows, not approved in lactating dairy cows	OTC	Oral
46.3	**Sulfamethazine**	Sulfamethazine-3	Approved in cows, not approved in lactating dairy cows	OTC	Oral
47	**Sulfaquin-oxaline**	Sulfaquinoxaline	Prohibited for ELDU in food-producing animals (AMDUCA)	OTC	Oral, drench
48.1	**Tetracycline**	Tetracycline Hydrochloride-1	Not approved in food-producing animals	OTC	Oral
48.2	**Tetracycline**	Tetracycline	Not approved in food-	Rx	Topical

Appendix 3.2: Selected 54 Drugs (Including 99 Formulations, approval status, marketing status, and route of administration) |

#	54 Drugs	Drug Formulation	Approval Status [1]	Market Status [2]	Route of Administration [3]
		hydrochloride-2	producing animals		
49	**Thiabendazole**	Thiabendazole-2	Approved in lactating dairy cows	OTC	Oral, drench, paste, medicated feed
50	**Tildipirosin**	Tildipirosin	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous
51	**Tilmicosin phosphate**	Tilmicosin phosphate	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous or intrammary
52	**Tripelennamine**	Tripelemamine	Approved in lactating dairy cows	Rx	Intramuscular, intravenous
53	**Tulathromycin**	Tulathromycin	Approved in cows, not approved in lactating dairy cows	Rx	Subcutaneous
54	**Tylosin**	Tylosin-2	Approved in cows, not approved in lactating dairy cows	OTC	Intramuscular

OTC=over the counter; Rx=prescription; NE=Not established
[1] Source: 21 CFR 500-599 (check)
[2] Source: 21 CFR 500-599, NADA). If the drug is not approved, it is assumed for the purpose of this analysis that the drug is sold OTC.
[3] Ibid.
[4] Persistence of approved drugs can be found in http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=558. Persistence of unapproved drugs was determined from scientific literature. For detailed reference, see Appendix 5.10.

APPENDIX 4.1: EXCLUDED DAIRY PRODUCTS FOR EVALUATION

Due to the lack of protein-binding data, we decided not to evaluate protein-enriched dairy powders, such as whey-protein concentrate and milk-protein concentrate, in the model. Without a proper estimate for the absolute and relative binding properties of drug residues to different protein components of milk, incorporation of these products into the multicriteria-based ranking model may have led to erroneous conclusions. Moreover, accurate serving-size estimates for products such as whey-protein powders are difficult to obtain, because they are not regularly included in standard databases, such as the National Health and Nutrition Examination Survey (NHANES) (CDC, 2011). However, such products are reconstituted prior to consumption; therefore, the absolute amount consumed of the concentrated product is likely low, contributing to our decision to exclude them.

We also did not evaluate "special" products, such as Greek yogurt or fortified products separately in the processing part of the model, because these products are adequately captured by the overall 12 categories we selected, and potential differences from these "archetypical" products cannot be captured by the multicriteria-based ranking model. For instance, at the same fat level, Greek yogurt typically has more protein than traditional yogurt (USDA/ARS 2011) (see also http://www.diffen.com/difference/Greek_Yogurt_vs_Regular_Yogurt). However, because we do not consider protein-binding data in the model, we do not expect significant differences between traditional yogurt and Greek yogurt at the same fat level in the model, in terms of drug-residue concentration.

We decided not to evaluate infant formula in our multicriteria-based ranking model. Although it is important to evaluate the public-health risks associated with the potential presence of drug residues in infant formula, because it is widely consumed by a highly susceptible subgroup, we decided to exclude it from our model, based on the following analysis.

Almost all dairy-based infant-formula products on the U.S. market are formulated with vegetable oil instead of dairy-based fats (based on review of ingredient lines of infant formulas on the U.S. market and internal communication with FDA's infant-formula subject-matter expert) (memo from an internal FDA meeting on November 9, 2012). Therefore, for drug residues that partition mostly in the milk-fat phase, minimum concentrations of residue would be expected in infant formula. Most commercial dairy-based infant formulas contain non-fat dairy-protein ingredients, such as non-fat dry milk, whey powder, whey-protein concentrate, milk-protein concentrate, or hydrolyzed milk-protein concentrate ((based on review of ingredient lines of infant formulas on the U.S. market and internal communication with FDA's infant-formula subject-matter expert).

In terms of protein, reconstituted or ready-to-drink (ready-to-feed) infant formula typically has about 2% protein or less (Codex 2011). The protein level is lower than the level in cow's milk (about 3.3%). The whey-to-casein ratio in cow's milk is about 20:80, while that in human milk is about 60:40 (Blanchard *et al*., 2013). Most of the infant formula is formulated with a variety of dairy-protein ingredients, to mimic the 60:40 casein-to-whey ratio (Blanchard *et al*., 2013). Therefore, both the protein content and the protein profile (e.g. whey-to-casein ratio) of infant formula (ready-to-drink basis) are generally considerably different from those of cow's milk.

To generate adequate predictions of drug-residue concentration based on protein content and protein profile (*e.g.,* whey-to-casein ratio), data on drug binding to milk-protein fractions are critical. However, such data are very limited in the literature. In addition, many of these non-fat dairy proteins used for infant formula, such as protein hydrolysates, caseinates, milk-protein concentrates, and whey-protein concentrates, go through extensive processing (Bargeman, 2003). Very limited data are available on the impact of these types of processing conditions on drug-residue concentrations. Some limited study of penicillin (a drug that partitions mostly in the water phase of milk) suggests that penicillin is greatly reduced after ultrafiltration and diafiltration (Cayle *et al*., 1986; Kosikowski and Jimenez-Flores, 1985), which are typical processing steps used during the manufacturing of whey-protein concentrates and milk- protein concentrates (Bargeman, 2003).

For water-soluble drugs, non-fat dry milk is likely the only significant ingredient that can contribute to drug residues in infant formula. However, for most infant formula, if non-fat dry milk is used as an ingredient, whey-protein concentrate is typically added to increase the ratio of whey to casein, to mimic the ratio found in human milk (as noted, whey-to-casein ratio is about 20:80 in cow's milk and about 60:40 in human milk) (Blanchard *et al.,* 2013). Thus, with only a few exceptions, non-fat dry milk is unlikely to be the sole contributor of dairy proteins in infant formula.

Therefore, under the most conservative assumption – *i.e.,* that all of the drug is bound to milk protein (no preferential binding to individual milk-protein fractions) or that all of the protein is contributed by non-fat dry milk – the maximum drug-residue concentration in reconstituted infant formula would be about 60% of the level in the initial "raw" milk (*i.e.,* changing from 3.3% to 2%). However, in reality, based on the above analysis, the levels are likely to be much lower. Because of the lack of data on drug binding to milk protein; the unknown impact of processing used for the various types of protein ingredients in infant formula; and the lower protein concentration in infant formula on a ready-to-drink infant formula, compared with that in "raw" milk, we excluded infant formula from this multicriteria-based ranking.

APPENDIX 5.1: SUMMARY OF THE RESULTS FROM THE EXPERT ELICITATION

A modified Delphi approach, which included two rounds of expert elicitation and one live webinar between rounds to discuss results from the first round of elicitation, was chosen for this expert elicitation. Two panels of 9 experts each were assembled – one to address drug-specific knowledge gaps related to the likelihood and magnitude of drug administration and the likelihood of residue contamination of the on-farm bulk-tank milk, and the second to address the relative importance of criteria and sub-criteria contained in FDA's multicriteria-based ranking model and to inform weighting used in the model. The method for expert identification, the applied selection criteria, and the composition of the two panels is detailed in the reference (Versar 2014). Also included in the reference is a description of the process used to derive and pilot-test the questions for both rounds of elicitation, a description of the software platform and the timeframe of the expert elicitation, a summary of the background information provided to the experts prior to the elicitation, a description of the webinar content, and changes made in response to the webinar discussions. In short, panel 1 was asked to answer a total 6 questions, of which 5 questions required an answer for each of 54 drugs included in the multicriteria-based ranking, whereas panel 2 was asked to answer 5 questions related to the relative importance of the overall model criteria as well as model sub-criteria. Detailed results for both rounds of elicitation as well as changes between first and second round of elicitation for both panels are provided in the reference. A short summary of the most pertinent round 2 results for panels 1 and 2 is provided below.

Table A5.1 Responses[a] of 9 experts (A – I) regarding relative importance of model criteria

Model criteria	A	B	C	D	E	F	G	H	I
Likelihood and magnitude of drug use in dairy cows	2	1	1	5	1	4	1	1	1
Likelihood of drug residues entering on farm bulk milk tank (given drug administration to dairy cows)	1	2	2	1	3	1	3	5	2
Impact of processing on drug residue in the milk supply	5	5	5	3	2	5	4	4	5
Magnitude of consumption of dairy products	4	4	3	2	4	2	2	2	3
Health effects from human exposure	3	3	4	4	5	3	5	3	4

a: 1 being the most important criterion (please see Versar (2014) for sub-criteria weighting and additional details)

Table A5.2 Overview of responses, Panel 1, round 2, for 9 experts and questions 1 – 5

Explanation of result categories:
A = zero probability; B = low probability (> 0 – 25%); C = moderate probability (>50% - 75%); D = high probability (> 75% probability); E = very high probability (> 75% probability); F = no response;

G = negligible; H = infrequent (2-5 x/ year); I=moderate (6-30x / year); J = high (> 30x / year); K = no response;

L= negligible (< 1%); M = low (1 – 25%); N = moderate (> 25- 50%); O= high (>50 – 75 %); P= very high (> 75%); Q= no response;

R= negligible (<0.1%); S=low (0.1 – 2%); T=moderate (>2 – 5%); U= high (>5 – 10%); V=very high (> 10%); W= no response.

Please see Versar 2014 for more details and for round 1 results.

Table A5.2 Distribution of 9 expert responses for 54 drugs in response to question 1. Percentage of dairy herds to which drug is administered during calendar year

Drugs	A	B	C	D	E	F
Acetylsalicylic Acid	-	3	4	-	1	1
Albendazole	-	4	1	-	-	4
Amikacin	4	1	-	-	-	4
Amoxicillin	-	6	-	1	1	1
Ampicillin	-	-	5	2	2	-
Amprollium	3	2	-	-	-	4
Ceftiofur	-	-	1	3	5	-
Cephapirin	-	-	2	6	1	-
Chloramphenicol	6	2	-	-	-	1
Clorsulon	-	3	-	-	-	6
Cloxacillin	-	7	-	1	-	1
Danofloxacin	2	3	1	-	-	3
Dihydrostreptomycin	2	1	5	-	-	1
Doramectin	1	3	1	-	-	4
Enrofloxacin	2	6	-	-	-	1

Drugs	A	B	C	D	E	F
Eprinocectin	-	2	2	2	-	3
Erythromycin	2	4	1	-	-	2
Florfenicol	-	5	3	-	-	1
Flunixin	-	-	2	2	4	1
Furazolidone	4	2	-	-	-	3
Gamithromycin	-	4	1	-	-	4
Gentamicin	1	7	-	-	-	1
Hetacillin	-	4	3	-	-	2
Ivermectin	-	4	1	2	-	2
Kanamycin	2	2	-	-	-	5
Ketoprofen	4	3	-	-	-	2
Levamisole	1	3	-	-	-	5
Lincomycin	-	5	1	-	-	3
Meloxicam	-	5	2	-	-	2
Moxidectin	-	2	3	1	-	3
Naproxen	4	-	-	-	-	5
Neomycin	1	7	-	-	-	1
Nitrofurazone	4	2	-	-	-	3
Novobiocin	-	7	-	-	-	2
Oxfendazole	-	3	-	-	-	6
Oxytetracycline	-	1	2	4	2	-
Penicillin G	-	-	2	5	2	-
Phenylbutazone	3	5	-	-	-	1
Pirlimycin	-	4	2	2	-	1
Spectinomycin	-	8	-	-	-	1
Streptomycin	-	5	-	-	-	4
Sulfabromomethazine	2	-	-	-	-	7
Sulfachlorphyridazine	1	2	-	-	-	6
Sulfadimethoxine	-	3	3	1	-	2
Sulfaethoxypyridazine	2	-	-	-	-	7

Drugs	A	B	C	D	E	F
Sulfamethazine	1	6	-	-	-	2
Sulfaquinoxaline	2	-	-	-	-	7
Tetracycline	-	-	5	3	1	-
Thiabendazole	2	1	-	-	-	6
Tildipirosin	-	3	-	-	-	6
Tilmicosin	-	7	-	1	-	1
Tripelemamine	2	3	-	-	-	4
Tulathromycin	-	6	-	1	-	2
Tylosin	-	6	-	1	-	2

Table A5.3 Distribution of 9 expert responses for 54 drugs in response to question 2. Percentage of dairy cows within herds to which drug is administered during calendar year

Drugs	A	B	C	D	E	F
Acetylsalicylic Acid	-	5	3	-	-	1
Albendazole	-	2	1	2	-	4
Amikacin	4	1	-	-	-	4
Amoxicillin	-	4	-	2	2	1
Ampicillin	-	5	3	1	-	-
Amprollium	3	2	-	-	-	4
Ceftiofur	-	-	1	7	1	-
Cephapirin	-	-		5	4	-
Chloramphenicol	6	2	-	-	-	1
Clorsulon	-	3	-	-	-	6
Cloxacillin	-	-	3	3	2	1
Danofloxacin	2	3	1	-	-	3
Dihydrostreptomycin	1	-	-	1	6	1
Doramectin	1	2	-	2	-	4
Enrofloxacin	2	6	-	-	-	1
Eprinocectin	-	-	-	3	3	3
Erythromycin	1	5	1	-	-	2

Drugs	A	B	C	D	E	F
Florfenicol	-	6	2	-	-	1
Flunixin	-	3	4	1	-	1
Furazolidone	4	2	-	-	-	3
Gamithromycin	-	4	1	-	-	4
Gentamicin	1	6	1	-	-	1
Hetacillin	-	3	2	2	-	2
Ivermectin	-	2	-	3	2	2
Kanamycin	1	3	-	-	-	5
Ketoprofen	4	3	-	-	-	2
Levamisole	1	3	-	-	-	5
Lincomycin	-	6	-	-	-	3
Meloxicam	-	7	-	-	-	2
Moxidectin	-	-	1	2	3	3
Naproxen	4	-	-	-	-	5
Neomycin	1	7	-	-	-	1
Nitrofurazone	4	2	-	-	-	3
Novobiocin	-	1	-	1	5	2
Oxfendazole	-	3	-	-	-	6
Oxytetracycline	-	5	2	2	-	-
Penicillin G	-	4	1	2	2	-
Phenylbutazone	3	5	-	-	-	1
Pirlimycin	-	5	2	1	-	1
Spectinomycin	-	7	1	-	-	1
Streptomycin	-	5	-	-	-	4
Sulfabromomethazine	2	-	-	-	-	7
Sulfachlorphyridazine	1	2	-	-	-	6
Sulfadimethoxine	-	6	1	-	-	2
Sulfaethoxypyridazine	2	-	-	-	-	7
Sulfamethazine	1	6	-	-	-	2
Sulfaquinoxaline	2	-	-	-	-	7

Drugs	A	B	C	D	E	F
Tetracycline	-	6	2	1	-	-
Thiabendazole	2	1	-	-	-	6
Tildipirosin	-	3	-	-	-	6
Tilmicosin	-	7	-	1	-	1
Tripelemamine	2	3	-	-	-	4
Tulathromycin	-	6	-	1	-	2
Tylosin	-	6	1	-	-	2

Table A5.4 Distribution of 9 expert responses for 54 drugs in response to question 3. Average number of treatments per year

Drugs	G	H	I	J	K
Acetylsalicylic Acid	4	2	2	-	1
Albendazole	3	2	-	-	4
Amikacin	4	1	-	-	4
Amoxicillin	2	5	-	1	1
Ampicillin	-	7	1	1	-
Amprollium	5	-	-	-	4
Ceftiofur	1	4	3	1	-
Cephapirin	1	6	1	1	-
Chloramphenicol	8	-	-	-	1
Clorsulon	3	-	-	-	6
Cloxacillin	4	2	1	1	1
Danofloxacin	5	-	1	-	3
Dihydrostreptomycin	4	4	-	-	1
Doramectin	4	1	-	-	4
Enrofloxacin	6	2	-	-	1
Eprinocectin	3	3	-	-	3
Erythromycin	3	4	-	-	2
Florfenicol	3	4	1	-	1
Flunixin	1	3	4	-	1

Drugs	G	H	I	J	K
Furazolidone	6	-	-	-	3
Gamithromycin	3	2	-	-	4
Gentamicin	5	3	-	-	1
Hetacillin	4	1	2	-	2
Ivermectin	3	4	-	-	2
Kanamycin	3	1	-	-	5
Ketoprofen	6	1	-	-	2
Levamisole	4	-	-	-	5
Lincomycin	5	1	-	-	3
Meloxicam	3	3	1	-	2
Moxidectin	3	3	-	-	3
Naproxen	4	-	-	-	5
Neomycin	6	2	-	-	1
Nitrofurazone	5	1	-	-	3
Novobiocin	2	5	-	-	2
Oxfendazole	1	2	-	-	6
Oxytetracycline	2	4	2	1	-
Penicillin G	1	6	1	1	-
Phenylbutazone	6	2	-	-	1
Pirlimycin	2	4	2	-	1
Spectinomycin	3	5	-	-	1
Streptomycin	2	3	-	-	4
Sulfabromomethazine	2	-	-	-	7
Sulfachlorphyridazine	3	-	-	-	6
Sulfadimethoxine	4	2	1	-	2
Sulfaethoxypyridazine	2	-	-	-	7
Sulfamethazine	5	2	-	-	2
Sulfaquinoxaline	2	-	-	-	7
Tetracycline	2	5	2	-	-
Thiabendazole	3	-	-	-	6

Drugs	G	H	I	J	K
Tildipirosin	-	3	-	-	6
Tilmicosin	4	3	1	-	1
Tripelemamine	4	1	-	-	4
Tulathromycin	4	2	1	-	2
Tylosin	2	4	1	-	2

Table A5.5 Distribution of 9 expert responses for 54 drugs in response to question 4. Likelihood of drug entering cow's milk after administration

Drugs	L	M	N	O	P	Q
Acetylsalicylic Acid	3	2	1	1	1	1
Albendazole	-	-	2	-	2	5
Amikacin	1	-	2	2	-	4
Amoxicillin	-	-	4	-	4	1
Ampicillin	-	-	3	2	4	-
Amprollium	1	-	2	-	-	6
Ceftiofur	-	-	2	3	4	-
Cephapirin	-	-	1	2	6	-
Chloramphenicol	-	1	1	4	2	1
Clorsulon	-	-	2	-	1	6
Cloxacillin	-	-	2	-	6	1
Danofloxacin	-	-	1	2	3	3
Dihydrostreptomycin	1	2	-	-	5	1
Doramectin	-	-	1	1	3	4
Enrofloxacin	-	-	1	3	4	1
Eprinocectin	3	2	-	1	-	3
Erythromycin	-	-	1	2	4	2
Florfenicol	-	1	3	2	2	1
Flunixin	-	-	3	1	4	1
Furazolidone	2	-	3	-	-	4
Gamithromycin	-	-	1	2	2	4
Gentamicin	1	-	2	1	4	1

Drugs	L	M	N	O	P	Q
Hetacillin	-	-	1	1	5	2
Ivermectin	-	-	2	3	2	2
Kanamycin	1	1	-	-	2	5
Ketoprofen	-	-	4	1	1	3
Levamisole	-	-	2	-	1	6
Lincomycin	-	-	3	1	1	4
Meloxicam	-	-	2	1	4	2
Moxidectin	1	3	1	1	-	3
Naproxen	-	1	1	-	1	6
Neomycin	3	1	2	1	1	1
Nitrofurazone	2	-	3	-	-	4
Novobiocin	-	2	-	1	4	2
Oxfendazole	-	-	-	1	1	7
Oxytetracycline	-	1	1	2	5	-
Penicillin G	-	-	2	2	5	-
Phenylbutazone	-	-	2	2	3	2
Pirlimycin	-	-	1	2	5	1
Spectinomycin	-	2	2	3	1	1
Streptomycin	-	2	2	-	1	4
Sulfabromomethazine	-	-	2	-	1	6
Sulfachlorphyridazine	-	-	2	1	1	5
Sulfadimethoxine	-	2	1	3	2	1
Sulfaethoxypyridazine	-	-	2	-	1	6
Sulfamethazine	-	2	3	2	1	1
Sulfaquinoxaline	-	-	2	-	1	6
Tetracycline	-	-	2	3	4	-
Thiabendazole	-	-	1	-	1	7
Tildipirosin	-	-	-	1	2	6
Tilmicosin	-	1	-	3	4	1
Tripelemamine	1	-	-	-	1	7

Drugs	L	M	N	O	P	Q
Tulathromycin	-	-	1	1	5	2
Tylosin	-	1	2	2	2	2

Table A5.6 Distribution of 9 expert responses for 54 drugs in response to question 5. Likelihood of contaminated milk entering bulk-milk tank

Drugs	R	S	T	U	V	W
Acetylsalicylic Acid	4	3	-	-	1	1
Albendazole	-	1	2	-	1	5
Amikacin	1	1	3	-	-	4
Amoxicillin	1	4	1	2	-	1
Ampicillin	1	5	-	3	-	-
Amprollium	1	2	-	-	-	6
Ceftiofur	2	2	2	3	-	-
Cephapirin	1	5	-	3	-	-
Chloramphenicol	2	2	2	1	1	1
Clorsulon	-	1	2	-	-	6
Cloxacillin	1	4	2	1	-	1
Danofloxacin	-	2	3	1	-	3
Dihydrostreptomycin	3	3	2	-	-	1
Doramectin	-	1	2	-	2	4
Enrofloxacin	-	1	5	2	-	1
Eprinocectin	2	3	-	1	-	3
Erythromycin	-	3	4	-	-	2
Florfenicol	-	2	5	1	-	1
Flunixin	-	2	4	2	-	1
Furazolidone	3	1	1	-	-	4
Gamithromycin	-	2	2	-	1	4
Gentamicin	1	3	3	1	-	1
Hetacillin	2	3	1	1	-	2
Ivermectin	-	1	2	2	2	2
Kanamycin	2	1	1	-	-	5

Drugs	R	S	T	U	V	W
Ketoprofen	-	1	4	1	-	3
Levamisole	-	-	3	-	-	6
Lincomycin	1	2	2	-	-	4
Meloxicam	1	2	3	1	-	2
Moxidectin	-	3	3	-	-	3
Naproxen	1	-	2	-	-	6
Neomycin	3	3	2	-	-	1
Nitrofurazone	2	1	2	-	-	4
Novobiocin	1	5	1	-	-	2
Oxfendazole	-	-	1	1	-	7
Oxytetracycline	-	4	1	3	1	-
Penicillin G	1	4	1	2	1	-
Phenylbutazone	1	1	4	-	1	2
Pirlimycin	-	2	3	3	-	1
Spectinomycin	1	5	2	-	-	1
Streptomycin	2	2	1	-	-	4
Sulfabromomethazine	-	-	2	-	-	7
Sulfachlorphyridazine	-	1	1	1	-	6
Sulfadimethoxine	-	4	1	1	1	2
Sulfaethoxypyridazine	-	1	1	-	-	7
Sulfamethazine	-	3	2	2	-	2
Sulfaquinoxaline	-	-	2	-	-	7
Tetracycline	-	4	1	4	-	-
Thiabendazole	-	-	2	-	-	7
Tildipirosin	-	1	1	-	1	6
Tilmicosin	1	-	5	1	1	1
Tripelemamine	1	-	1	-	-	7
Tulathromycin	-	1	4	-	2	2
Tylosin	-	2	5	-	-	2

APPENDIX 5.2: SUMMARY OF MULTICRITERIA-BASED RANKING CRITERIA

Table A5.7 Summary of scoring for each criterion A. Likelihood of Drug-Administration (LODA) to lactating dairy cows

$$A_i = \left(\frac{1}{\sum_{j=1}^{4} w1_j}\right)\sum_{j=1}^{4} a_{ij} * w1_j$$

where
A_i is the likelihood of use of a drug in dairy cows score of the i^{th} drug
j = 1, 2, 3, ….n, and represents the four sub-criteria that define criterion A
a_{ij} is the score of the i^{th} drug with respect to the j^{th} sub-criterion
$w1_j$ is the weight of the j^{th} sub-criterion of the likelihood se of a drug in dairy cows determined by external experts

Sub-criteria	Scoring basis	Value	Score
A1. LODA based on surveys and formal expert elicitation	A1.1 LODA based on USDA study	<0.005	1
A1. LODA based on surveys and formal expert elicitation	A1.1 LODA based on USDA study	>0.005	3
A1. LODA based on surveys and formal expert elicitation	A1.1 LODA based on USDA study	>0.02	5
A1. LODA based on surveys and formal expert elicitation	A1.1 LODA based on USDA study	>0.04	7
A1. LODA based on surveys and formal expert elicitation	A1.1 LODA based on USDA study	> 0.08	9
A1. LODA based on surveys and formal expert elicitation	A1.2 LODA based on Veterinary Survey	>1 and ≤1.5	1
A1. LODA based on surveys and formal expert elicitation	A1.2 LODA based on Veterinary Survey	>1.5 and ≤2	3
A1. LODA based on surveys and formal expert elicitation	A1.2 LODA based on Veterinary Survey	>2 and ≤ 3	5
A1. LODA based on surveys and formal expert elicitation	A1.2 LODA based on Veterinary Survey	>3 and ≤4	7
A1. LODA based on surveys and formal expert elicitation	A1.2 LODA based on Veterinary Survey	> 4	9
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	=0% (% dairy cows herds administered/yr)	1
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>0-25% (% dairy cows herds administered/yr)	3
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>25%-50% (% dairy cows herds administered/yr)	5
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>50%-75% (% dairy cows herds administered/yr)	7
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>75% (% dairy cows herds administered/yr)	9

Sub-criteria	Scoring basis	Value	Score
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	=0% (% dairy cows (w/in a herd) administered the drug/yr))	1
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>0-25% (% dairy cows (w/in a herd) administered the drug/yr))	3
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>25%-50% (% dairy cows (w/in a herd) administered the drug/yr))	5
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>50%-75% (% dairy cows (w/in a herd) administered the drug/yr))	7
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>75% (% dairy cows (w/in a herd) administered the drug/yr))	9
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	<1 time (Ave # treatments/lactating dairy cow/yr)	1
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	3-5 X/yr (Ave # treatments/lactating dairy cow/yr)	3
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	6-30 X/yr (Ave # treatments/lactating dairy cow/yr)	5
A1. LODA based on surveys and formal expert elicitation	A1.3 LODA based on expert elicitation	>30 X/yr (Ave # treatments/lactating dairy cow/yr)	9
A.2. LODA based on drug marketing status	FDA prescription status	Drug formulations available by prescription (Rx)	5
A.2. LODA based on drug marketing status	FDA prescription status	Drug formulations available over-the-counter (OTC)	7
A.2. LODA based on drug marketing status	FDA prescription status	Drug formulations available by Rx & OTC	7
A.3. LODA based on drug approval status	FDA drug approval status for use in lactating dairy cows	Prohibited for ELDU in food-producing animals (AMDUCA)	1
A.3. LODA based on drug approval status	FDA drug approval status for use in lactating dairy cows	Drug not approved in food-producing animals	3

Sub-criteria	Scoring basis	Value	Score
A.3. LODA based on drug approval status	FDA drug approval status for use in lactating dairy cows	Drug approved in other food-producing animals	5
A.3. LODA based on drug approval status	FDA drug approval status for use in lactating dairy cows	Drug approved in cows, not approved in lactating dairy cows	7
A.3. LODA based on drug approval status	FDA drug approval status for use in lactating dairy cows	Drug approved in lactating dairy cows	9
A.4. LODA based on evidence of drug's use on dairy farms score based on farm inspection data	Number of FDA dairy farm inspections that identified the drug on the farm	Drug not identified in 0-1 inspections	1
A.4. LODA based on evidence of drug's use on dairy farms score based on farm inspection data	Number of FDA dairy farm inspections that identified the drug on the farm	Drug identified in >1 inspections	3
A.4. LODA based on evidence of drug's use on dairy farms score based on farm inspection data	Number of FDA dairy farm inspections that identified the drug on the farm	Drug identified in >10 inspections	5
A.4. LODA based on evidence of drug's use on dairy farms score based on farm inspection data	Number of FDA dairy farm inspections that identified the drug on the farm	Drug identified in >50 inspections	7
A.4. LODA based on evidence of drug's use on dairy farms score based on farm inspection data	Number of FDA dairy farm inspections that identified the drug on the farm	Drug identified in >150 inspections	9

Table A5.8 Summary of scoring for each criterion B. Likelihood of the drug's presence (LODP) in milk (bulk-tank or bulk-milk pickup tanker) milk

$$B_i = \left(\frac{1}{\sum_{j=1}^{3} w2_j}\right)\sum_{j=1}^{3} b_{ij} * w2_j$$

Where:

B_i = the score of the i^{th} drug on the likelihood of drug presence (LODP) in bulk-tank milk.

j = 1, 2, 3 represent the three sub-criteria that define B1.

b_{ij} = the score of the i^{th} drug with respect to the j^{th} sub-criterion.

$w2_j$ = the weight of the j^{th} sub-criterion of the likelihood of drug presence (LODP) in bulk-tank milk.

Sub-criteria	Scoring basis	Value	Score
B1. LODP based on evidence that the drug has been identified in milk	B1.1 LODP based on NMDRD	Drug identified in the milk	9
B1. LODP based on evidence that the drug has been identified in milk	B1.1 LODP based on NMDRD	Drug class identified in the milk	7
B1. LODP based on evidence that the drug has been identified in milk	B1.1 LODP based on NMDRD	Drug not identified in the milk	3
B1. LODP based on evidence that the drug has been identified in milk	B1.2 LODP based on sampling plan (CVM)	Positive outside limit	9
B1. LODP based on evidence that the drug has been identified in milk	B1.2 LODP based on sampling plan (CVM)	Positive but not outside limit	5
B1. LODP based on evidence that the drug has been identified in milk	B1.2 LODP based on sampling plan (CVM)	Sampled but not positive	3
B1. LODP based on evidence that the drug has been identified in milk	B1.2 LODP based on sampling plan (CVM)	Drug not sampled	3
B2. LODP based drug misadministration likelihood and consequences)	B2.1 Likelihood of misadministration (based on drug's approval status)	Drug approved in lactating dairy cows	3
B2. LODP based drug misadministration likelihood and consequences)	B2.1 Likelihood of misadministration (based on drug's approval status)	Drug approved in cows, not approved in lactating dairy cows	5
B2. LODP based drug misadministration likelihood and consequences)	B2.1 Likelihood of misadministration (based on drug's approval status)	Drug approved in other food-producing animals	7
B2. LODP based drug misadministration likelihood and	B2.1 Likelihood of misadministration	Prohibited for ELDU in food-	9

Sub-criteria	Scoring basis	Value	Score
consequences)	(based on drug's approval status)	producing animals (AMDUCA)	
B2. LODP based drug misadministration likelihood and consequences)	B2.1 Likelihood of misadministration (based on drug's approval status)	Drug not approved in food-producing animals	9
B2. LODP based drug misadministration likelihood and consequences)	B2.2 Potential consequence of misadministration (based on drugs potential for long-term persistence in the milk)	Drug does not have an official milk-discard time (MDT)	9
B2. LODP based drug misadministration likelihood and consequences)	B2.2 Potential consequence of misadministration (based on drugs potential for long-term persistence in the milk)	MDT ≥ 200	9
B2. LODP based drug misadministration likelihood and consequences)	B2.2 Potential consequence of misadministration (based on drugs potential for long-term persistence in the milk)	200 > MDT ≥ 100	7
B2. LODP based drug misadministration likelihood and consequences)	B2.2 Potential consequence of misadministration (based on drugs potential for long-term persistence in the milk)	100 > MDT ≥ 65	5
B2. LODP based drug misadministration likelihood and consequences)	B2.2 Potential consequence of misadministration (based on drugs potential for long-term persistence in the milk)	65 > MDT ≥ 25	3
B2. LODP based drug misadministration likelihood and consequences)	B2.2 Potential consequence of misadministration (based on drugs potential for long-term persistence in the milk)	25>MDT	1
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.1 Likelihood of drug getting into cow's milk (udder milk)	<1%	1
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.1 Likelihood of drug getting into cow's milk (udder milk)	1%-25%	3

Sub-criteria	Scoring basis	Value	Score
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.1 Likelihood of drug getting into cow's milk (udder milk)	>25%-50%	5
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.1 Likelihood of drug getting into cow's milk (udder milk)	>50%-75%	7
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.1 Likelihood of drug getting into cow's milk (udder milk)	>75%	9
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.2 Likelihood of drug (in udder milk) getting to the milk	<0.1%	1
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.2 Likelihood of drug (in udder milk) getting to the milk	0.1-2%	3
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.2 Likelihood of drug (in udder milk) getting to the milk	>2%-5%	5
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.2 Likelihood of drug (in udder milk) getting to the milk	>5%-10%	7
B3. LODP based on expert elicited score for likelihood of a drug getting into the bulk milk tank	B3.2 Likelihood of drug (in udder milk) getting to the milk	>10%	9

Table A5.9 Summary of scoring for each criterion C. Relative exposure to drug residues in milk and milk products

C=C1*C2

Sub-criteria	Scoring basis	Value	Score
C1. Impact of processing on drug residue concentrations present in "raw" milk	Product composition (C1.1), heat degradation (C1.2), and water removal scores (C1.3) C1=C1.1*C1.2*C1.3	C1*C2 >6	9
C2. Magnitude of consumption of dairy products (g/kg bw/day)	Meant intakes of dairy products by consumer (C2.1), % individuals consuming dairy products (C2.2), and proportion of lifetime years spent in an	C1*C2<=6	5

Sub-criteria	Scoring basis	Value	Score
	average lifetime (C2.3). C2=C2.1*C2.2*C2.3		

Table A5.10 Summary of scoring for each criterion D. Potential for a Human Health hazard

Scoring basis	Value	Score
Drug hazard value (ug/kg bw/day)	A hazard value cannot be established	9
Drug hazard value (ug/kg bw/day)	0<HV<1	7
Drug hazard value (ug/kg bw/day)	1≤HV<15	5
Drug hazard value (ug/kg bw/day)	15≤HV<40	3
Drug hazard value (ug/kg bw/day)	HV≥40	1

APPENDIX 5.3: CALCULATION OF EXPERT ELICITATION SCORES FROM RAW DATA

Background

The following section will discuss how the raw results from the expert elicitations were converted into final scores for inclusion into the multicriteria-based ranking model. Following the general assumptions typically made for expert elicitations using a (modified) Delphi method as was used in the present study, the results from the second round of elicitation were deemed to have converged to the true estimates, whereas the results of the first round of elicitation may not have converged. Therefore, only the results of the second round of expert elicitation were used - for panel 1 as well as panel 2 (see reference (Versar 2014) for a comparison of round 1 and 2 results).

Weighting of Panel 1 Results

Responses to questions 1 to 5 were converted into scores and included in the multicriteria-based ranking model. Question 6 provided qualitative information on factors with relevance for the likelihood of drug administration resulting in drug residues in the on-farm bulk-milk tank. Responses to this question were used to inform the overall multicriteria-based ranking assessment structure but not directly translated into quantitative model inputs.

2.a. Calculation of scores for question 1.

For each given drug, scores were calculated as follows: each expert's response for that given drug was assigned a score based on the response category selected by the expert for the given drug (*i.e.,* 'zero' -> 1, 'low' -> 3, 'moderate' -> 5, 'high; ->7 and 'very high' -> 9, 'no response' -> 0) and the sum of the responses for all experts for the given drug was calculated. To account for responses in the 'no-response' category, this sum was subsequently divided by the total number of experts that provided responses in categories other than the 'no-response' category. Final model scores were generated based on these average weighted scores by assigning values at or below 2 a scores of 1, values above 2 and equal to or below 4 a scores of3, values above 4 to equal to or below 6 a value 5, values above 6 and equal to or below 8 a score of 7, and values above 8 a score of 9.

2.b. Calculation of scores for question 2.

Scores for question 2 were calculated exactly as described under 2.a.

2.c. Calculation of scores for question 3.

Scores for question 3 were calculated exactly as described under 2.a, with the exaction that the following translation of response categories to scores was used: 'negligent' -> 1, 'infrequent' -> 3, 'moderate' -> 5, 'high' -> 9.

2.d. Calculation of scores for question 4.

Scores for question 4 were calculated exactly as described under 2.a, with the exaction that the following translation of response categories to scores was used: 'negligent' -> 1, 'low' -> 3, 'moderate' -> 5, 'high' -> 7, 'very high' -> 9.

2.e. Calculation of scores for question 5.

Scores for question 5 were calculated exactly as described under 2.d.

Weighting of Panel 2 Results

Responses to questions 1 to 4 were used to derive relative criterion weights for the multicriteria-based ranking model. For each model criterion or sub-criterion (depending on the questions), weights were calculated as follows: each expert's rank provided for each criterion or sub-criterion was assigned a score based on the rank selected by the expert for the given criterion or sub-criterion (*i.e.,* 'one' -> 9, 'two' -> 7, 'three' -> 5, 'four; ->3 and 'five' -> 1), the sum of the responses for all experts for the given criterion or sub-criterion was calculated, and averaged across the 9 experts by dividing the sum by the number of experts. Relative criterion weights were subsequently calculated from these averages by dividing the average criterion weight by the sum of all average criterion weights obtained for all criteria or sub-criteria.

APPENDIX 5.4: DIFFERENT METHODS OF WEIGHTING CRITERIA

Direct weighting, swing weighting, and pairwise comparison are some of the most commonly used weighting methods and will therefore be briefly summarized below:

In direct weighting methods such as point allocation, categorization or ranking, decision makers directly assign numerical weights to individual criteria (Sinha *et al.,* 2009). Direct weighting methods are easy to implement, but often generate ordinal results that are difficult to use in value functions, and direct weighting methods often appear to be less effective than more intricate weighting methods (Sinha *et al.,* 2009).

In the swing weighting methods, on the contrary, the decision maker identifies the most important criterion as the criterion that he would prefer most to 'swing' from its worst to best (or neutral to best) value, followed by identification of the next most important criterion and so forth (Sinha *et al.,* 2009, Belton and Stewart, 2002, and Department for Communities and Local Government, 2009).

Proportional weights are subsequently assigned to all criteria relative to the most important criterion (Sinha *et al.,* 2009). Swing weighting methods are thought to have better range sensitivity than direct weights, but can be impractical if the number of criteria is large (Sinha *et al.,* 2009 and Department for Communities and Local Government, 2009).
In pairwise comparisons such as the analytic hierarchy process (AHP), the relative weights of the criteria are found computationally, based on a matrix of pairwise comparisons between criteria (Yoe, 2002 and Sinha *et al.,* 2009). To generate this matrix, decision makers have to consider each criterion in relation to every other criterion in the analysis (Yoe, 2002 and Sinha *et al.,* 2009). Pairwise comparisons can therefore quickly become cumbersome for analyses with several criteria (Yoe, 2002 and Sinha *et al.,* 2009). Moreover, even though AHP uses additive value functions it differs from the above-mentioned utility-function based approaches in fundamental ways because ratios of criteria are evaluated (Stewart, 1992). In addition, weights derived based on AHP are more difficult to interpret than direct or swing weights as they are more strongly affected by criterion scales. However, methods such as AHP are uniquely suited to combine weights from different decision makers and allow conflicts among decision makers to be easily resolved, and are commonly used in practice (Stewart, 1992 and Sinha *et al.,* 2009).

For more details on different methods of weighting criteria, see Thokala, 2011.

APPENDIX 5.5: CRITERION A: USDA NAHMS STUDY 2007 DATA

NAHMS Study 2007

The likelihood of drug administration (LODA Factor score A.1.1.) is estimated, based on 2007 USDA NAHMS survey results for all 99 drug formulations in this multicriteria-based ranking. The NAHMS Dairy 2007 study evaluated the use of antibiotics for disease prevention, disease treatment, and growth promotion on U.S. dairies. In the study, producers provided information on dairy cows disease incidence, the number of dairy cows treated with antibiotics, and the antibiotic that was used for the majority of those animals during each study year (USDA, 2007, 2008, and 2009). The study collected information over a 12-month period on dairy cows herd size for each operation, dairy management practices, disease incidence within small, medium and large herds, and antimicrobial treatment for the reported disease conditions within small, medium and large dairy herds. See table and figure below for data representing the percent of cows affected by disease or disorder (respiratory, digestive, reproductive, mastitis, lameness, or others) and data representing the percent of cows on operations treated with a particular drug class (primary drug class).

Table A5.11 Percent of dairy cows within herds affected by disease or disorder

Dairy Cows	Respiratory	Digestive	Reproductive	Mastitis	Lameness	Other
% Dairy Cows within Herds	2.9	6	10	18.2	12.5	0.7

Source: Dr. Jason Lombard[27] (USDA APHIS)'s analysis based on NAHMS Dairy 2007.

27 Jason.E.Lombard@aphis.usda.gov

Figure A5.1 Percent of dairy cows affected by disease or disorder

Table A5.12 Percent of dairy cows treated by a specific drug class for a particular disease or disorder in herds

Drug Class	Respiratory	Digestive	Reproductive	Mastitis	Lameness	Other
Aminocyclitol	3.3	0	0.2	2.9	0	0
Aminoglycoside	0.6	6.4	0	0.2	0	0
Beta-lactam: non-cephalosporin	11	30.3	19.7	19.1	19.5	29.9
Beta-lactam: Cephalosporin	70.5	36	27.9	53.2	27.2	23.6
Florfenicol	1.9	0.4	0.2	0	0.5	0
Lincosamide	0	0	0	19.4	0	0
Macrolide	1.1	1.1	0	0.2	0.5	0
Sulfonamide	2.8	15.6	0.2	1.2	4.2	0
Tetracycline	6.4	7	44.4	2	42.1	2.6
Other	2.4	3.2	7.4	1.8	6	43.9
Antihistamine	2.4	3.2	7.4	1.8	6	43.9
Antiparasitic	2.4	46	7.4	1.8	6	43.9
NSAID	2.4	3.2	7.4	1.8	6	43.9

Source: NAHMS Dairy 2007 Part V (USDA, 2009).

Notably, mastitis[28] was the leading reported disease in the dairy cows. Other important diseases, in which the majority of cows were treated include respiratory diseases, reproductive diseases, and lameness (see table below). Beta-lactams[29], especially cephalosporin, were the most reported primary drug classes used in U.S. dairy cows. Other more highly reported drugs in all farms included lincosamides (which was used primarily to treat mastitis on 19.4% of cow) and tetracycline (which was used to treat lameness in 42.1% of cows and to treat reproductive disorders in 44.4% of cows).

Beta-lactams, especially cephalosporin, were the most reported primary drug classes used in U.S. dairy cows. Beta-lactam antibiotics are the most widely used group of antimicrobial drugs in dairy cows; their characteristics include low price, good efficacy against a wide spectrum of pathogens, and low potential for adverse side-effects (Sundlof *et al*., 1995; Andrew, S.M., 2009). They comprise a broad class of antibiotics, including penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems (FDA, 2011). Other studies have reported the most frequently reported penicillin G as the most frequently used in dairy cows (most common), followed by, ceftiofur, cloxacillin, cephapririn, and ampicillin (Sundlof *et al*., 1995; Andrew, S.M., 2009; USDA, 2008).

Other more highly reported drugs in all farms included the lincosamides (which was used primarily to treat mastitis on 19.4% of cow) and tetracycline (which was used to treat lameness in 42.1% of cows and to treat reproductive disorders in 44.4% of cows).

Table A5.13 Percent affected cows treated (with an antibiotic)

Disease or Disorder	Percent
Respiratory	96.4
Diarrhea or other digestive problem	32.3
Reproductive	74.7
Mastitis	89.9
Lameness	56.5
Other	66.2

Source: USDA NAHMS Dairy 2007 Part V (USDA, 2009).

28 Mastitis is a clinical or subclinical inflammation of the udder, usually resulting from exposure to a pathogenic microorganism, which can affect lactating or dry cows as well as heifers (Hettinga *et al*.,2008, Nickerson, 2009, Barkema *et al*.,2006, and Sato *et al*.,2008).

29 Beta-lactam antibiotics are the most widely used group of antimicrobial drugs in dairy cattle; their characteristics include low price, good efficacy against a wide spectrum of pathogens, and low potential for adverse side-effects (Sundlof *et al*., 1995; Andrew, S.M., 2009). They comprise a broad class of antibiotics, including penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems (FDA, 2011). The most frequently reported uses in dairy cattle have been of penicillin G (most common), ceftiofur, cloxacillin, cephapririn, and ampicillin (Sundlof *et al*., 1995; Andrew, S.M., 2009; USDA, 2008).

LODA Factor score A1.1

The likelihood of drug administration (LODA Factor score A.1.1.) is described below:

The likelihood that a drug is used to treat dairy cows, T(i) is determined by summing the likelihood that the drug is used to treat specific conditions in dairy cows, S1(i,j,), across all "j" disease conditions as follows:

$$T(i) = \sum_{j=1}^{6} S1(i,j)$$

Where:

Let P1(j) = the percent of cows in all herds affected by a disease or disorder, where "j" represents the disease or disorder (Respiratory, Digestive, Reproductive, Mastitis, Lameness, or Other).

Let P2(j,k) represent the percent of cows on operations treated by a specific drug class for a particular disease or disorder. Here, "j" represents the disease or disorder (respiratory, digestive, reproductive, mastitis, lameness, or other) and "k" represents the drug class (Aminocyclitol, Aminoglycoside, Beta-lactam, Cephalosporin, Florfenicol, Lincosamide, Macrolide, Sulfonamide, Tetracycline, Other, Antihistamine, Antiparasitic, or NSAID) used for treatment.

The likelihood that specific drug classes are used to treat cows (Q1), was determined by multiplying the likelihood of cows having a condition (P1), by the likelihood that a drug class is used to treat the condition in cows (P2), as follows:

$Q1(j,k) = P1(j) \times P2(j,k)$

For any drug i, within a drug class, the likelihood that the drug is used to treat specific conditions in cows (S1), was determined by multiplying the likelihood that specific drug classes are used to treat cows (Q1), by the classifier (1 or 0) of whether a drug belongs to a class R1(k), and the indicator (1 or 0) of whether the drug is used to treat the conditions, h(i,j), as follows:

$S1(i,j) = Q1(j,k) \times R1(i,k) \times h(i,j)$

See table below for the T(i) value for the 54 drugs (for the 99 formulations).

Table A5.14 Total likelihood of using drug T(i) for 54 drugs (for 99 formulations)

Drug	Total likelihood of using drug, T(i)= Sum (h(i,j) across disease conditions, j)
Acetylsalicylic Acid	3.77E-03
Albendazole	1.75E-02
Amikacin sulfate-1	0.00E+00
Amikacin sulfate-2	0.00E+00
Amoxicillin tryhydrate-1	2.76E-02
Amoxicillin tryhydrate-2	1.82E-02
Amoxicillin tryhydrate-3	3.48E-02
Ampicillin Sodium	5.28E-03
Ampicillin tryhydrate-1	3.19E-03
Ampicillin tryhydrate-2	2.14E-02
Ampicillin tryhydrate-3	2.14E-02
Amprolium	1.75E-02
Ceftiofur Crystalline Free Acid	8.23E-02
Ceftiofur Hydrochloride-1	8.23E-02
Ceftiofur Hydrochloride-2	9.68E-02
Ceftiofur sodium	5.44E-02
Cephapirin Benzathine	9.68E-02
Cephapirin Sodium	9.68E-02
Chloramphenicol-1	5.69E-03
Chloramphenicol-2	5.69E-03
Chloramphenicol-3	3.07E-03
Clorsulon	1.75E-02
Cloxacillin Benzathine	3.48E-02
Cloxacillin Sodium	3.48E-02
Danofloxacin mesylate	6.96E-04
Dihydrostreptomycin Sulfate	3.84E-03
Doramectin	2.05E-02
Enrofloxacin	6.96E-04
Eprinomectin-1	2.05E-02
Eprinomectin-2	2.05E-02
Erythromycin-1	3.19E-04
Erythromycin-2	3.64E-04
Florfenicol-1	1.18E-03
Florfenicol-2	5.51E-04
Florfenicol-3	5.51E-04
Flunixin Meglumine-1	6.96E-04

Drug	Total likelihood of using drug, T(i)= Sum (h(i,j) across disease conditions, j)
Flunixin Meglumine-2	6.96E-04
Furazolidone	3.07E-03
Gamithromycin	3.19E-04
Gentamicin Sulfate-1	0.00E+00
Gentamicin Sulfate-2	0.00E+00
Hetacillin Potassium	3.48E-02
Ivermectin-1	2.05E-02
Ivermectin-2	2.05E-02
Ivermectin-3	2.05E-02
Ivermectin-4	2.05E-02
Ivermectin-5	2.05E-02
Ivermectin-6	2.05E-02
Kanamycin	0.00E+00
Kanamycin Sulfate	0.00E+00
Ketoprofen	1.08E-02
Levamisole	1.75E-02
Levamisole hydrochloride	1.75E-02
Levamisole phosphate	1.75E-02
Lincomycin Hydrochloride	0.00E+00
Lincomycin Hydrochloride Monohydrate	0.00E+00
Meloxicam	3.07E-03
Moxidectin-1	2.05E-02
Moxidectin-2	2.05E-02
Naproxen	3.07E-03
Neomycin Sulfate	3.84E-03
Nitrofurazone	3.07E-03
Novobiocin Sodium	3.28E-03
Oxfendazole-1	1.75E-02
Oxfendazole-2	1.75E-02
Oxytetracycline hydrochloride-1	5.87E-02
Oxytetracycline hydrochloride-2	1.03E-01
Oxytetracycline-3	1.03E-01
Penicillin G Procaine-1	3.19E-03
Penicillin G Procaine-2	3.48E-02
Penicillin G Procaine-3	3.19E-03
PenicillinG benzathine&Penicillin G Procaine	2.35E-02
Phenylbutazone-1	3.07E-03
Phenylbutazone-2	3.07E-03
Pirlimycin Hydrochloride	3.53E-02

Drug	Total likelihood of using drug, T(i)= Sum (h(i,j) across disease conditions, j)
Spectinomycin Hydrochloride	9.57E-04
Spectinomycin Sulfate	9.57E-04
Streptomycin Sulfate	4.38E-03
Sulfabromomethazine Sodium	1.78E-02
Sulfachlorpyridazine-1	2.00E-04
Sulfachlorpyridazine-2	2.00E-04
Sulfadimethoxine-1	6.06E-03
Sulfadimethoxine-2	6.06E-03
Sulfadimethoxine-3	6.06E-03
Sulfaethoxypyridazine-1	1.78E-02
Sulfaethoxypyridazine-2	1.78E-02
Sulfaethoxypyridazine-3	1.46E-02
Sulfamethazine-1	1.78E-02
Sulfamethazine-2	1.78E-02
Sulfamethazine-3	1.78E-02
Sulfaquinoxaline	9.36E-03
Tetracycline Hydrochloride-1	6.06E-03
Tetracycline Hydrochloride-2	5.28E-02
Thiabendazole-2	2.05E-02
Tildipirosin	3.19E-04
Tilmicosin Phosphate	6.83E-04
Tripelennamine	3.07E-03
Tulathromycin	6.25E-04
Tylosin-2	1.31E-03

APPENDIX 5.6: Criterion A: Sundlof data

Table A5.15 Data from Sundlof *et al.* for 54 drugs (99 formulations) (1995)

Drugs	Sundlof Value
Acetylsalicylic Acid	2.8
Albendazole	1.5
Amikacin sulfate-1	1.7
Amikacin sulfate-2	1.7
Amoxicillin tryhydrate-1	2.8
Amoxicillin tryhydrate-2	1.7
Amoxicillin tryhydrate-3	2.8
Ampicillin Sodium	1.7
Ampicillin tryhydrate-1	3.5
Ampicillin tryhydrate-2	1.7
Ampicillin tryhydrate-3	1.7
Amprolium	1.5
Ceftiofur Crystalline Free Acid	4.5
Ceftiofur Hydrochloride-1	4.5
Ceftiofur Hydrochloride-2	4.5
Ceftiofur sodium	4.5
Cephapirin Benzathine	3.6
Cephapirin Sodium	3.6
Chloramphenicol-1	1.7
Chloramphenicol-2	1.7
Chloramphenicol-3	1.7
Clorsulon	1.5
Cloxacillin Benzathine	3.8
Cloxacillin Sodium	3.8
Danofloxacin mesylate	1.7
Dihydrostreptomycin Sulfate	2.2
Doramectin	1.5
Enrofloxacin	1.7
Eprinomectin-1	1.5
Eprinomectin-2	1.5
Erythromycin-1	1.7
Erythromycin-2	2.8
Florfenicol-1	1.7
Florfenicol-2	1.7
Florfenicol-3	1.7
Flunixin Meglumine-1	3.8

Drugs	Sundlof Value
Flunixin Meglumine-2	3.8
Furazolidone	3
Gamithromycin	1.7
Gentamicin Sulfate-1	2.2
Gentamicin Sulfate-2	2.2
Hetacillin Potassium	2.5
Ivermectin-1	1.5
Ivermectin-2	1.5
Ivermectin-3	1.5
Ivermectin-4	1.5
Ivermectin-5	1.5
Ivermectin-6	1.5
Kanamycin	1.7
Kanamycin Sulfate	1.7
Ketoprofen	2.2
Levamisole	1.5
Levamisole hydrochloride	1.5
Levamisole phosphate	1.5
Lincomycin Hydrochloride	1.7
Lincomycin Hydrochloride Monohydrate	1.7
Meloxicam	2.2
Moxidectin-1	1.5
Moxidectin-2	1.5
Naproxen	2.2
Neomycin Sulfate	1.7
Nitrofurazone	3.2
Novobiocin Sodium	1.7
Oxfendazole-1	1.5
Oxfendazole-2	1.5
Oxytetracycline hydrochloride-1	1.7
Oxytetracycline hydrochloride-2	1.7
Oxytetracycline-3	4.3
Penicillin G Procaine-1	5
Penicillin G Procaine-2	5
Penicillin G Procaine-3	1.7
PenicillinG benzathine&Penicillin G Procaine	1.7
Phenylbutazone-1	3
Phenylbutazone-2	3
Pirlimycin Hydrochloride	2.6
Spectinomycin Hydrochloride	2.4

Drugs	Sundlof Value
Spectinomycin Sulfate	2.4
Streptomycin Sulfate	1.7
Sulfabromomethazine Sodium	3
Sulfachlorpyridazine-1	1.3
Sulfachlorpyridazine-2	1.3
Sulfadimethoxine-1	3.5
Sulfadimethoxine-2	3.5
Sulfadimethoxine-3	3
Sulfaethoxypyridazine-1	3
Sulfaethoxypyridazine-2	3
Sulfaethoxypyridazine-3	1.3
Sulfamethazine-1	1.3
Sulfamethazine-2	1.3
Sulfamethazine-3	1.3
Sulfaquinoxaline	1.3
Tetracycline Hydrochloride-1	2.8
Tetracycline Hydrochloride-2	2.8
Thiabendazole-2	1.5
Tildipirosin	1.7
Tilmicosin Phosphate	1.7
Tripelennamine	2.8
Tulathromycin	1.7
Tylosin-2	2.8

Source: Sundlof *et al.*, 1996.

APPENDIX 5.7: CRITERION A: ON-FARM INSPECTION DATA

Table A5.16 FDA On-farm inspection data for 54 drugs (99 formualtions)

Drug	Farms Found	% Farms (Out of 979 Total Farms) Found with Drug
Acetylsalicylic Acid	352	36%
Albendazole	2	0.2%
Amikacin sulfate-1	0	0.0%
Amikacin sulfate-2	2	0.2%
Amoxicillin tryhydrate-1	1	0.1%
Amoxicillin tryhydrate-2	5	0.5%
Amoxicillin tryhydrate-3	82	8.4%
Ampicillin Sodium	1	0.1%
Ampicillin tryhydrate-1	427	43.6%
Ampicillin tryhydrate-2	0	0.0%
Ampicillin tryhydrate-3	5	0.5%
Amprolium	44	4.5%
Ceftiofur Crystalline Free Acid	351	35.9%
Ceftiofur Hydrochloride-1	544	55.6%
Ceftiofur Hydrochloride-2	500	51.1%
Ceftiofur sodium	632	64.6%
Cephapirin Benzathine	298	30.4%
Cephapirin Sodium	377	38.5%
Chloramphenicol-1	1	0.1%
Chloramphenicol-2	2	0.2%
Chloramphenicol-3	0	0.0%
Clorsulon	7	0.7%
Cloxacillin Benzathine	109	11.1%
Cloxacillin Sodium	49	5.0%
Danofloxacin mesylate	4	0.4%
Dihydrostreptomycin Sulfate	143	14.6%
Doramectin	0	0.0%
Enrofloxacin	193	19.7%
Eprinomectin-1	26	2.7%
Eprinomectin-2	0	0.0%
Erythromycin-1	11	1.1%
Erythromycin-2	0	0.0%
Florfenicol-1	321	32.8%
Florfenicol-2	7	0.7%
Florfenicol-3	0	0.0%

Drug	Farms Found	% Farms (Out of 979 Total Farms) Found with Drug
Flunixin Meglumine-1	669	68.3%
Flunixin Meglumine-2	38	3.9%
Furazolidone	1	0.1%
Gamithromycin	0	0.0%
Gentamicin Sulfate-1	0	0.0%
Gentamicin Sulfate-2	36	3.7%
Hetacillin Potassium	63	6.4%
Ivermectin-1	0	0.0%
Ivermectin-2	0	0.0%
Ivermectin-3	15	1.5%
Ivermectin-4	0	0.0%
Ivermectin-5	9	0.9%
Ivermectin-6	0	0.0%
Kanamycin	0	0.0%
Kanamycin Sulfate	0	0.0%
Ketoprofen	0	0.0%
Levamisole	0	0.0%
Levamisole hydrochloride	2	0.2%
Levamisole phosphate	0	0.0%
Lincomycin Hydrochloride	4	0.4%
Lincomycin Hydrochloride Monohydrate	45	4.6%
Meloxicam	0	0.0%
Moxidectin-1	0	0.0%
Moxidectin-2	0	0.0%
Naproxen	0	0.0%
Neomycin Sulfate	65	6.6%
Nitrofurazone	3	0.3%
Novobiocin Sodium	4	0.4%
Oxfendazole-1	0	0.0%
Oxfendazole-2	0	0.0%
Oxytetracycline hydrochloride-1	40	4.1%
Oxytetracycline hydrochloride-2	97	9.9%
Oxytetracycline-3	193	19.7%
Penicillin G Procaine-1	599	61.2%
Penicillin G Procaine-2	125	12.8%
Penicillin G Procaine-3	5	0.5%
PenicillinG benzathine&Penicillin G Procaine	7	0.7%
Phenylbutazone-1	0	0.0%

Drug	Farms Found	% Farms (Out of 979 Total Farms) Found with Drug
Phenylbutazone-2	1	0.1%
Pirlimycin Hydrochloride	249	25.4%
Spectinomycin Hydrochloride	25	2.6%
Spectinomycin Sulfate	25	2.6%
Streptomycin Sulfate	3	0.3%
Sulfabromomethazine Sodium	0	0.0%
Sulfachlorpyridazine-1	2	0.2%
Sulfachlorpyridazine-2	0	0.0%
Sulfadimethoxine-1	229	23.4%
Sulfadimethoxine-2	45	4.6%
Sulfadimethoxine-3	9	0.9%
Sulfaethoxypyridazine-1	0	0.0%
Sulfaethoxypyridazine-2	0	0.0%
Sulfaethoxypyridazine-3	0	0.0%
Sulfamethazine-1	1	0.1%
Sulfamethazine-2	104	10.6%
Sulfamethazine-3	14	1.4%
Sulfaquinoxaline	0	0.0%
Tetracycline Hydrochloride-1	79	8.1%
Tetracycline Hydrochloride-2	0	0.0%
Thiabendazole-2	0	0.0%
Tildipirosin	0	0.0%
Tilmicosin Phosphate	106	10.8%
Tripelennamine	49	5.0%
Tulathromycin	129	13.2%
Tylosin-2	209	21.3%

Source: FDA Farm Inspection Data for October 1, 2008 to December 31, 2014 (FDA, 2014)
Total Farms Searched: 979 Farms.

APPENDIX 5.8: CRITERION B: DRUGS IDENTIFIED IN NMDRD (2000-2013)

National Milk Drug Residue Database - Summary of data from Table 7.1, fiscal years 2000 to 2013:

Table A5.17 Grade A bulk-milk pick-p tanker testing (2000-2013)

Drugs	Total Positive Tests	Total Tests	Table 7.1 Sample result (Where Positives found?)
AMINOGLYCOSIDES	11	4,716	1
AMPHENICOLS	-	1,756	0
BETA lactams	17,355	43,123,539	1
Ceftiofur	-	609	0
CHLORAMPHENICOL	-	886	0
Chlortetracycline	-	4	0
Cloxacillin	17	9,580	1
ENROFLOXACIN	9	32,760	1
FLORFENICOL	-	-	0
Gentamicin	-	719	0
MACROLIDES	4	20,619	1
MULTIPLE DRUG FAMILY TEST	-	1,014	0
Neomycin	8	6,144	1
NOVOBIOCIN	-	158	0
SPECTINOMYCIN	-	51	0
Sulfachloropyridazine	-	812	0
Sulfadimethoxine	6	10,373	1
Sulfamethazine	132	175,110	1
Sulfanilamide	1	468	1
Sulfathiazole	-	1,055	0
SULFONAMIDES	197	917,820	1
Tetracycline	1	8,864	1
TETRACYCLINES	176	1,122,779	1
TETRACYCLINES	16	45,886	1
Tilmicosin	-	38	0
TOTAL	17,933	45,485,760	

Source: National Milk Drug Residue Database 2000-2013 (GLH, Inc., 2000-2013). http://www.kandc-sbcc.com/nmdrd/

Table A5.18 Data for 54 drugs from NMDRD 2000-2013

Drugs	Specific drug identified by name and positive in NMDRD (2000-2013)	Drug (Non-specific) identified in milk supply (milk sample positive for drug in NMDRD (2000-2013)
Acetylsalicylic acid	0	0
Albendazole	0	0
Amikacin	0	1
Amoxicillin	0	1
Ampicillin	0	1
Amprolium	0	0
Ceftiofur	0	1
Cephapirin	0	1
Chloramphenicol	0	0
Clorsulon	0	0
Cloxacillin	1	1
Danofloxacin	0	1
Dihydrostreptomycin	0	1
Doramectin	0	0
Enrofloxacin	1	1
Eprinomectin	0	0
Erythromycin	0	1
Florfenicol	0	0
Flunixin	0	0
Furazolidone	0	0
Gamithromycin	0	1
Gentamicin	0	1
Hetacillin	0	1
Ivermectin	0	0
Kanamycin	0	1
Ketoprofen	0	0
Levamisole	0	0
Lincomycin	0	0
Meloxicam	0	0
Moxidectin	0	0
Naproxen	0	0
Neomycin	1	1
Nitrofurazone	0	0
Novobiocin	0	0
Oxfendazole	0	0
Oxytetracycline	0	1
Penicillin	0	1
Phenylbutazone	0	0

Drugs	Specific drug identified by name and positive in NMDRD (2000-2013)	Drug (Non-specific) identified in milk supply (milk sample positive for drug in NMDRD (2000-2013)
Pirlimycin	0	0
Spectinomycin	0	0
Streptomycin	0	1
Sulfabromomethazine	0	1
Sulfachlorpyridazine	0	1
Sulfadimethoxine	1	1
Sulfaethoxypyridazine	0	1
Sulfamethazine	1	1
Sulfaquinoxaline	0	1
Tetracycline	1	1
Thiabendazole	0	0
Tildipirosin	0	1
Tilmicosin	0	1
Tripelennamine	0	0
Tulathromycin	0	1
Tylosin	0	1

0=no; 1=yes.
Source: National Milk Drug Residue Database 2000-2013 (GLH, Inc., 2000-2013). http://www.kandc-sbcc.com/nmdrd/

APPENDIX 5.9: CRITERION B: DRUGS IDENTIFIED IN CVM SAMPLING DATA

Table A5.19 FDA milk drug residue sampling survey

Drugs	Drug Class	# of Samples Analyzed	# of Samples Positive	Samples Outside US Limit
Ampicillin	Beta- Lactam	1912	0	0
Cephapirin	Beta- Lactam	1912	0	0
Chloramphenicol	Chloramphenicol	1912	0	0
Cloxacillin	Beta- Lactam	1912	0	0
Doramectin	Anthelmintics	1713	1	1
Eprinomectin	Anthelmintics	1691	4	0
Erythromycin	Macrolides	1912	0	0
Florfenicol	Other	1912	10	10
Flunixin	NSAIDs	1912	0	0
Gentamicin	Aminoglycosides	1912	1	1
Ivermectin	Anthelmintics	651	0	0
Moxidectin	Anthelmintics	651	0	0
Naproxen	NSAIDs	1695	0	0
Neomycin	Aminoglycosides	1912	0	0
Oxytetracycline	Tetracyclines	1912	0	0
Penicillin	Beta- Lactam	1912	0	0
Phenylbutazone	NSAIDs	1694	0	0
Sulfachlorpyridazine	Sulfonamides	1912	0	0
Sulfadimethoxine	Sulfonamides	1912	0	0
Sulfamethazine	Sulfonamides	1912	2	1
Sulfaquinoxaline	Sulfonamides	191	0	0
Tetracycline	Tetracyclines	1912	0	0
Thiabendazole	Anthelmintics	1912	0	0
Tilmicosin	Macrolides	1912	1	1
Tripelennamine	Other	1912	0	0
Tulathromycin	Macrolides	1912	2	2
Tylosin	Macrolides	1912	0	0

FDA Milk Drug Residue Sampling Survey (FDA, 2015a and FDA, 2015b).

APPENDIX 5.10: CRITERION B: REFERENCE FOR DRUG PERSISTENCE DATA

Table A5.20 Reference for drug persistence data for 54 drugs (99 formulations)

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
1	**Acetylsalicylic acid**	Acetylsalicylic acid	MDT < 25	24 hrs (FARAD)
2	**Albendazole**	Albendazole	100> MDT ≥ 65	NE (FDA 21 CFR 520.45b); 72 hours (3 days) (Moreno *et al*., 2005);
3.1	**Amikacin**	Amikacin sulfate-1	NE	NE (Sheep milk, At 9.5 h post-administration [7.5 mg/kg bw], 75% of Cmax [0.89 ug/mL] was left in milk after IV injection and 64% of Cmax [0.21 ug/mL] was left in milk after IM injection; Haritova and Lashev, 2004)
3.2	**Amikacin**	Amikacin sulfate-2	NE	NE
4.1	**Amoxicillin**	Amoxicillin trihydrate-1	100> MDT ≥ 65	96 hr (FDA 21 CFR 522.88)
4.2	**Amoxicillin**	Amoxicillin trihydrate-2	100> MDT ≥ 65	96 hr for oral (FDA 21 CFR 522.88)
4.3	**Amoxicillin**	Amoxicillin trihydrate-3	65> MDT ≥ 25	60 hr (FDA 21 CFR 526.88)
5.1	**Ampicillin**	Ampicillin sodium	NE	NE (When 75 mg total was administered to goats intramammary along with Curaclox LC and 200 mg sodium coloxacillin, the milk withdrawl time was 80 hr; Karzis *et al*., 2007) The authors say this is similar to what is found for cows.
5.2	**Ampicillin**	Ampicillin trihydrate-1	65> MDT ≥ 25	48 hrs (FDA 21 CFR 522.90b)
5.3	**Ampicillin**	Ampicillin trihydrate-2	NE	Ampicillin tryhyrdate-2 is indicated for oral administration. Ampicillin was administered orally in milk to calves at the dose 7 mg/kg bw. Peak concentrations occurred around approximately 0.22 ug/mL at 3 hr. By 6 hr, plasma concentrations had reached approximately 0.15 ug/mL (Palmer *et al*., 1983).
5.4	**Ampicillin**	Ampicillin trihydrate-3	NE	NE
6	**Amprolium**	Amprolium	NE	NE (FDA 21 CFR 520.100); 3 days (72 hrs) for 20% oral solution administered at 4mL/20kg bw according to Kepro, 2015.

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
7.1	**Ceftiofur**	Ceftiofur crystalline free acid	0	0 hrs (FDA, 2005)
7.2	**Ceftiofur**	Ceftiofur hydrochloride-1	0	0 hrs; 2 days (48 hrs) (FDA, 1998) "…a two day withdrawal period is established for the use of ceftiofur HCl in cows by BOTH the subcutaneous and intramuscular routes of administration.
7.3	**Ceftiofur**	Ceftiofur hydrochloride-2	200 > MDT ≥ 100	72 hrs (FDA 21 CFR 526.313) when administered for no more than 8 d; 30 day dry-off period may be used for food with no milk discarded due to ceftiofur residues (720 hrs) (FDA 21CFR 526.313); 72 hrs (Zoetisus, 2006)
7.4	**Ceftiofur**	Ceftiofur sodium	0	0 hrs (Zoetisus, 2014)
8.1	**Cephapirin**	Cephapirin benzathine	200 > MDT ≥ 100	72 hrs after calving, if administered before 30 days (720 hrs) prior to calving (FDA 21 CFR 526.363)
8.2	**Cephapirin**	Cephapirin sodium	100> MDT ≥ 65	96 hrs (FDA 21 CFR 526.365)
9.1	**Chloram-phenicol**	Chloramphenicol -1	NE	NE (FDA 21CFR 520.390)
9.2	**Chloram-phenicol**	Chloramphenicol -2	NE	NE (At 36 hrs 0 ug/mL of chloramphenicol was found in cows dosed at 11mg/kg bw IM and IV, Sisodia *et al*.,1973)
9.3	**Chloram-phenicol**	Choramphenicol-3	NE	NE
10	**Clorsulon**	Clorsulon	NE	NE (At 141.6 days, milk levels in cows fell below the 0.1 ppm tolerance for clorsulon in cows muscle. (Chiu *et al*., 1989). The dose administered was orally at 7 mg/kg bw. According to Sundlof 1992, oral administration prolongs the half life of clorsulon in the plasma by 64% in sheep and 91% in goats compared to IV administration. This suggests that when clorsulon is administered via IV, it might have a withdrawl time shorter than that when administered orally.)
11.1	**Cloxacillin**	Cloxacillin benzathine	200 > MDT ≥ 100	72 hrs after calving and must stop drug 30 days (720 hrs) prior to calving (FDA 21 CFR 526.464b)
11.2	**Cloxacillin**	Cloxacillin sodium	65> MDT ≥ 25	48 hrs (FDA 21 CFR 526.464c, 21 CFR 526.464d)
12	**Danofloxacin**	Danofloxacin mesylate	NE	NE 74 hrs. Administered (18% solution, pfizer) to cows via SC injection at 6 mg/kg bw. Time to safe concentration software (European Union, WTM 1.4) calculated a milk withdrawl time of 73.48 hrs. (Mestorino *et al*., 2009)

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
13	**Dihydrostrepto-mycin**	Dihydrostreptomycin sulfate	NE	NE (21 CFR 520.534) 96 hours for intramammary administration (FARAD; Gehring *et al.*, 2005). A solution [Devomycin D, Norbrook] containing streptomycin sulfate (150 mg/ml), dihydrostreptomycin sulfate (150 mg/mL), chlorocresol (1 mg/ml) and sodium metabisulphate (1 mg/mL) has a milk withdrawl time of 48 hours when given IM a maximum of 3 days. The Merck Mannual is saying 100-200 d milk discard times for aminoglycosides given parenterally; if given by udder infusion, 2-3 d.
14	**Doramectin**	Doramectin	100> MDT ≥ 65	96 (FARAD for intramammary). Unable to confirm 96 h. FARAD Newsletter from 2004 says that Doramectin can be detected in milk residues for up to 60 days.
15	**Enrofloxacin**	Enrofloxacin	NE	NE Notril Max by Norbrook containing 100 mg of Enrofloxacin, 20 mg benzyl alcohol and bitam-1-ol 30 mg, recommends a milk withdrawl time of 84 hrs for SC injections.
16	**Eprinomectin**	Eprinomectin-1	0	0 hr for all cows, including dairy for NADA 141-079 (accessdata.fda.gov)
		Eprinomectin-2	NE	0 days. Unable to confirm 0 hrs. Upon SC injection of 0.2 mg/kg, the Tmax was 49.8 h with a Cmax of 6.4 ng/mL. (Baoliang *et al*., 2006).
17	**Erythromycin**	Erythromycin-1	NE	NE In lactating goats administered 15 mg/kg bw SC, the Tmax was 1.64h with Cmax of 0.49 ug/mL. The elimination half-life was 3.89 h with SD 1.16 h. The drug was 95.36% bioavailable. (Ambros *et al*., 2007)
		Erythromycin-2	65> MDT ≥ 25	36 hrs FDA 21 CFR 526.820
18	**Florfenicol**	Florfenicol-1	100> MDT ≥ 65	72 hrs (Payne, (The Compendium North American Ed, Food Animal) Confirmed in (Ruiz *et al.*, 2010.) although Merck Manual, 2012, withdrawal time for florfenicol is 28 d
		Florfenicol-2	65> MDT ≥ 25	Unable to find sources
		Florfenicol-3	200 > MDT ≥ 100	120 hrs (FARAD Intrammary Admin.)
19	**Flunixin**	Flunixin meglumine-1	65> MDT ≥ 25	72 hrs for IM admin. (Smith *et al*., 2008). For 36 hrs for IV admin after the last treatment the milk must not be used (FDA, Animal Drugs, Accessdata and FARAD).
		Flunixin meglumine-2	200 > MDT ≥ 100	120 hrs (FARAD Intrammary Admin.) A more relevant route of administration, oral (137-409), FARAD recommends 48 hrs milk

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
				withdrawal time following a single oral dose (Smith *et al.,* 2008)
20	**Furazolidone**	Furazolidone	200 > MDT ≥ 100	In cows dosed orally with a capsul containing 0.88mg/kg bw of furazolidone, furaltadone, nitrofurazone and 4.4 mg nitrofurantonin (n = 1 cow), residues reached below the FDA tolerance of 2 ppb at 72 hrs post administration (Chu and Lopez, 2007).
21	**Gamithromycin**	Gamithromycin	100> MDT ≥ 65	72 hrs for IM or IV (Damian *et al.,* 1997) 96 hrs (Payne, The Compendium North American Ed). Here is a literature comparision for another macrolide (erythromycin-2) for which a MWT is already established. A study by Bajwa *et al.*, 2007 suggests intramammary administration of 0.55 mg/kg bw erythromycin (assuming 544 kg dairy cow) results in a plasma half-life of 11.85 hr with a max plasma concentration of 50 ug/mL and plasma AUC of 12.84 ug*hr/mL; however as the concentration of erythromycin increases, so does the half life as Burrows *et al.,* 1989 reported 26.87 hrs with dose between 15-30 mg/kg SC. For gamithromycin administered SC at 3 mg/kg bw, a plasma half-life of 51.2 hr with a max plasma concentration of 0.175 ug/mL and an AUC of 4.55 ug*hr/mL (Huang *et al.*, 2010).
22	**Gentamicin**	Gentamicin sulfate-1	0	NE 0 hrs - Pink eye spray at the labeled dose, no witholding period for food products intened for human consumption (FARAD withdrawl date calculator)
		Gentamicin sulfate-2	NE	In cows dosed orally with a capsul containing 0.88mg/kg bw of furazolidone, furaltadone, nitrofurazone and 4.4 mg nitrofurantonin (n = 1 cow), residues reached below the FDA tolerance of 2 ppb at 72 hrs post administration (Chu and Lopez, 2007)
23	**Hetacillin**	Hetacillin potassium	100> MDT ≥ 65	72 hrs (FDA, accessdata.fda.gov)
24	**Ivermectin**	Ivermectin-1	MDT ≥ 200	The peak plasma time in male cows upon IM administration is 2.25 +/- 0.88 d with elimination half-life of 5.2 d +/-1.11 (Lifschitz *et al*., 1999). For conservative calculations, the peak plasma time is (2.25+0.88) 3.13 d and the elimination half-life is (5.2+1.11) 6.31 d. To reduce Ivermectin-1 concentration by 99% of the peak, it will take 6.54 half lives. Therefore, if we conservatively multiply 6.31 d by 6.54 and achieve 41.26 d or 990.4 hrs. The elimination half-life presented within this reference accounted for absorption time to peak plasma concentration.

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
		Ivermectin-2	100> MDT ≥ 65	72 hrs (21 CFR 526.1130) Unable to confirm 72 hrs. Given that Ivermectin-2 is administered to horses via paste and Ivermectin-4 is administed at a similar dose (approx. 250 ug/kg bw) via paste in cows, it would seem that Ivermectin-2 would have a similar milk withdrawal time as Ivermectin 4, which is 28 days (672 hrs).
		Ivermectin-3	MDT ≥ 200	47 days (1128 hrs) (Baynes *et al.,* 2000)
		Ivermectin-4	MDT ≥ 200	28 days (672 hrs) (Baynes *et al.,* 2000)
		Ivermectin-5	MDT ≥ 200	53 days (1272 hrs) (Baynes *et al.,* 2000)
		Ivermectin-6	MDT ≥ 200	28 days (672 hrs) (Baynes *et al.,* 2000) While this source does say 28 d for milk withdrawl time for oral, this was for a dose of 200 ug/kg bw. As shown in the FDA accessdata.fda.gov, NADA 140-988 is to be administered in a large oral bolous dose of 1.74 grams (sustained release) with a minimum cows weight of 125 kg. This is the equivalent 13.76 mg/kg bw, which is 55 times greater than the dose administered in Ivermectin-4. Therefore, it is likely it would take longer for Ivermectin-6 to clear the milk and thus, longer milk withdrawal times.
25	**Kanamycin**	Kanamycin	MDT ≥ 200	Unable to find reference for topical/othalmological ointment.
		Kanamycin sulfate	NE	NE (21 CFR 520.1197) The calculated elimination period (withdrawal period) of cows administered kanamycin (50 mg/mL) was 2.4 to 5.2 (mean 3.8) days for milk, so, conservatively 125 hrs.
26	**Ketoprofen**	Ketoprofen	MDT < 25	NE; (24 hrs FARAD NSAID 1997 and Smith *et al.,* 2008)
27	**Levamisole**	Levamisole	NE	NE Levamisole is a topical application (139-887; 140-844). When cows are administered a drench of levamisole HCL, milk tests below the 0.1 ppm level set by the FDA (50 ppb) 24 hr after administration (FAO, 1994).
		Levamisole hydrochloride	MDT < 25	IV= 24 hrs, IM= 24 hrs, FARAD (Damian *et al.,* 1997) After treatment of cows with 8 mg/kg bw, via drench, pellets, bolus or injectable (sc) administration, residues of levamisole HCL were equal to or less than the 0.1 ppm residue level set by the FDA in milk at 24 hrs. (FAO, 1994).

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
		Levamisole phosphate	NE	NE (21 CFR 520.1242) This levamisole drug formulation is administered via SC injection at approximately 8 mg/kg bw (assuming 544 kg cow). After treatment of cows with 8 mg/kg bw, via drench, pellets, bolus or injectable (sc) administration, residues of levamisole HCL were equal to or less than the 0.1 ppm residue level set by the FDA in milk at 24 hrs (FAO, 1994).
28	**Lincomycin**	Lincomycin hydrochloride	NE	NE (21 CFR 520.1242) Lincomycin HCl is administered via OS, IM/IV. In cows receiving 4.14 mg/kg bw (intramammary) total dose over 24 hr, residues were detected at 0.13ppm in milk at 48 hr. In cows (n= 24) administered 7.28 mg/kg bw total dose (intramammary) over 24 hr total, residues were not detected in milk at 96 hrs post-administration and below the swine muscle tolerance of 0.1 ppm at 72 hr. (FAO, 2003).
		Lincomycin hydrochloride monohydrate	NE	NE In a similar FAO document listed above is also for lincomycin hydrochloride monohydrate, even though the experiments were performed using the HCl formulation only. (FAO, 2003). According to Bela Pharm Lincomycin hydrochloride monohydrate has a withdrawal time in swine meat of 7 d.
29	**Meloxicam**	Meloxicam	200 > MDT ≥ 100	Milk withdrawal 120 hrs (Smith *et al.* 2008) in the UK.
30	**Moxidectin**	Moxidectin-1	0	0 hr milk discard time for 141-099 (accessdata.fda.gov)
		Moxidectin-2	200 > MDT ≥ 100	NADA 141-220 is administered via SC injection at 0.2mg/kg bw. Milk residues are available for dairy sheep administered moxidectin by SC injection at 0.2 mg/kg bw. Sheep were milked 2X per day. Resultes showed moxidectin in milk at 35 d; however, concentrations were below the tolerance for residues in cows muscle (50 ppb) by approximately 15 d post-exposure. The elimination half life was 22.8 days with milk concentration levels greater than plasma concentration levesl at all time points assessed (Imperiale *et al.*, 2004b)
31	**Naproxen**	Naproxen	0	0 hrs Unable to find references for this number and on pubmed, including pharmacokinetics in cows.
32	**Neomycin**	Neomycin sulfate	NE	NE Cows were administered neomycin intramammary according to the manufacturers instructions. 4 different formulations were used, each containing another antibiotic as well. The detection limit of the assay was 0.15 ug/mL, which is also the FDAs residue tolerance level in milk.

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
				The last milking where residues were detected ranged from 4.3-14.8 milkings (upper limit in 95% confidence interval). Considering there were two milkings a day, the milk withdrawal time ranges from 51.6 to 177.6 hrs (Moretain and Boisseau, 1993).
33	**Nitrofurazone**	Nitrofurazone	NE	NE (21 CFR 520.1468) Cows were dosed with 65.6 mg, 131.2 mg and 470 mg (4X, 1 per 24 hr) radiolabeled nitrofurazone by intramammary, IU and topical, respecitvely. Residues remained the longest in milk from topical administration. By 84 hrs post-treatment, residues were no longer deteced in milk after intramammary and intrauterine administration. At 144 hrs, nitrofurazone residues were still detected at the last experimental time of 144 hrs (0.242 ppb) (Smith *et al.*, 1998). The indication of the NADA numbers listed is via topical or opthalmic administration.
34	**Novobiocin**	Novobiocin sodium	100> MDT ≥ 65	72 hrs (6 milkings) (accessdata.fda.gov)
35	**Oxfendazole**	Oxfendazole-1	NE	NE FAO recommends a MRL of 100 ug/L. In cows administered 7.5 mg/kg bw orally, oxfendazole was below the limit of quanitification (5 ug/L) at 96 hrs and below the FAO milk residue recommendation at 72 hrs. At a lower dose (4.5 mg/kg bw) administered orally, the milk residues of oxfendazole were below LOQ at 84 hrs and below the FAO milk residue recommendation at 60 hrs (Livingston, 1991); however, the indication for oxfendazole-1 is intramammary.
		Oxfendazole-2	200 > MDT ≥ 100	72 hrs after last milking in lactating cows or 30 days (720 hrs) prior to calving in dry cows (21 CFR 526.1590) At 72 hrs after SC administration at 3 mg/kg bw to cows, no residues were detected in milk. Residues of 5 ppb were found at 60 hrs (Moreno *et al.,* 2005).
36	**Oxytetracycline**	Oxytetracycline hydrochloride-1	200 > MDT ≥ 100	Oxytetracycline was administered orally in water to cows at the dose 9 mg/kg bw. Peak concentrations occurred around approximately 1.1 ug/mL at 2 hr. By 24 hr, plasma concentrations had reached approximately 0.2 ug/mL (Palmer, *at el*, 1983).
		Oxytetracycline hydrochloride-2	200 > MDT ≥ 100	96 hours for IM or SC for short acting formula. (Haskell *et al.,* 2003)
		Oxytetracycline-3	200 > MDT ≥ 100	168 hrs for intrauterine exposure to up to 2 g of long acting, non-aqueous solution (Martin-Jimenez *et al.,* 1997). For intrauterine administration in an aqueous solution, 72 hrs. (Haskell *et al.*, 2003); 96

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
				hours for IM or SC for short acting formula. (Haskell *et al.*, 2003)
37	**Penicillin**	Penicillin g procaine-1	65> MDT ≥ 25	48 hrs (4 milkings) (accessdata.fda.gov)
		Penicillin g procaine-2	100> MDT ≥ 65	10 mL in sesame oil, 60 hrs (5 milkings); 6 mL peanut oil dosed twice, 60 hrs (5 milkings) after last treatment and 84 hrs (7 milkings) after treatment if dosed 3 times. Used 72 - Mid point between 60 – 84 (accessdata.fda.gov)
		Penicillin g procaine-3	200 > MDT ≥ 100	48 hrs w approved use; ELU = 120 hrs (Payne, The Compendium North American Ed) (21CFR 526.1696) Penicillin G procaine 3 is indicated for dogs/cats via intramuscular injection at 22000 units/kg at 24 hr intervals. In cows administered a much lower dose (6600 units/kg) intramuscular the milk withdrawal time is 48 hrs (accessdata.fda.gov).
		Penicillin G benzathine & Penicillin G Procaine	MDT ≥ 200	60-84 hrs-lactating; dry cows, 72hrs following calving (21 CFR 526.1696); 432 hrs w/ ELU
38	**Phenylbuta-zone**	Phenylbutazone-1	MDT ≥ 200	NE (21 CFR 526.1696); 432 hrs w/ ELU Zero tolerance policy for residues due to potential to cause aplastic anemia (Smith *et al.*, 2008).
		Phenylbutazone-2	MDT ≥ 200	NE; 432 hrs w/ ELU Zero tolerance policy for residues due to potential to cause aplastic anemia (Smith *et al.*, 2008). .
39	**Pirlimycin**	Pirlimycin hydrochloride	65> MDT ≥ 25	36 hrs regardless of treatment duration (accessdata.fda.gov)
40	**Spectinomycin**	Spectinomycin hydrochloride	100> MDT ≥ 65	NE (21 CFR 520.1720); 96 hrs (Damian *et al.*, 1997). Spectinomycin HCl is indicated for poultry and swine. In the USA, there is a no tolerance limit for spectinomycin in whole eggs. Chickens dosed with 50 mg/kg bw via water for 7 days, no residues were detected at 0 days post treatment (Goetting *et al.*, 2011)
		Spectinomycin sulfate	65> MDT ≥ 25	MRL set by JECFA is 0.2 mg/L. In lactating cows administered 30 mg/kg bw/d intramuscularly for 5 days, spectinomycin residues fell below 100 ppb at 36 hrs. In a second study, spectinomycin was undectable in milk after intramuscualr administration at 24 hrs post treatment (EMA, 2000a).
41	**Streptomycin sulfate**	Streptomycin sulfate	100> MDT ≥ 65	96 hrs for ELU (Payne, The Compendium North American Ed) (21 CFR 520.2123). Lactating she-buffaloes were administered 10 mg/kg bw streptomycin via intramuscular injection. The drug entered milk at 3

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
				h and was no longer detected at 10 hr post administration.
42	**Sulfabromo-methazine**	Sulfabromomethazine sodium	100> MDT ≥ 65	96 hrs (accessdata.fda.gov)
43	**Sulfachlor-pyridazine**	Sulfachlorpyridazine-1	200 > MDT ≥ 100	Plasma half-life when administered to cows in conjuction with trimethoprim was 13.1 +/- 0.86 h. Route and dose not specified. Abstract only (Rolinski and Duda, 1984). To achieve a 1% plasma concentration compared to the original dose would take 6.54 half-lives. Therefore, at ((13.1+0.86 h) * 6.54) 91.3 hrs.
		Sulfachlorpyridazine-2	100> MDT ≥ 65	See Sulfachloropyridazine-1. Little data is available for the PK in any animal except horses.
44	**Sulfa-dimethoxine**	Sulfadimethoxine-1	65> MDT ≥ 25	60 hrs (accessdata.fda.gov) for NADA 031-715 - oral administration of 1.25-2.5g per 45.5 kg bw.
		Sulfadimethoxine-2	65> MDT ≥ 25	60 hrs (accessdata.fda.gov) for NADA 041-245, 200-038, 200-177 - IV administration of 50 mg/kg initial dose and 25 mg/kg every 24 hrs after.
		Sulfadimethoxine-3	NE	The dose administered here is 1.25 X that of sulfadimethoixine-1, 2. This is also a sustained release formula, therefore, the milk withdrawal time may be slightly longer. This is not to be used in lactating dairy cows.
45	**Sulfaethoxy-pyridazine**	Sulfaethoxypyridazine-1	100> MDT ≥ 65	72 hrs (accessdata.fda.gov) for oral administration of 55 mg/kg bw/d for 4 days
		Sulfaethoxypyridazine-2	100> MDT ≥ 65	72 hrs (accessdata.fda.gov) for IV administration of 55 mg/kg bw/d for not more than 4 days
		Sulfaethoxypyridazine-3	NE	The dose administered here is 4 X that of sulfaethoxypryidazine-1, 2. This is also a controlled release formula; therefore, the milk withdrawal time may be slightly longer. This is not to be used in lactating dairy cows.
46	**Sulfamethazine**	Sulfamethazine-1	NE	96 hrs (Merck Vet Mannual Online, updated 2012)
		Sulfamethazine-2	NE	96 hrs (Merck Vet Mannual Online, updated 2012). 10 days milk; references not listed – (Medford Vet Clinic, 2015); 21 CFR 522.2260 specifies 10 d withdrawal before slaughter.
		Sulfamethazine-3	NE	96 hrs (Merck Vet Mannual Online, updated 2012)
47	**Sulfaquin-oxaline**	Sulfaquinoxaline	NE	Unable to find much information. In rabbits dosed with 50 mg/kg sulfaquinoxaline, the mean plasma half-life for the drug and its metabolie was 12.7+/-8 h and 15.4 +/- 3.5 hr, respectively. (Eppel and

54 Drugs	54 Drug Names	Drug Formulation	Milk Discard Time (MDT) (hours)	References Estimated Drug Persistence in Cow/Milk/ FDA/ FARAD/ Other published data/ Ref/hours
				Thiessen, 1984).
48	**Tetracycline**	Tetracycline Hydrochloride-1	NE	NE (21 CFR 520.2260a) (21 CFR 520.2261a) In cows administered 10 mg/kg tetracycline hydrochloride IV, milk residues were below the 2 ppm tolerance (sum of tetracyclines in milk) at 96 hrs post-administration (Rodrigues *et al.,* 2010); however, drugs with the specified NADA numbers are adminisered orally.
		Tetracycline hydrochloride-2	NE	NE (21 CFR 520.2325) Unable to locate available information for pharmacokinetics of tetracycline administered topically to animals.
49	**Thiabendazole**	Thiabendazole-2	100> MDT ≥ 65	96 hrs (accessdata.fda.gov)
50	**Tildipirosin**	Tildipirosin	NE	The peak plasma concentration of female and male cows dosed with 4 mg/kg SC was 0.711+/-0.274 ug/mL at 0.69 +/- 0.26 h. The terminal plasma half-life was 210 +/- 53 hours. (Menge *et al.,* 2012)
51	**Tilmicosin phosphate**	Tilmicosin phosphate	NE	0 hrs (Merck Vet Manual, updated 3/2012)
52	**Tripelennamine**	Tripelemamine	MDT < 25	24 hrs (accessdata.fda.gov)
53	**Tulathromycin**	Tulathromycin	NE	Goats were administered 2.5 mg/kg SC tulathromycin and plasma samples analyzed using mass spec (LOQ 2 ng/mL, using first dose administration data). The maximum concentration in plasma was 1.0 +/- 0.42 ug/mL at 0.6 +/- 0.98 h. The terminal elimination half-life was 45.7 +/- 17.6 hrs. (Romanet *et al.,* 2012)
54	**Tylosin**	Tylosin-2	MDT < 25	24 hrs. According to the Merck Veterinary Mannual 96 hours for milk discard time and a drug withdrawal time of 21 d in cows (IM administration 10-20mg/kg).

1 NE: Not established

APPENDIX 5.11: CRITERION C: PROCESSING STEPS OTHER THAN HEATING

To determine the impact of processing, we began by reviewing the breadth of dairy products available on the market in the U.S. This review identified compositional changes (*i.e.,* changes in the relative content of fat, protein, water, and solids) as well as five distinct types of processes that may impact drug residue concentrations but that are not adequately captured by compositional changes: heating, culturing, aging (during cheese formation), drying and freezing. Heating of dairy products during processes such as pasteurization, cheese making or retort processing can lead to the degradation of drug residues, even though the impact differs by compound and time-temperature combination. A considerable number of scientific studies have been conducted to evaluate the impact of different heat treatments on drug residue concentrations, and because of the amount of available data and the complex differences among heat treatments these data are shown separately (see Appendix 5.14). During culturing and aging, for instance during yogurt or cheese making, drugs may become physically bound to microorganisms or the microorganisms may degrade the active compound. In addition, pH changes during culturing or aging may change the protonation of a compound, thus potentially changing partitioning behavior, even though acidification typically occurs after separation so that differences in partitioning behavior should not have a considerable impact on drug residue concentrations during culturing or aging. Only a very small number of studies have investigated the impact of culturing on drug residue concentrations (see Table below), indicating either no impact on the drug residue concentrations or only a moderate decrease (once concentrations due to water loss have been accounted for, that we capture among the compositional changes). In the absence of sufficient data to allow extrapolation we decided not to consider the impact of culturing or aging further in our multicriteria-based ranking, pending availability of sufficient scientific data. Similarly, freezing may possibly lead to the degradation of some drugs, but few available data indicate no impact of freezing. Therefore, we did not include the impact of freezing in our multicriteria-based ranking model. Drying can lead to selective water removal, thus concentrating water-soluble drugs beyond those concentrations predicted by compositional changes alone. Even though data are scarce (see Table below) we decided to incorporate the impact of drying in the multicriteria-based ranking model because it can be easily calculated and may lead to a substantial concentration of water-soluble drugs in certain dried products.

Table A5.21 Literature review for processing steps (except for heating)

Drug	pH change /culturing-Decrease [%]	pH change / culturing -Reference	Cheese aging - Impact	Cheese aging - Reference	Drying - Impact	Drying - Reference	Freezing -Impact	Freezing - Reference
Acetylsalicylic acid	-	-	-	-	-	-	-	-
Albendazole	-	-	-	-	-	-	-	-
Amikacin	-	-	-	-	-	-	-	-
Amprolium	-	-	-	-	-	-	-	-
Amoxicillin	-	-	-	-	-	-	-	-
Ampicillin	-	-	-	-	-	-	-	-

Drug	pH change /culturing-Decrease [%]	pH change / culturing -Reference	Cheese aging - Impact	Cheese aging - Reference	Drying - Impact	Drying - Reference	Freezing -Impact	Freezing - Reference
Ceftiofur	-	-	-	-	-	-	-	-
Cephapirin	-	-	-	-	-	-	-	-
Chloramphenicol	-	-	-	-	-	-	-	-
Clorsulon	-	-	-	-	-	-	-	-
Cloxacillin	35 – 40	Grunwald and Petz 2003	-	-	-	-	-	-
Danofloxacin	-	-	-	-	-	-	-	-
Dihydrostreptomycin	-	-	-	-	-	-	-	-
Doramectin	-	-	-	-	-	-	-	-
Enrofloxacin	-		-	-	-	-	-	-
Eprinomectin	none (for Ivermectin)	Cerkvenik *et al*. 2004	increase (moisture loss)	Cerkvenik *et al*. 2004, Imperiale *et al*. 2004a	-	-	-	-
Erythromycin	-	-	-	-	-	-	-	-
Florfenicol	-	-	-	-	-	-	-	-
Furazolidone	-	-	-	-	-	-	-	-
Flunixin	-	-	-	-	-	-	-	-
Gamithromycin	-	-	-	-	-	-	-	-
Gentamycin	-	-	-	-	-	-	-	-
Hetacillin	-	-	-	-	-	-	-	-
Ivermectin	none (for Ivermectin)	Cerkvenik *et al*. 2004	increase (moisture loss)	Cerkvenik *et al*. 2004, Imperiale *et al*. 2004a	-	-	-	-
Kanamycin	-	-	-	-	-	-	-	-
Ketoprofen	-	-	-	-	-	-	-	-
Levamisole	-	-	-	-	-	-	-	-
Lincomycin	-	-	-	-	-	-	-	-
Meloxicam	-	-	-	-	-	-	-	-
Moxidectin	-	-	increase (moisture loss)	Cerkvenik *et al*. 2004, Imperiale *et al*. 2004b	-	-	-	-
Naproxen	-	-	-	-	-	-	-	-
Neomycin	-	-	-	-	-	-	-	-
Nitrofurazone	-	-	-	-	-	-	-	-
Novobiocin	-	-	-	-	-	-	-	-
Oxfendazole	-	-	-	-	-	-	-	-
Oxytetracycline	none	Hassani, *et al*. 2008	-	-	-	-	-	-

Drug	pH change /culturing-Decrease [%]	pH change / culturing -Reference	Cheese aging - Impact	Cheese aging - Reference	Drying - Impact	Drying - Reference	Freezing -Impact	Freezing - Reference
Penicillin	0 – 50 43 – 47	Adetunji 2011 Grunwald and Petz 2003	decrease (blue mold ripened cheese) no impact (other cheeses)	Ledford and Kosikowski 1965	-		-	-
Phenylbutazone	-	-	-	-	-	-	-	-
Pirilomycine	-	-	-	-	-	-	-	-
Spectinomycin	-	-	-	-	-	-	-	-
Streptomycin	-	-	-	-	-	-	-	-
Sulfabromomethazine	-	-	-	-	-	-	-	-
Sulfachlorpyridazine	-	-	-	-	-	-	-	-
Sulfadimethoxine	-	-	-	-	-	-	-	-
Sulfaethoxypyridazine	-	-	-	-	-	-	-	-
Sulfamethazine	-	-	-	-	**Spray drying:** <10x concentration	Malik *et al.* 1994	none	Papapanagiotou *et al.* 2005; Das and Bawa 2010
Sulfaquinoxaline	-	-	-	-	-	-	-	-
Tetracycline	none	Hassani *et al.* 2008	-	-	-	-	-	-
Thiabendazole	-	-	-	-	-	-	-	-
Tilmicosin	-	-	-	-	-	-	-	-
Tildipirosin								
Tirpelennamine	-	-	-	-	-	-	-	-
Tulathromycin	-	-	-	-	-	-	-	-
Tylosin	-	-	-	-	-	-	-	-

APPENDIX 5.12: CRITERION C: MAJOR METABOLITES FOR THE 54 SELECTED PHARMACEUTICAL DRUGS

Approach for addressing metabolites in the multicriteria-based ranking

After administration to animals or humans, pharmaceutical drugs are often metabolized in the liver, kidney, or other tissues, thereby changing the structure and physico-chemical properties of the active compound and often increasing the rate of excretion, for instance by increasing the number of hydrophilic moieties and thus facilitating renal excretion. The rate of metabolite formation and the exact metabolites being formed, however, differ by drug class and individual compound. In addition, factors such as host species, age, live stage, or the presence of diseases or disorders can impact metabolite formation, and the ratio of parent compound to different metabolites may differ among organs (*e.g.,* muscle, liver, udder). Some drugs do not appear to be metabolized to a significant extent if administered to animals or humans while others are almost completely metabolized shortly after administration. Here, we reviewed the available data regarding metabolite formation to determine when partitioning behavior would have to be predicted separately for the parent compound and the major metabolites, drawing upon regulatory data (*e.g.,* data obtained to support NADA applications) where possible. However, for certain drugs, the metabolites have not been characterized, a priori precluding a separate prediction of the partitioning behavior for these metabolites due to a lack of available data. For other drugs, data were not available in milk (*e.g.,* data for muscle or kidney only), or only available in other host species than lactating dairy cows, and in some cases data had to be extrapolated from other, closely related drugs in the same drug class. In addition, the metabolite data analyzed in this multicriteria-based ranking, which has primarily been generated to obtain regulatory drug approval for a new drug or formulation, is typically only collected in healthy cows. Because in some cases clinically sick animals may fail to metabolize drugs to the same extent as healthy cows, actual ratios of parent to major metabolites in treated cows may differ from those reported in the available literature, and the ratio of parent to metabolite may change over the course of the withdrawal time.

To determine the extent to which the different drugs included in this multicriteria-based ranking model are metabolized if administered to lactating dairy cows despite the data limitations discussed above, as well as the nature of the metabolites and the relative ratio of parent to metabolite at different times post administration, the following approach was chosen:

1. Determine marker residue (21 CFR 556, Subpart B) if applicable;
2. Review drug-specific published data from regulatory agencies regarding metabolite formulation after administration to lactating dairy cows if available (*e.g.,* FDA NDAs, EMA documents, and data submitted to regulatory agencies in other countries);

3. Review drug-specific published data from regulatory agencies regarding metabolite formation in relevant animals other than lactating dairy cows (*e.g.,* non-lactating cows or other species) if no data available for lactating dairy cows;
4. Review drug- specific data published in peer-reviewed journals regarding metabolite formation in lactating dairy cows or other relevant species (if steps a – c did not generate sufficient data).

The goal was to evaluate:

1) whether drug is metabolized after administration to lactating dairy cows;
2) ratio of parent to metabolites (if ratio variable over withdrawal time minimum and maximum are considered);
3) nature of metabolites (to determine partitioning behavior).

Drugs that are not substantially metabolized were not investigated further because it was assumed that the drug residue was present (almost) exclusively in form of the parent drug (unless the metabolite was the marker residue). Similarly, drugs for which no specific metabolite was identified were not further investigated due to the lack of a clearly identified metabolite for further study. For all other drugs the marker residue or the major metabolite were chosen for further analysis. If one major metabolite could not be identified unequivocally, multiple common metabolites were analyzed and, if necessary, the one with properties most dissimilar to the parent drug was chosen.

For drugs for which the metabolite(s) were further considered (see Table below), this step was followed by a comparison of the physico-chemical properties of the parent and metabolite(s) to determine:

1) whether parent and metabolite(s) differed sufficiently in partitioning behavior to fall within separate drug partitioning categories (based on an analysis of chemical structures which included comparison of log(Papp) values where applicable); and
2) if parent and metabolite(s) fell within different partitioning categories: for each dairy product in the model, determine the compound (*i.e.,* parent or metabolite) most concentrated in the specific product.

Table A5.22 Drug metabolites

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
Acetylsalicylic acid	yes	extensively metabolized	-	Salicylic acid	Parent and major metabolite account for >90% of total residue in tissue; minor metabolites: salicyluric acid, salicyluric glucuronide, salicyl ester glucuronide, salicyl phenol glucuronide, gentistic acid, and gentisuric acid.	Metabolite main active compound; limited data on other metabolites or depletion kinetics in bovine milk	EMA, 1999a
Albendazole	yes	extensively metabolized; marker residue selected	Albendazole 2-aminosulfone	2-albendazole, sulfone, sulfoxide	Extensively metabolized	Data for cows kidney	FDA, 1989
Amikacin	-	not extensively metabolized	-	-	Very limited data available; data for streptomycin, gentamycine and neomycin; but aminoglycosides do not appear to be metabolized extensively in humans or farm animals	Very limited data available; data for streptomycin, gentamycine and neomycin; but aminoglycosides do not appear to be metabolized extensively in humans or farm animals	FAO, 1995
Amprolium	-	not identified	Parent	Unidentified	Major metabolite accounts for ~ 50% of total residue	No data for cows available; numerous minor metabolites	EMA, 2001a
Amoxicillin	yes	not extensively metabolized but metabolite of allergic potential	Parent	Penicilloic acid	Parent predominant, penicillic acid accounts for ~ 10 – 25% of total residue	Metabolite of allergic potential	USP, 2007a; EMA, 2008

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
Ampicillin	yes	not extensively metabolized but metabolite of allergic potentialn	Parent	Penicilloic acid	Parent predominant, penicillic acid accounts for ~ 10 – 25% of total residue (data for Amoxicillin)	Metabolite of allergic potential	USP, 2007a; EMA, 2008
Ceftiofur	yes	extensively metabolized	Desfuroylceftiofur	Desfuroylceftiofur cysteine disulfide (DCD)	Parent initially predominant residue in milk, metabolite later predominant.	-	FDA, 2005
Cephapirin	yes	extensively metabolized	Parent	Desacetylcefapirin	Relative frequency of metabolite in milk unclear	Major metabolite in cow's milk	EMA, 2001b
Chloramphenicol	yes	extensive metabolization appears possible	n/a	Chloramphenicol-glucuronide, chloramphenicol base, hydroxyamphenicol	unclear and species-dependent	Minor metabolites may also be present	EMA, 2009a
Clorsulon	-	not extensively metabolized	Parent	Acetaldehyde derivative and butyric acid derivative	Parent accounts for majority of total residue; 2 major metabolites account for < 10% of total residue each	Several other minor metabolites; data collected in steers.	EMA, 1995a; FDA 1991a
Cloxacillin	yes	not extensively metabolized but metabolite of allergic potential	Parent	Penicilloic acid	Parent dominant residue	Metabolite of allergic potential	EMA, 2008
Danofloxacin	yes	extensively metabolized, metabolite more toxic than parent	Parent	Desmethyldanofloxacin, danofloxacin acyl-glucuronide, danofloxacin N-oxide	Extensively metabolized, primarily to N-desmethyl metabolite (~ 40% of total residue in cows liver)	Desmethyldanofloxacin higher toxicity; data collected in steers	FDA, 2002; FDA, 2000
Dihydrostreptomycin	-	not extensively metabolized	Parent	-	Very limited data available; data for	Very limited data available; data for	FAO, 1995

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
					streptomycin, gentamycine and neomycin; but aminoglycosides do not appear to be metabolized extensively in humans or farm animals	streptomycin, gentamycine and neomycin; but aminoglycosides do not appear to be metabolized extensively in humans or farm animals	
Doramectin	-	only minor metabolites	Parent	-	Parent accounts for 60 – 70% of total residue in cow's kidney and for 90% in cow's fat	3 minor metabolites detected; data based on cows tissue	FDA, 1996
Enrofloxacin	yes	extensively metabolized	Desethylene ciprofloxacin	Ciprofloxacin	Ciprofloxacin more concentrated in milk than parent	Other metabolites may be present but are likely less important	Idowu *et al.*,2010
Eprinomectin	-	not extensively metabolized	Eprinomectin B1a	M1 (24a-hydroxymethyl metabolite)	Parent compounds (B1a & B1b) account for majority of total residue in milk (~ 80 – 86% of total residue)	See reference for details on minor metabolites; potential differences in metabolism between genders	EMA 1996a
Erythromycin	-	significant concentration of major metabolite in cow's milk unlikely	Parent	N-methyl-erythromycin	Major metabolite only in bile and feces (in rat studies).	Data not based on cow's milk.	EMA, 2009b
Florfenicol	yes	marker residue	Florfenicol amine	florfenicol amine; 2-pyrrolidone	Parent accounts for majority of total residue	Most metabolites disappear quickly after administration; see reference for data on minor metabolites; data not specific to lactating dairy cows	USP, 2007b
Flunixin meglumine	yes	extensively metabolized	Flunixin free acid	5-hydroxy flunxin	Metabolite predominant residue in milk	See references for other, minor metabolites	FDA, 2004

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
Furazolidone	yes	mutagenic potential for metabolite	-	3-amino-oxazolidone-2	Up to 20% of total residue in swine liver	Main metabolite is mutagenic	EMA, 2009c; NIH, 2002
Gamithromycin	-	not extensively metabolized	Parent	N-despropyl N-desmethyl delads	Parent accounts for majority of total residue; major metabolite for approx. 10% of total residue	Data based on cow's kidney; see reference for more details	FDA, 2011
Gentamicin	-	not extensively metabolized	Parent	-	Data for gentamicin indicate that parent does not appear to be metabolized extensively in humans or farm animals	Data for gentamicin indicate that parent does not appear to be metabolized extensively in humans or farm animals	FAO, 1997
Hetacillin	yes	metabolite of allergic potential	-	Ampicillin; penicollic acid	Rapidly metabolized in aqueous solutions by hydrolysis to ampicillin; 10 – 25 % of dose excreted as penicollic acid;	Metabolized to ampicillin (active metabolite); penicollic acide of allergic potential; data not specific to lactating dairy cows	USP, 2003a,d
Ivermectin	yes	extensively metabolized	22,23-dihydroavermectin B1 a	24-OH-H2B1a	Parent accounts for > 50% of total residue in kidney and fat; major metabolite accounts for up to 20% of total residue	Metabolites include non-polar, polar and drug-like metabolites; parent and metabolite ratio changes with days after drug administration; see reference for details; data for steers	FDA, 1990
Kanamycin	-	not extensively metabolized	-	-	Very limited data available; data for streptomycin, gentamycine and neomycin only; but aminoglycosides do not appear to be	Very limited data available; data for streptomycin, gentamycine and neomycin only; but aminoglycosides do not appear to be	FAO, 1995

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
					metabolized extensively in humans or farm animals	metabolized extensively in humans or farm animals	
Ketoprofen	yes	extensively metabolized	-	RP 69400 (2-(phenyl 3-alpha-hydroxybenzoyl) propionic acid)	Metabolite accounts for majority of total residue	Ratio of parent to metabolite varies by tissue and species; parent and metabolite not detected in milk under recommended use; some minor metabolites	EMA, 1995b
Levamisole	yes	potentially extensively metabolized	Parent	S-cysteinyl-glycin conjugate	Unclear but unchanged proportion of total residue appears relatively small	Additional unidentified metabolite reported as major metabolite; based on liver data; see reference for additional information	EMA, 1996b; EMA, 2009d
Lincomycin	yes	extensively metabolized	Parent	Sulphoxide, N-desmethyl linomycin, N-desmethyl lincomycin sulphoxide	Extensively metabolized (based on data for rats)	~ 16 metabolites detected; metabolite profiles not for lactating dairy cows; see reference for details	EMA, 1998
Meloxicam	yes	extensively metabolized	-	5-hdyroxy methyl-meloxicam; 5-carboxy-meloxicam; oxalyl metabolite	Extensively metabolized in cows; 5-hydroxy methyl compound main metabolite	No milk metabolite profile data for cows available but metabolite profiles qualitatively similar across species (see reference for details)	EMA, 1999b
Moxidectin	-	not extensively metabolized	Parent	C-29/C-30 hydroxymethyl metabolite, C-14 hydroxymethoyl metabolite	Parent accounts for majority of total residue	Metabolite profile in milk and fat very similar	FDA, 1999
Naproxen	yes	extensively	-	acyl glucuronide,	Extensively	Based on human	Vree *et al.*,

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
		metabolized		isolgucuronide, O-desmethylnaproxen	metabolized	plasma and urine data; several other metabolites (see reference)	1993
Neomycin	-	not extensively metabolized	Parent	-	Data for neomycin indicates that parent does not appear to be metabolized extensively in humans or farm animals	Data for neomycin indicates that parent does not appear to be metabolized extensively in humans or farm animals	FAO, 1995
Nitrofurazone	-	not identified	-	unidentified	Extensively metabolized but no detailed metabolism studies for food animals available	Likely 5-nitro group reduced to amine; see reference for details	FAO, 1992
Novobiocin	-	not extensively metabolized	Parent	Epoxide metabolites & conjugated metabolites	Parent is predominant molecule; only parent appears to be present in milk.	See reference for minor metabolites and other details	EMA, 1999c; NIH 2006
Oxfendazole	yes	extensively metabolized	Fendbendazole	Oxfendazole sulphone	Extensively metabolized	Oxfendazole is the sulfoxide metabolite of fenbendazole; some metabolites potentially teratogenic; data for cow's milk limited	EMA, 2009e
Oxytetracycline	-	not extensively metabolized	Parent	-	Not known to be biotransformed to any significant extent	Residue distribution of oxy-/chlor-/tetracycline likely identical in food-producing animals	EMA, 1995c, USP, 2003c
Penicillin	yes	not extensively metabolized but metabolite of allergic potential	Parent & salts	Penicilloic acid	Parent predominant	Metabolite of allergic potential	EMA, 2008
Phenylbutazone	yes	extensively metabolized	-	Oxyphenbutazone	Primarily metabolized prior to excretion	Available data for lactating dairy cows	NIH, 2011

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
						scarce; data for humans; see reference for minor metabolites.	
Pirlimycin	yes	frequency of major metabolites somewhat unclear	Parent	Pirlimycin sulfoxide	Parent predominant residue.	-	USP, 2003b
Spectinomycin	-	not extensively metabolized	Parent	-	Not extensively metabolized; parent accounts for ~ 80% of total residue in kidney and 100% in milk	Limited data available for lactating dairy cows	EMA, 2001c
Streptomycin	-	not extensively metabolized	Parent	-	Very limited data available; data for streptomycin, gentamycine and neomycin; but aminoglycosides do not appear to be metabolized extensively in humans or farm animals	Very limited data available; data for streptomycin, gentamycine and neomycin; but aminoglycosides do not appear to be metabolized extensively in humans or farm animals	FAO, 1995; EMA 2001c
Sulfabromomethazine	yes	extensively metabolized	Parent	N(4)-acetyle metabolite	Extensively metabolized	Data extremely scarce; inference based on related sulfonamides, but sulfonamide metabolism depends on species & compound; hydroxyl metabolites potentially also formed; see reference for details	Korpimäki *et al.*, 2004
Sulfachlorpyridazine	yes	extensively metabolized	Parent	N(4)-acetyle metabolite	Extensively metabolized	Data extremely scarce; inference based on related sulfonamides, but sulfonamide	Korpimäki *et al.*, 2004

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
						metabolism depends on species & compound; hydroxyl metabolites potentially also formed	
Sulfadimethoxine	yes	extensively metabolized	Parent	N(4)-acetyle sulfadimethoxine	Extensively metabolized but metabolite concentration in milk lower than parent compound;	Other metabolites including N(4)-lactose conjugate and hydroxyl metabolites likely also present.	Nouws *et al.*, 1988; Paulson *et al.*, 1992; Chiesa *et al.*, 2012
Sulfaethoxypyridazine	yes	extensively metabolized	Parent	N(4)-acetyle metabolite	Extensively metabolized	Data extremely scarce; inference based on related sulfonamides, but sulfonamide metabolism depends on species & compound; hydroxyl metabolites potentially also formed	Korpimäki *et al.*, 2004
Sulfamethazine	yes	extensively metabolized	Parent	N(4)-acetylsuphamethazine;	Extensively metabolized	Data based on cow's milk; metabolism of sulfonamides varies considerably by compound and animal species; metabolites hydroxylated at methyl group of pyrimidine side chain and other metabolites such as N(4)-lactose conjugate and N(4) glucose conjugate also likely present.	Nouws *et al.*, 1988; Paulson *et al.*, 1992
Sulfaquinoxaline	yes	extensively metabolized	Parent	N(4)-acetyle metabolite	Extensively metabolized	Data scarce; hydroxyl metabolites potentially	Paulson *et al.*, 1992

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
						also formed, other metabolites such as N(4)-lactose conjugate likely also present	
Tetracycline	no	not extensively metabolized	Parent	-	Not known to be biotransformed to any significant extent	Residue distribution of oxy-/chlor-/tetracycline likely identical in food-producing animals	EMA, 1995c; USP 2003c
Thiabendazole	yes	extensively metabolized; major metabolite of particular toxicity potential	Parent	5-hydroxythiabendazole	Ratio of metabolite to total residue unclear.	Various minor metabolites; 5-hydroxythiabendazole metabolite likely the toxic metabolite; metabolite profile in milk unclear	EMA, 2004a; EMA, 2009f
Tilmicosin	-	not extensively metabolized (major metabolite is active isomer)	Parent	Tilmicosin cis-8 epimer (*i.e.*, active isomer)	Parent accounts for most of total residues; parent and major metabolite account for about 96% of total residue;	T9, T10 and O-desmethyl litmicosin are minor metabolites but may not all be excreted in milk (see reference)	EMA, 2000b
Tildipirosin	yes	potentially extensively metabolized	-	Sulphate conjugates of tildipirosin (M7, M4)	Major metabolite accounted for up to ~ 50% of total residue	Data based on rats and dogs; no data available for lactating dairy cows	EMA, 2010
Tripelennamine	yes	extensively metabolized	Parent	hydroxytripelennamine glucuronide; N-glucuronide; N-oxide	Extensively metabolized	Data based on residues in human urine; other metabolites reported (see reference for details)	Chaudhuri *et al.*, 1976
Tulathromycin	-	not extensively metabolized	CP-60,300	Some minor metabolites	Metabolites only minor contributors to total residues	Data not for lactating dairy cows; see reference for minor metabolites; metabolite profiles appear similar across	EMA, 2004b

Parent drug	Metabolite further considered	Rationale	Marker residue (21 CFR 556, Subpart B)	Major metabolites	Relative Frequency of metabolite	Comments	References
						species	
Tylosin	yes	extensively metabolized	Parent	Dihydroxydesmycosin	Extensively metabolized but parent appears to be predominant residue	Several other minor metabolites; metabolite profiles appear qualitatively similar across species, but differences in respective quantities (see reference for details)	EMA, 1997; EMA, 2009g

APPENDIX 5.13: CRITERION C: PARTITIONING BEHAVIOR (BASED ON NCBI PUBCHEM, AVAILABLE AT HTTP://PUBCHEM.NCBI.NLM.NIH.GOV/) OF THE 54 SELECTED DRUGS

Rationale: For each drug included in the multicriteria-based ranking, the partitioning behavior in milk and milk products was determined based on log (Papp) values, where Papp is the apparent partition coefficient. Partitioning behavior was calculated from available data as shown in table A5.13.

In addition, for drugs identified in Appendix 5.12 as meriting further study, attempts were made to determine whether the partitioning behavior of the major metabolite is likely very different from that of the parent drug. To determine the partitioning behavior of the metabolite the following approach was chosen:

a. Determine log (Papp) or log (P) value using the PubChem, EMBL, or other applicable databases (if applicable);
b. Determine log Papp or P value from the peer-reviewed literature (if applicable);
c. Determine relative partitioning behavior of parent and major metabolite based on structural analysis (if steps a and b did not generate sufficient data for a determination of partitioning behavior).

The goal was to evaluate:

1) whether the partitioning behavior of the major metabolite is likely very different from that of the parent drug;
2) in which way the partitioning behavior of the major metabolite differs from that of the parent (*i.e.,* more or less hydrophobic);

Major metabolites for which the partitioning behavior was determined to be similar to that of the parent drug were not considered further for the Product Composition Score (C1.1). Major metabolites for which partitioning behavior was determined to be significantly different from parent drug were considered if the concentration of the metabolite in a product was likely higher than that of the parent drug to allow for an evaluation of a worst-case scenario. This was the case for only two drugs: albendazole and meloxicam. In both of these cases, the major metabolite(s) was/were significantly more water soluble than that parent.

Experimental data on drug partitioning in milk products is shown in the table below.

Table A5.23 Partition coefficients for drugs and their metabolites

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
Acetylsalicylic acid	yes	Salicylic acid	1.2	2.3	-2.11	-	PubChem	no	Within same log (P) or log (Papp) category
Albendazole	yes	2-albendazole, sulfone, sulfoxide	2.9	1.4	1.6	-	PubChem	yes	In different log (P) or log (Papp) category
Amikacin	-	-	-7.9	-	-10.62	-	PubChem	no	-
Amprolium	-	-	2.1	-	2.09	-	-	no	-
Amoxicillin	yes	Penicilloic acid	-2	-	-6.4	-	-	no	-
Ampicillin	yes	Penicilloic acid	-1.1	n/a	-5.46	Penicilloic acid is a carboxylic acid of the corresponding parent drug; it will be more water soluble than the parent	Structural analysis	no	Likely within same log (P) or log (Papp) category
Ceftiofur	yes	Desfuroylceftiofur cysteine disulfide (DCD)	0.2	n/a	-2.90	Metabolite is more water soluble	Structural analysis	no	Likely within same log (P) or log (Papp) category
Cephapirin	yes	Desacetylcephapirin	-1.1	-1.7	-5.14	-	PubChem	no	Within same category
Chloramphenicol	yes	Chloramphenicol-glucuronide,	1.1	-0.4	1.1	-	PubChem	no	Within same category

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
		chloramphenicol base, hydroxyamphenicol							
Clorsulon	-	-	1.2	-	1.2	-	PubChem	no	-
Cloxacillin	yes	Penicilloic acid	2.4	n/a	-1.96	Penicilloic acid is a carboxylic acid of the corresponding parent drug; it will be more water soluble than the parent	Structural analysis	no	Likely within same log (P) or log (Papp) category
Danofloxacin	yes	Desmethyldanofloxacin, danofloxacin acyl-glucuronide	-0.3	-0.8	-2.50	-	PubChem	no	Within same log (P) or log (Papp) category
Dihydrostreptomycin	-	-	-8.2	-	-14.5	-	PubChem	no	-
Doramectin	-	-	4.5	-	4.5	-	-	no	-
Enrofloxacin	yes	Ciprofloxacin	-0.2	-3.16	-1.21	Other literature references cite KoW of -0.12 for Ciprofloxacin (metabolite); see Ross *et al.*, 1992	PubChem	no	Within the same log (P) or log (Papp) category
Eprinomectin	-	-	3.5	-	3.5	Values for B1a and B1b	PubChem	no	-
Erythromycin	-	-	2.7	-	1.32	-	PubChem	no	-

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
Florfenicol	yes	florfenicol amine; 2-pyrrolidone	0.80	-0.2 /0.8	0.80	Values for different metabolites	PubChem	no	Within same log (P) or log (Papp) category
Flunixin meglumine	yes	4.1	-1.00	3.7	-1.00	-	PubChem	no	Within same log (P) or log (Papp) category
Furazolidone	yes	3-amino-2-oxazolidone	-0.10	-0.8	-0.10	-	PubChem	no	Within same log (P) or log (Papp) category
Gamithromycin	-	-	4.9	-	2.94	-	PubChem	no	-
Gentamicin	-	-	-4.1	-	-6.82	-	PubChem	no	-
Hetacillin	yes	Ampicillin; penicollic acid	-0.6	n/a	-4.95	Penicilloic acid is a carboxylic acid of the corresponding parent drug; it will be more water soluble than the parent	Structural analysis	no	Likely within same log (P) or log (Papp) category
Ivermectin	yes	24-OH-H2B1a	4.10	n/a	4.10	More water soluble because of demethylation and being hydrolyzed	Structural analysis	no	Likely within same log (P) or log (Papp) category
Kanamycin	-	-	-6.9	-	-9.62	-	PubChem	no	-

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
Ketoprofen	yes	RP 69400	3.1	n/a	0.75	More water soluble due to the addition of a hydroxyl group	Structural analysis	no	Likely within same log (P) or log (Papp) category
Levamisole	yes	S-cysteinyl-glycin conjugate	1.8	n/a	-1.40	More water soluble due to the addition of polar groups	Structural analysis	no	Likely within same log (P) or log (Papp) category
Lincomycin	yes	Sulphoxide, N-desmethyl linomycin, N-desmethyl lincomycin sulphoxide	0.2	n/a	-0.84	Slightly more water soluble due to structural changes	Structural analysis	no	Likely within same log (P) or log (Papp) category
Meloxicam	yes	5-hyroxy methyl-meloxicam; 5-carboxy-meloxicam; oxalyl metabolite	3.0	1.5	0.0	Kow value for 5-carboxy - meloxicam	PubChem	yes	In different log (P) or log (Papp) categories
Moxidectin	-	-	4.30	-	4.30	-	PubChem	no	-
Naproxen	yes	acyl glucuronide, isolgucuronide, O-desmethylnaproxen;	3.3	n/a	0.65	More water soluble due to glucuronization	Structural analysis	-	-
Neomycin	-	-	-9	-	-11.72	-	PubChem	no	-
Nitrofurazone	-	-	0.20	-	0.20	-	PubChem	no	-
Novobiocin	-	-	3.3	-	1.00	-	PubChem	no	-
Oxfendazole	yes	Oxfendazole sulphone	2.30	n/a	2.30	Essentially the same or slightly more	Structural analysis	no	Likely within same log (P) or log (Papp)

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
						water soluble due to conversion to sulphone			group
Oxytetracycline	-	-	-1.6	-	-5.60	-	PubChem	no	-
Penicillin G	yes	Penicilloic acid	1.8	-	-2.55	Penicilloic acid is a carboxylic acid of the corresponding parent drug; it will be more water soluble than the parent	Structural analysis	no	Likely within same log (P) or log (Papp) category
Phenylbutazone	yes	Oxyphenbutazone	3.2	2.7	1.04	-	PubChem	no	Within same log (P) or log (Papp) category
Pirlimycin	yes	Pirlimycin sulfoxide	1.7	n/a	1.38	More soluble due to conversion to sulphone	Structural analysis	no	Likely within same log (P) or log (Papp) category
Spectinomycin	-	-	-3.1	-	-4.88	-	PubChem	no	-
Streptomycin	-	-	-8	-	-12.15	-	PubChem	no	-
Sulfabromomethazine	yes	N(4)-acetyle metabolite	1	n/a	0.84	More water soluble due to acetylation	Structural analysis	no	Likely within same log (P) or log (Papp) category
Sulfachlorpyridazine	yes	N(4)-acetyle metabolite	1	n/a	0.05	More water soluble due to	Structural analysis	no	Likely within same log (P)

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
						acetylation			or log (Papp) category
Sulfadimethoxine	yes	N(4)-acetyle sulfadimethoxine	1.6	n/a	0.91	More water soluble due to acetylation	Structural analysis	no	Likely within same log (P) or log (Papp) category
Sulfaethoxypyridazine	yes	N(4)-acetyle metabolite	0.7	n/a	-0.25	More water soluble due to acetylation	Structural analysis	no	Likely within same log (P) or log (Papp) category
Sulfamethazine	yes	N(4)-acetylsuphamethazine;	0.3	n/a	0.24	More water soluble due to acetylation	Structural analysis	no	Likely within same log (P) or log (Papp) category
Sulfaquinoxaline	yes	N(4)-acetyle metabolite	1.7	1.5	0.52	-	PubChem	no	Likely within same log (P) or log (Papp) category
Tetracycline	-	-	-2	-	-6.22	-	PubChem	no	-
Thiabendazole	yes	5-hydroxythiabendazole	2.50	2.1	2.50	-	PubChem	no	Within same log (P) or log (Papp) category
Tilmicosin	-	-	3.6	-	0.82	-	PubChem	no	-
Tildipirosin	yes	Sulphate conjugate of tildipirosin (M7) and M4	4.3	n/a	1.30	More water soluble due to addition of sulphate group	Structural analysis	no	Likely within same log (P) or log (Papp) category
Tripelennamine	yes	hydroxytripelennamine glucuronide; N-	3.3	n/a	1.06	More water soluble due to	Structural analysis	no	Likely within same log (P)

Parent drug	Major metabolite determined to merit further analysis (see Appendix 5.12)	Major metabolites	Log (P) parent[1]	Log (P) major metabolite[1]	Log (Papp) parent[1]	Other comments	Reference metabolite	Parent & metabolite both considered in multicriteria-based ranking	Rational for considering / not considering metabolite separately from parent
		glucuronide; N-oxide				glucuronidation and addition of hydroxyl group			or log (Papp) category
Tulathromycin	-	-	3.8	-	2.1	-	PubChem	no	-
Tylosin	yes	Dihydroxydesmycosin	1.0	n/a	1.0	More water soluble due to structural changes	Structural analysis	no	Likely within same log (P) or log (Papp) category

Table A5.24 Summary of experimental data on drug partitioning in milk and milk products

Drug	$[Drug]_{cream}/[Drug]_{milk}$ [a]	$[Drug]_{soft\text{-}cheese}/[Drug]_{milk}$ [b]	$[Drug]_{ripened/aged\text{-}cheese}/[Drug]_{milk}$ [c]	Reference
Albendazole	-	1.21-1.96 (metabolites)	1.63-1.94 (Metabolites, Pecorino)	Fletouris *et al*., 1998; De Liguoro *et al*., 1996
Choramphenicol	1.06-8.10	-	-	Ziv and Rasmussen 1975
Dihydrostreptomycin	0.28-0.98	-	-	Ziv and Rasmussen 1975
Eprinomectin	-	3.4	~12-20, 3.1-5.4	Anastasio *et al*. 2005, Imperiale *et al.*, 2006
Erythromycin	1.0	-	-	Hakk, 2015
Ivermectin	18	2.54, 2.76	3.99-4.3, 3-9, 1.7-4.5	Hakk, 2015; Cerkvenik *et al*. 2004; Anastasio *et al*., 2002; Imperiale *et al*., 2004a
Ketoprofen	1.1			Hakk, 2015
Levamisole	-	1.53-1.73	2.33-2.69	Whelan *et al*., 2010
Moxidectin	-	2.4	1.8-4.7	Imperiale *et al.,* 2004b
Oxytetracyline	0.2	-	-	Adetunji, 2011; Ziv and Rasmussen, 1975, Hakk, 2015
Penicillin	0.3, 0.32-2.06	0.51	1.24	Hakk, , 2015; Adetunji, 2011; Cayle *et al*., 1986; Gurnwald and Petz, 2003; Ziv and Rasmussen, 1975
Streptomycin	-	0.65	-	Adetunji, 2011
Sulfadimethoxine	1.1	-	-	Hakk, 2015
Tetracycline	0.42-3.28	0.7	-	Anastasio *et al*., 2005, Imperiale *et al*., 2006

[a] Ratio of the concentration of a drug in cream (80% lipids) to the concentration of that drug in "raw" (whole) milk.
[a] Ratio of the concentration of a drug in soft-cheese to the concentration of that drug in "raw" (whole) milk.
[a] Ratio of the concentration of a drug in ripended or aged cheese to the concentration of that drug in "raw" (whole) milk.

APPENDIX 5.14: CRITERION C: HEAT STABILITY OF THE 54 DRUGS

Data availability on heat stability varies considerably among drugs. Experimental data under the typical dairy processing conditions are only available for a limited number of drugs, such as penicillin. In many cases, data are either not available or only available for heating in non-dairy systems, such as boiling in water and roasting/frying of animal meat. In addition, even under very similar heating conditions, results from different studies are not always consistent due to differences in methodologies. Because of this data limitation, when assigning numerical numbers of heat inactivation for the various drugs under the various heat processing conditions, we used expert judgment and followed several general criteria.

- Data for dairy systems (e.g. heating in milk) are given the highest weight, followed by data for other fluid systems (e.g. water), and then data for solid food systems (e.g. animal tissue).
- When heat inactivation data are not available for a drug, but are available for closely related drugs in the same drug family, the most conservative values (i.e. the least heat inactivation) for those closely related drugs are used.
- When no heat inactivation, we assumed that the drug was not inactivated by heat during processing.
- When literature provides a range of heat inactivation values for a given time-temperature combination, the most conservative value (i.e. the least heat inactivation) is used.
- In cases where the extent of heat inactivation was reported in the literature in the format of "> X%", we used value X as the extent of inactivation.
- In cases where the extent of heat inactivation was reported in the literature as not significant (NS) or in the format of "< X%", or the drug was described as "stable", we assigned the value of "0" as the extent of inactivation for that particular heating condition.
- In cases where the extent of heat inactivation was reports as a low positive value, we assume that the positive value was caused by measurement variability and assigned the value of "0" as the extent of heat inactivation.

Table A5.25 Heat stability of the 54 drugs

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Acetylsalicylic acid	No inactivation data available; assume no inactivation.	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Albendazole	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 82°C	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 82°C	17	Cooper *et al.*, 2011	Roasting or frying of bovine muscle and liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Albendazole	Muscle meat; Frying 4-6 min on each sides; Maximum internal temperature at 55°C	Muscle meat; Frying 4-6 min on each sides; Maximum internal temperature at 55°C	1	Cooper *et al.*, 2011	Roasting or frying of bovine muscle and liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Albendazole	Liver sample; Frying 14-19 min total; Maximum internal temperature at 94°C	Liver sample; Frying 14-19 min total; Maximum internal temperature at 94°C	14	Cooper *et al.*, 2011	Roasting or frying of bovine muscle and liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Albendazole	Pasteurization (not further specified)	Pasteurization (not further specified)	0 (parent compound not found in milk; data on metabolites)	Fletouris *et al.*, 1998	Data suboptimal and approximation only	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Albendazole	Cheese making	Cheese making	0 (parent compound not found in milk, data on metabolites)	De Liguoro *et al.*, 1996	Data suboptimal and approximation only	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Amikacin	60 min	56 °C	Stable	Delaney *et al.*, 1992	Heating in plasma	Pasteurization: 0% Longer impact: 17%	Sterilization: 95%	Cheese making: 0% Processed cheese: 17%
Amikacin	15 min	121°C	Heat stable based on minimum inhibitory concentration (MIC) method (heated in broth)	Traub and Leonhard 1995	The study characterized amikacin as having the same heat stability as two other aminoglycosides: gentamycin and kanamycin. Thus, we assigned % inactivation based on data from reference 117.	Pasteurization: 0% Longer impact: 17%	Sterilization: 95%	Cheese making: 0% Processed cheese: 17%
Amprolium	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Amoxicillin	30 min	63 °C	6.3	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	15 sec	72 °C	<0.1	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Amoxicillin	20 min	120 °C	47.6	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	4 sec	140 °C	0.5	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	10 min	40 °C	10	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	10 min	83 °C	9	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	30 min	60 °C	11	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	20 min	120 °C	>88	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	10 sec	140 °C	14	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%
Amoxicillin	15 min	121°C	Partially heat-stable based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 9%	Sterilization: 48%	Cheese making: 0% Processed cheese: 9%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ampicillin	30 min	63 °C	3.3	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	15 sec	72 °C	<0.1	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	20 min	120 °C	84	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	4 sec	140 °C	2.1	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	10 min	40 °C	non-significant reduction (NS)	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	10 min	83 °C	12	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	30 min	60 °C	9	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	20 min	120 °C	>88	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ampicillin	10 sec	140 °C	9	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ampicillin	15 min	121°C	Partially heat-stable based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 12%	Sterilization: 84%	Cheese making: 0% Processed cheese: 12%
Ceftiofur	10 min	40 °C	NS - 17	Zorraquino *et al.*, 2008a	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ceftiofur	30 min	60 °C	6 - 18	Zorraquino *et al.*, 2008a	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%
Ceftiofur	30 min	63 °C	16 - 41	Roca *et al.*, 2011	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ceftiofur	15 sec	72 °C	<1	Roca *et al.*, 2011	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%
Ceftiofur	10 min	83 °C	9 - 35	Zorraquino *et al.*, 2008a	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ceftiofur	20 min	120 °C	80 - 100	Roca *et al.*, 2011	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%
Ceftiofur	20 min	120 °C	> 89	Zorraquino *et al.*, 2008a	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ceftiofur	4 sec	140 °C	1 - 17	Roca *et al.*, 2011	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%
Ceftiofur	10 sec	140 °C	NS - 21	Zorraquino *et al.*, 2008a	No experimental data available for ceftiofur; estimation is based on experimental data for other cephalosporins (*i.e.*, Cefoperazone, Cefquinome, Cephalexin, Cephalonium, Cephapirin, Cephuroxime)	Pasteurization: 0% Longer impact: 9%	Sterilization: 80%	Cheese making: 0% Processed cheese: 9%
Cephapirin	30 min	63 °C	41.2	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 41%	Sterilization: 100 %	Cheese making: 0% Processed cheese: 41%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Cephapirin	15 sec	72 °C	<1	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 41%	Sterilization: 100 %	Cheese making: 0% Processed cheese: 41%
Cephapirin	20 min	120 °C	99.5	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 41%	Sterilization: 100 %	Cheese making: 0% Processed cheese: 41%
Cephapirin	4 sec	140 °C	3.8	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 41%	Sterilization: 100 %	Cheese making: 0% Processed cheese: 41%
Chloramphenicol	30 min	100°C	7	Franje *et al.*, 2010	Heating in water	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	60 min	100°C	12	Franje *et al.*, 2010	Heating in water	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	10 min	70°C	10	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	20 min	70°C	20	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	30 min	70°C	30	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Chloramphenicol	10 min	80°C	22	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	20 min	80°C	33	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	30 min	80°C	45	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	10 min	90°C	11	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	20 min	90°C	15	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	30 min	90°C	25	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	10 min	100°C	11	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	20 min	100°C	20	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Chloramphenicol	30 min	100°C	35	Moats 1988	-	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Chloramphenicol	15 min	121°C	Heat stable based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 22%	Sterilization: 35%	Cheese making: 0% Processed cheese: 22%
Clorsulon	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 84°C	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 84°C	0	Cooper *et al.,* 2011	Roasting or frying of bovine muscle and liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Clorsulon	Muscle meat; Frying 4-6 min on each sides; maximum internal temperature at 70°C	Muscle meat; Frying 4-6 min on each sides; maximum internal temperature at 70°C	0	Cooper *et al.,* 2011	Roasting or frying of bovine muscle and liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Clorsulon	Liver sample; Frying 14-19 min total; maximum internal temperature at 89°C	Liver sample; Frying 14-19 min total; maximum internal temperature at 89°C	9	Cooper *et al.,* 2011	Roasting or frying of bovine muscle and liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	10 min	40 °C	NS	Zorraquino *et al.,* 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Cloxacillin	30 min	60 °C	7	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	30 min	63 °C	7	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	30 min	65 °C	NS	Mishra 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	15 sec	72 °C	<0.1	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	10 min	83 °C	NS	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	15 min	90 °C	26 - 34	Grunwald and Petz 2003	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	20 min	120 °C	53	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	20 min	120 °C	72	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Cloxacillin	4 sec	140 °C	0.6	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Cloxacillin	10 sec	140 °C	7	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 53%	Cheese making: 0% Processed cheese: 0%
Danofloxacin	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Dihydrostreptomycin	20 – 30 min	70 °C	8	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	10 min	80 -90 °C	8	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	20 min	80 °C	25	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	30 min	80 °C	33	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Dihydrostreptomycin	20 min	90 °C	18	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	30 min	90 °C	33	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	10 min	100 °C	18	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	20 min	100 °C	33	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	30 min	100 °C	42	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	280 - 1320 min	71 °C	100	Moats 1988	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	30 min	60 °C	NS	Zorraquino *et al.*, 2009	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Dihydrostreptomycin	20 min	120 °C	98	Zorraquino *et al.*, 2009	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Dihydrostreptomycin	10 sec	140 °C	26	Zorraquino *et al.*, 2009	No data available for Dihydrostreptomyci; used data for Streptomycin	Pasteurization: 0% Longer impact: 8%	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Doramectin	No inactivation data available. Doramectin is closely related to Ivermectin. Therefore, data for ivermectin are used	No inactivation data available. Doramectin is closely related to Ivermectin. Therefore, data for ivermectin are used	No inactivation data available. Doramectin is closely related to Ivermectin. Therefore, data for ivermectin are used	No inactivation data available. Doramectin is closely related to Ivermectin. Therefore, data for ivermectin are used	No inactivation data available. Doramectin is closely related to Ivermectin. Therefore, data for ivermectin are used	Pasteurization: 0% Longerimpact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	15 sec	72°C	0	Roca *et al.*, 2010	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	20 min	120 °C	5	Roca *et al.*, 2010	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	4 sec	140 °C	0	Roca *et al.*, 2010	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	10 min	40 °C	NS	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Enrofloxacin	30 min	60 °C	NS	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	10 min	83 °C	NS	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	20 min	120 °C	18	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	10 sec	140 °C	NS	Zorraquino *et al.*, 2008a	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	180 min	100 °C	Stable	Lolo *et al.*, 2006	Heating in water in thermostatic oven at 100 °C	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Enrofloxacin	Frying, microwaving, boiling, roasting, grilling of chicken breast, leg, and liver	Frying, microwaving, boiling, roasting, grilling of chicken breast, leg, and liver	No effect	Lolo *et al.*, 2006	Data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Ciprofloxacin* (Enrofloxacin metabolite)	15 sec	72°C	0	Roca *et al.*, 2010	Ciprofloxacin is the major Enrofloxacin metabolite and itself a pharmaceutical drug	Pasteurization: 0% Longer impact: 0%	Sterilization: 13%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ciprofloxacin* (Enrofloxacin metabolite)	20 min	120 °C	13	Roca *et al.*, 2010	Ciprofloxacin is the major Enrofloxacin metabolite and itself a pharmaceutical drug	Pasteurization: 0% Longer impact: 0%	Sterilization: 13%	Cheese making: 0% Processed cheese: 0%
Ciprofloxacin* (Enrofloxacin metabolite)	4 sec	140 °C	0	Roca *et al.*, 2010	Ciprofloxacin is the major Enrofloxacin metabolite and itself a pharmaceutical drug	Pasteurization: 0% Longer impact: 0%	Sterilization: 13%	Cheese making: 0% Processed cheese: 0%
Ciprofloxacin* (Enrofloxacin metabolite)	15 min	121°C	Heat stable based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 13%	Cheese making: 0% Processed cheese: 0%
Eprinomectin	30 min	65 °C	0 - 5.6	Imperiale *et al.*, 2009	Consulted references for other macrocyclic lactones, including moxidectin and ivermectin.	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Eprinomectin	15 sec	75 °C	0 - 4.6	Imperiale *et al.*, 2009	Consulted references for other macrocyclic lactones, including moxidectin and ivermectin.	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Erythromycin	30 min	60 °C	21	Zorraquino *et al.*, 2011	More heat labile than other macrolides	Pasteurization: 21% Longer impact: 30%	Sterilization: 93%	Cheese making: 21% Processed cheese: 30%
Erythromycin	20 min	120 °C	>93	Zorraquino *et al.*, 2011	More heat labile than other macrolides	Pasteurization: 21% Longer impact: 30%	Sterilization: 93%	Cheese making: 21% Processed cheese: 30%
Erythromycin	10 s	140 °C	30	Zorraquino *et al.*, 2011	More heat labile than other macrolides	Pasteurization: 21% Longer impact: 30%	Sterilization: 93%	Cheese making: 21% Processed cheese: 30%
Erythromycin	15 min	121°C	Heat labile based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 21% Longer impact: 30%	Sterilization: 93%	Cheese making: 21% Processed cheese: 30%
Florfenicol	30 min	100 °C	2	Franje *et al.*, 2010	Heating in water; more heat stable in water than chloramphenicol	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Florfenicol	60 min	100 °C	3	Franje *et al.*, 2010	Heating in water; more heat stable in water than chloramphenicol	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Furazolidone	No inactivation data available; assume no inactivation.	No inactivation data available; assume no inactivation.	No inactivation data available; assume no inactivation.	No inactivation data available; assume no inactivation.	No inactivation data available; assume no inactivation.	Pasteurization: 0% Longer impact: 0%	Sterilization: 0 %	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Flunixin	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0 %	Cheese making: 0% Processed cheese: 0%
Gamithromycin	No data available; assume similar behavior as other macrolides; use the data for Tylosin (Zorraquino *et al.*,2011)	No data available; assume similar behavior as other macrolides; use the data for Tylosin (Zorraquino *et al.*,2011)	No data available; assume similar behavior as other macrolides; use the data for Tylosin (Zorraquino *et al.*,2011)	No data available; assume similar behavior as other macrolides; use the data for Tylosin (Zorraquino *et al.*,2011)	No data available; assume similar behavior as other macrolides; use the data for Tylosin (Zorraquino *et al.*,2011)	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese:10%
Gentamicin	30 min	60 °C	NS	Zorraquino *et al.*, 2009	-	Pasteurization: 0 % Longer impact: 20%	Sterilization: 97%	Cheese making: 0% Processed cheese: 20%
Gentamicin	20 min	120 °C	97	Zorraquino *et al.*, 2009	-	Pasteurization: 0 % Longer impact: 20%	Sterilization: 97%	Cheese making: 0% Processed cheese: 20%
Gentamicin	10 sec	140 °C	20	Zorraquino *et al.*, 2009	-	Pasteurization: 0 % Longer impact: 20%	Sterilization: 97%	Cheese making: 0% Processed cheese: 20%
Gentamicin	15 min	121°C	Heat stable based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0 % Longer impact: 20%	Sterilization: 97%	Cheese making: 0% Processed cheese: 20%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Hetacillin	No data available; assume similar inactivation kinetics as ampicillin (Tsuji, *et al.*, 1977)	No data available; assume similar inactivation kinetics as ampicillin (Tsuji, *et al.*, 1977)	No data available; assume similar inactivation kinetics as ampicillin (Tsuji, *et al.*, 1977)	No data available; assume similar inactivation kinetics as ampicillin (Tsuji, *et al.*, 1977)	No data available; assume similar inactivation kinetics as ampicillin (Tsuji, *et al.*, 1977)	Pasteurization: 0% Longer impact: 12%	Sterilization: 84 %	Cheese making: 0% Processed cheese: 12%
Ivermectin	30 min	65°C	0 – 3.2	Imperiale *et al.*, 2009	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Ivermectin	15 sec	75°C	0 - 5	Imperiale *et al.*, 2009	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Ivermectin	30 min	90°C	0	Cerkvenik *et al.*, 2004	Observations for yogurt made after heating at 90°C/30 min	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Ivermectin	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 70°C	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 70°C	0	Cooper *et al.*, 2011	Data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Ivermectin	Muscle meat; Frying 4-6 min on each sides; Maximum internal temperature at 84°C	Muscle meat; Frying 4-6 min on each sides; Maximum internal temperature at 84°C	14	Cooper *et al.*, 2011	Data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Ivermectin	Liver sample; Frying 14-19 min total; Maximum internal temperature at 89°C	Liver sample; Frying 14-19 min total; Maximum internal temperature at 89°C	23	Cooper *et al.*, 2011	Data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Kanamycin	30 min	60°C	NS	Zorraquino *et al.*, 2009	-	Pasteurization: 0% Longer impact: 17%	Sterilization: 95%	Cheese making: 0% Processed cheese: 17%
Kanamycin	20 min	120 °C	95	Zorraquino *et al.*, 2009	-	Pasteurization: 0% Longer impact: 17%	Sterilization: 95%	Cheese making: 0% Processed cheese: 17%
Kanamycin	10 sec	140 °C	17	Zorraquino *et al.*, 2009	-	Pasteurization: 0% Longer impact: 17%	Sterilization: 95%	Cheese making: 0% Processed cheese: 17%
Kanamycin	15 min	121°C	Heat stable based on MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 17%	Sterilization: 95%	Cheese making: 0% Processed cheese: 17%
Ketoprofen	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0 %	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Levamisole	Liquid whey was boiled	Liquid whey was boiled	~ 0	Whelan *et al.*, 2010	Cheese making data, no direct heat stability info; data approximated	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Levamisole	240 min	100°C	Stable	Rose *et al.,* 1995	Heating in water	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Levamisole	Cooking of pig muscle (microwaving, boiling, roasting, grilling, and frying)	Cooking of pig muscle (microwaving, boiling, roasting, grilling, and frying)	0 – 11, stable	Rose *et al.,* 1995	Cooking of pig muscle; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Levamisole	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 87°C	Muscle meat; Roasting at 190°C for 40 min; Maximum internal temperature at 87°C	0	Cooper *et al.,* 2011	Roasting or frying of bovine muscle or liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Levamisole	Muscle meat; Frying 4-6 min on each sides; Maximum internal temperature at 57°C	Muscle meat; Frying 4-6 min on each sides; Maximum internal temperature at 57°C	11	Cooper *et al.,* 2011	Roasting or frying of bovine muscle or liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Levamisole	Liver sample; Frying 14-19 min total; Maximum internal temperature at 91°C	Liver sample; Frying 14-19 min total; Maximum internal temperature at 91°C	42	Cooper *et al.,* 2011	Roasting or frying of bovine muscle or liver; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Lincomycin	30 min	60°C	NS	Zorraquino *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Lincomycin	20 min	120 °C	5	Zorraquino *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Lincomycin	10 sec	140 °C	5	Zorraquino *et al.*, 2011	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Meloxicam	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Moxidectin	30 min	65 °C	0 – 2.3	Imperiale *et al.*, 2009	Consulted references for other macrocyclic lactones, including eprinomectin and ivermectin.	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Moxidectin	15 sec	75 °C	0 – 2.2	Imperiale *et al.*, 2009	Consulted references for other macrocyclic lactones, including eprinomectin and ivermectin.	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Naproxen	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Neomycin	30 min	60 °C	NS	Zorraquino *et al.*, 2009	-	Pasteurization: 0% Longer impact: 10%	Sterilization:98 %	Cheese making: 0% Processed cheese: 10%
Neomycin	20 – 30 min	70 °C	9 – 10	Moats 1988	-			
Neomycin	10 min	80 °C	10	Moats 1988	-			
Neomycin	20 min	80 °C	20	Moats 1988	-			
Neomycin	30 min	80 °C	30	Moats 1988	-			
Neomycin	10 min	90 °C	10	Moats 1988	-			
Neomycin	20 min	90 °C	15	Moats 1988	-			
Neomycin	30 min	90 °C	22.2	Moats 1988	-			
Neomycin	10 min	100 °C	20	Moats 1988	-			
Neomycin	20 min	100 °C	30	Moats 1988	-			
Neomycin	30 min	100 °C	35	Moats 1988	-			
Neomycin	20 min	120 °C	98	Zorraquino *et al.*, 2009	-			
Neomycin	10 sec	140 °C	40	Zorraquino *et al.*, 2009	-			

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Nitrofurazone	No inactivation data available for milk system. Pasteurization (64-66 °C for 4 min in water bath) and spray drying of liquid egg products led to 40 – 100 % inactivation (Cooper *et al.,*. 2008). Metabolites of nitrofuran decreased about 0 – 30% during cooking of pig muscle and liver (Cooper and Kennedy, 2007). (Cooper *et al*., 2011). Stability studies of the metabolites of nitrofuran antibiotics during storage and cooking. Food Additives and Contaminants. 24 (9): 935-942.)	No inactivation data available for milk system. Pasteurization (64-66 °C for 4 min in water bath) and spray drying of liquid egg products led to 40 – 100 % inactivation (Cooper *et al.,*. 2008). Metabolites of nitrofuran decreased about 0 – 30% during cooking of pig muscle and liver (Cooper and Kennedy, 2007). (Cooper *et al*., 2011). Stability studies of the metabolites of nitrofuran antibiotics during storage and cooking. Food Additives and Contaminants. 24 (9): 935-942.)	No inactivation data available for milk system. Pasteurization (64-66 °C for 4 min in water bath) and spray drying of liquid egg products led to 40 – 100 % inactivation (Cooper *et al.,*. 2008). Metabolites of nitrofuran decreased about 0 – 30% during cooking of pig muscle and liver (Cooper and Kennedy, 2007). (Cooper *et al*., 2011). Stability studies of the metabolites of nitrofuran antibiotics during storage and cooking. Food Additives and Contaminants. 24 (9): 935-942.)	No inactivation data available for milk system. Pasteurization (64-66 °C for 4 min in water bath) and spray drying of liquid egg products led to 40 – 100 % inactivation (Cooper *et al.,*. 2008). Metabolites of nitrofuran decreased about 0 – 30% during cooking of pig muscle and liver (Cooper and Kennedy, 2007). (Cooper *et al*., 2011). Stability studies of the metabolites of nitrofuran antibiotics during storage and cooking. Food Additives and Contaminants. 24 (9): 935-942.)	No inactivation data available for milk system. Pasteurization (64-66 °C for 4 min in water bath) and spray drying of liquid egg products led to 40 – 100 % inactivation (Cooper *et al.,*. 2008). Metabolites of nitrofuran decreased about 0 – 30% during cooking of pig muscle and liver (Cooper and Kennedy, 2007). (Cooper *et al*., 2011). Stability studies of the metabolites of nitrofuran antibiotics during storage and cooking. Food Additives and Contaminants. 24 (9): 935-942.)	Pasteurization: 0% Longer impact: 0%	Sterilization:30 %	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Novobiocin	Limited inactivation data available; assume no inactivation	Limited inactivation data available; assume no inactivation	Limited inactivation data available; assume no inactivation	Limited inactivation data available; assume no inactivation	Limited inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Novobiocin	15 min	121°C	Heat stable based on MIC method	Traub and Leonhard 1995	Based on heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	
Oxfendazole	0-180 min	100°C	~ 0-10; some instability found in boiling water after 3 hours	Rose *et al.,* 1997	Heating in water	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Oxytetracycline	30 min	62 °C	24	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	30 min	71 °C	36	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	190 min	71 °C	100	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	92 min	79 °C	100	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Oxytetracycline	60 min	85 °C	100	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	30 min	100 °C	75 - 100	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	60 min	100 °C	100	Moats 1988	-	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	15 min	100 °C	60 - 80	Hsieh 2011	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	15 min	121 °C	50 - 60	Hsieh 2011	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	20 – 30 min	118 - 121 °C	100	Hassani *et al.*, 2008	Estimation based on heating data in buffer	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	7 – 15 sec	135 – 140 °C	40 - 44	Hassani *et al.*, 2008	Estimation based on heating data in buffer	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Oxytetracycline	30 min	62 °C	~ 20	Rose *et al*., 1996	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	120 min	62 °C	~ 50	Rose *et al*., 1996	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	15 min	80 °C	~ 50	Rose *et al*., 1996	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	40 min	80 °C	~ 80	Rose *et al*., 1996	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	2 min	100 °C	~ 50	Rose *et al*., 1996	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Oxytetracycline	10 min	100 °C	~ 90	Rose *et al*., 1996	Heating in water	Pasteurization: 20% Longer impact: 36%	Sterilization: 100%	Cheese making: 20% Processed cheese: 36%
Penicillin	10 min	40 °C	NS	Zorraquino *et al.*, 2008	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Penicillin	30 min	60 °C	9	Zorraquino *et al.*, 2008	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	30 min	62 °C	8	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	30 min	62 °C	0 - 16	Shahani 1956	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	30 min	63 °C	6	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	10 – 30 min	70 °C	20 - 30	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	10 – 30 min	80 °C	10 - 33	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	10 – 30 min	90 °C	20 - 30	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	10 – 30 min	100 °C	10 - 32	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Penicillin	15 min	71 °C	10	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	1705 min	71°C	100	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	15 sec	72 °C	<0.1	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	10 min	83 °C	20	Zorraquino *et al.*, 2008	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	420 min	87 °C	100	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	230 min	93 °C	100	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	30 min	100 °C	20 – 40	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	60 min	100 °C	50 - 65	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Penicillin	90 min	100 °C	85 - 100	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	20 min	120 °C	61	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	20 min	120 °C	65	Zorraquino *et al.*, 2008	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	25 min	121 °C	100	Moats 1988	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	4 sec	140 °C	0.8	Roca *et al.*, 2011	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	10 sec	140 °C	NS	Zorraquino *et al.*, 2008	-	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Penicillin	15 min	121°C	Partially heat stable based MIC method	Traub and Leonhard 1995	Heating in broth; data suboptimal	Pasteurization: 0% Longer impact: 20%	Sterilization: 60%	Cheese making: 0% Processed cheese: 20%
Phenylbutazone	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization:0%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Pirlimycin	30 min	60°C	NS	Zorraquino *et al.*, 2011	No data available for pirlimycin; used data for a related Lincosamide, lincomycin	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Pirlimycin	20 min	120 °C	5	Zorraquino *et al.*, 2011	No data available for pirlimycin; used data for a related Lincosamide, lincomycin	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Pirlimycin	10 sec	140 °C	5	Zorraquino *et al.*, 2011	No data available for pirlimycin; used data for a related Lincosamide, lincomycin	Pasteurization: 0% Longer impact: 0%	Sterilization: 5%	Cheese making: 0% Processed cheese: 0%
Spectinomycin	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Streptomycin	20 – 30 min	70 °C	8	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	10 min	80 -90 °C	8	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	20 min	80 °C	25	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Streptomycin	30 min	80 °C	33	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	20 min	90 °C	18	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	30 min	90 °C	33	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	10 min	100 °C	18	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	20 min	100 °C	33	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	30 min	100 °C	42	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	280 - 1320 min	71 °C	100	Moats 1988	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	30 min	60 °C	NS	Zorraquino *et al.*, 2009	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Streptomycin	20 min	120 °C	98	Zorraquino *et al.*, 2009	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Streptomycin	10 sec	140 °C	26	Zorraquino *et al.*, 2009	-	Pasteurization: 0 % Longer impact: 8 %	Sterilization: 98%	Cheese making: 0% Processed cheese: 8%
Sulfabromomethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfachlorpyridazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0 %
Sulfadimethoxine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Sulfaethoxypyridazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	No data available; assume same properties as related sulfonamide sulfamethazine	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	30 – 60 min	65 °C	0 – 2.5	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	15 sec	72 °C	1	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	2 min	72 °C	0	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	10 min	72 °C	0	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	2 – 4 min	100 °C	9	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	10 min	100 °C	19	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	10 – 20 min	121 °C	19 – 22	Papapanagiotou *et al.*, 2005	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Sulfamethazine	2 – 10 min	97.5 °C	5 – 25	Das and Bawa 2010	-	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	15 min	100 °C	~ 5	Hsieh 2011	Heating in water	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	15 min	121 °C	~ 5	Hsieh 2011	Heating in water	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfamethazine	6 hours	100 °C	Stable	Rose *et al.,* 1995	Heating in water	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Sulfaquinoxaline	3, 6, and 9 min	170, 180, 190°C (deep-frying of chicken meat ball)	Comparable degradation as SMZ during various deep-frying conditions	Ismail-Fitry *et al.,* 2011	Assume similar to salfamethazine (SMZ)	Pasteurization: 0% Longer impact: 0%	Sterilization: 20%	Cheese making: 0% Processed cheese: 0%
Tetracycline	15 min	100 °C	~ 50 - 55	Hsieh 2011	Heating in water	Pasteurization: 20% (used results for oxytetracycline) Longer impact: 24%	Sterilization: 100%	Cheese making: 20% (used results for oxytetracycline) Processed cheese: 24%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tetracycline	15 min	121 °C	~ 75 - 100	Hsieh 2011	Heating in water	Pasteurization: 20% (used results for oxytetracycline) Longer impact: 24%	Sterilization: 100%	Cheese making: 20% (used results for oxytetracycline) Processed cheese: 24%
Tetracycline	20 – 30 min	118 - 121 °C	100	Hassani *et al.*, 2008	Estimation based on heating data in buffer	Pasteurization: 20% (used results for oxytetracycline) Longer impact: 24%	Sterilization: 100%	Cheese making: 20% (used results for oxytetracycline) Processed cheese: 24%
Tetracycline	7 – 15 sec	135 – 140 °C	23 - 24	Hassani *et al.*, 2008	Estimation based on heating data in buffer	Pasteurization: 20% (used results for oxytetracycline) Longer impact: 24%	Sterilization: 100%	Cheese making: 20% (used results for oxytetracycline) Processed cheese: 24%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tetracycline	15 min	121°C	Heat labile based on MIC data	Traub and Leonhard 1995	Heating in broth, data suboptimal	Pasteurization: 20% (used results for oxytetracycline) Longer impact: 24%	Sterilization: 100%	Cheese making: 20% (used results for oxytetracycline) Processed cheese: 24%
Thiabendazole	Microwave baking of pototao for 5 - 6.5 min with internal temperature at 98-102°C		Stable	Friar and Reynolds 1991	Data from microwave and oven baking of potato; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	Cheese making: 0% Processed cheese: 0%
Thiabendazole	Oven baking of potato for 50-60 min with internal temperature at 63-101°C		Stable	Friar and Reynolds 1991	Data from microwave and oven baking of potato; data suboptimal	Pasteurization: 0% Longer impact: 0%	Sterilization: 0%	
Tilmicosin	30 min	60°C	21 Erythromycin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tilmicosin	30 min	60°C	13 Spiramycin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%
Tilmicosin	30 min	60°C	NS Tylosin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tilmicosin	20 min	120 °C	> 93 Erythromycin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%
Tilmicosin	20 min	120 °C	64 Spiramycin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tilmicosin	20 min	120 °C	51 Tylosin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%
Tilmicosin	10 sec	140 °C	30 Erythromycin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tilmicosin	10 sec	140 °C	35 Spiramycin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%
Tilmicosin	10 sec	140 °C	12 Tylosin	Zorraquino *et al.*, 2011	Data based on related macrolide antibiotics (*i.e.,* Erythromycin, Spiramycin, Tylosin); Tilmicosin is closely related to Tylosin. Used the most conservative estimate based on Tylosin data.	Pasteurization: 0% Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%
Tilmicosin	60 min	100 °C	10 – 20 Spiramycin	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tilmicosin	120 min	100 °C	35 Spiramycin	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-
Tilmicosin	180 min	100 °C	50 Spiramycin	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-
Tilmicosin	20 min	120 °C	0 – 20 Spiramycin	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-
Tilmicosin	60 – 180 min	100 °C	85 – 100 Framycetine	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-
Tilmicosin	20 min	120 °C	75 Framycetine	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tilmicosin	60 – 180 min	100 °C	85 – 100 Oleandomycine	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-
Tilmicosin	20 min	120 °C	60 – 100 Oleandomycine	Moats 1988	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	-	-	-
Tildipirosin	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	Data based on related macrolide antibiotics (*i.e.,* Spiramycin, Framycetine, Oleandomycine)	Pasteurization: 0 % Longer impact: 10 %	Sterilization: 50 %	Cheese making: 0% Processed cheese: 0%
Tripelennamine	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	No inactivation data available; assume no inactivation	Pasteurization: 0% Longer impact: 0%	Sterilization: 0 %	Cheese making: 0% Processed cheese: 0%
Tulathromycin	No data available; assumed same as for Tilmicosin even though Tulathromycin is a triamilide	No data available; assumed same as for Tilmicosin even though Tulathromycin is a triamilide	No data available; assumed same as for Tilmicosin even though Tulathromycin is a triamilide	No data available; assumed same as for Tilmicosin even though Tulathromycin is a triamilide	No data available; assumed same as for Tilmicosin even though Tulathromycin is a triamilide	Pasteurization: 0 % Longer impact: 10 %	Sterilization: 50 %	Cheese making: 0% Processed cheese: 0%

Drug	Experimental heat stability data: Heating time	Experimental heat stability data: Heating temperature	Experimental heat stability data: Impact [% inactivation]	Experimental heat stability data: Reference	Experimental heat stability data: Comment	Drug inactivation as a function of processing types: Pasteurization[1]	Drug inactivation as a function of processing types: Sterilization/Retort[2]	Drug inactivation as a function of processing types: Pasteurized cheese making[3]
Tylosin	30 min	60°C	0	Zorraquino *et al.*, 2011	-	Pasteurization: 0 % Longer impact: 10%	Sterilization: 50%	Cheese making: 0% Processed cheese: 10%
	20 min	120 °C	51	Zorraquino *et al.*, 2011	-			
	10 sec	140 °C	12	Zorraquino *et al.*, 2011	-			

[1] for modeling purposes, 2 different types of pasteurization were assumed: (1) **pasteurization** (used for example in the manufacturing of fluid milk, butter, ice cream, heavy cream, NFDM, Whey); ;and (2) **longer impact pasteurization** (used for example in the manufacturing of yogurt or sour cream);
[2] for modeling purposes, one type of **sterilization** (*e.g.,* retort) was assumed, used for example in the manufacturing of evaporated milk;
[3] for modeling purposes, two types of pasteurized cheese manufacturing were assumed: (1) **cheese making** (used for example in the manufacturing of cheddar or mozzarella cheese); and (2) **processed cheese making** (used for example in the manufacturing of processed or 'American' cheese).

APPENDIX 5.15: CRITERION C: OVERVIEW OF DAIRY PRODUCT PROCESSING CONDITIONS

* Modeling category refers to multicriteria-based ranking model; for the purpose of this ranking, heat treatments were classified as follows:

1. **Pasteurization** (*e.g.*, HTST, LHLT, UHT): used for manufacturing of fluid milk, NFDM, ice cream, heavy cream, butter.
2. **Longer impact pasteurization** (*e.g.*, 85 – 95 °C / 15 - 30 min): used for manufacturing of yogurt and sour cream
3. **Sterilization** (*e.g.*, retorting conditions): used for manufacturing of evaporated milk
4. **Cheese manufacturing:** used for manufacturing of cottage cheese, mozzarella and cheddar cheese.
5. **Processed cheese manufacturing:** used for manufacturing of American cheese

Table A5.26 Overview of dairy product processing conditions

Dairy Product	Heating: Temperature / Time conditions	Heating: Modeling Category (see later)	pH change/ culturing	pH change/ culturing: Impact on model (see later)	Process	Impact on model (see later)	Comment	References
Fluid milk	Pasteurization: 72 °C / 15 sec (*i.e.*, HTST); 63 °C / 30 min (*i.e.*, LHLT); 140°C/ >2 sec (*i.e.*, UHT);	Pasteurization	-	-	-	-	-	HHS 2011
Yogurt	Higher impact pasteurization: 85 °C / 30 min; 95 °C/ 10 min;	Longer impact Pasteurization	Acidification (pH 4.6)	No change	-	-	-	Chandan and Shahani, 1993; Fox *et al.*, 2000a
Evaporated milk	Sterilization: 117 °C / 15 min; 126 °C / 2 min; 140°C / >2 sec (rare);	Sterilization	-	-	Drying 77% water remaining (vacuum drying)	Moderate increase	Drying results in concentration of water-soluble drugs (no change for fat-soluble	Bassette and Acosta. 1988

Dairy Product	Heating: Temperature / Time conditions	Heating: Modeling Category (see later)	pH change/ culturing	pH change/ culturing: Impact on model (see later)	Process	Impact on model (see later)	Comment	References
							drugs)(118)	
Non fat dried milk (NFDM)	Pasteurization: 72 °C / 15 sec 88 °C / 30 min (high heat); 70°C / 2 min (low heat)	Heat Treatment Spray Drying (similar impact as pasteurization)	-	-	Drying: < 5% water remaining (roller / spray drying)	Strong increase	Drying results in concentration of water-soluble drugs (no change for fat-soluble drugs)	USDEC 2009
Cottage cheese	Pasteurization: 72 °C / > 15 sec; Curd formation step 40 – 45 °C / ~ 4 hrs Curd cooking: 42 - 60 °C / 0 – 45 minutes	Cheese making	Acidification (pH 4.6)	No change	-	-	Separation of the phases occurs at pH 4.6.	Fox *et al.*, 2000a
Ice cream	Pasteurization: 68 °C / 30 min; 79 °C / 25 sec; 82 °C /15 sec;	Pasteurization	-	-	Freezing: - 18 °C	No change	Freezing results in no change because the limited available data suggests no impact of freezing on drug residue concentrations (see Table 7)	Jimenez-Flores *et al.*, 2006
Sour cream	Higher impact pasteurization: 85 – 95 °C / 15 -	Longer impact Pasteurization	Acidification (pH 4.5 – 4.6)	No change	-	-		Smiddy *et al.*, 2009

Dairy Product	Heating: Temperature / Time conditions	Heating: Modeling Category (see later)	pH change/ culturing	pH change/ culturing: Impact on model (see later)	Process	Impact on model (see later)	Comment	References
	30 min; Culturing: 20 – 24 °C / 14 – 24 hours;							
Heavy cream	Pasteurization: > 80 °C / 15 sec; 135 – 150 °C / 10 sec;	Pasteurization	-	-	-	-	Pasteurization occurs at temperatures higher than for fluid milk due to the higher fat content.	Smiddy *et al.*, 2009
Butter	Pasteurization: 85 °C / 15 sec	Pasteurization	-	-	-	-	Pasteurization occurs at temperatures higher than for fluid milk due to the higher fat content.	Wilbey, R.A. 2009
Mozzarella	Pasteurization; See fluid milk; Curd cooking: 60 – 65 °C / > 30 min	Cheese manufacturing	pH 5.2	No change	-	-	Separation of the phases occurs at pH 5.2.	Fox *et al.*, 2000b
Cheddar	Pasteurization; See fluid milk; Curd cooking: 35 –40 °C / > 30 min	Cheese manufacturing	pH 6 (curd formation); pH 5.2 (ripening)	No change	Aging	No change	Separation of the phases occurs at pH 6. Aging results in no change because limited available data	Lawrence *et al.*,1999

Dairy Product	Heating: Temperature / Time conditions	Heating: Modeling Category (see later)	pH change/ culturing	pH change/ culturing: Impact on model (see later)	Process	Impact on model (see later)	Comment	References
							suggest no impact of cheese aging on drug residue concentrations (see Table 7).	
Processed Cheese (American)	Pasteurization; See fluid milk; Curd cooking: See mozzarella & cheddar. Additional heating: 70 - 95 °C / 4 - 15 min (typical industry practice); 65.5 °C / 30 sec (legal minimum);	Processed cheese manufacturing	pH 5.8	No change	Aging	No change	Aging results in no change because limited available data suggest no impact of cheese aging on drug residue concentrations (see Table 7).	Fox *et al.*, 2000b

APPENDIX 5.16: CRITERION C: DAIRY PRODUCTS PRESENT IN FOODS CONSUMED BY WWEIA/NHANES RESPONDENTS

Table A5.27 Dairy products present in foods consumed by WWEIA/NHANES respondents

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Butter	13210180	Pudding, Mexican bread (Capirotada)	1.73
Butter	26311120	Lobster, baked or broiled	3.01
Butter	27135050	Veal Marsala	8.00
Butter	27146250	Chicken or turkey cordon bleu	7.19
Butter	27146400	Chicken kiev	9.65
Butter	27150060	Lobster newburg	6.00
Butter	27150070	Lobster with butter sauce (mixture)	3.00
Butter	27150130	Seafood newburg	6.11
Butter	27150230	Shrimp scampi	18.15
Butter	27220190	Sausage and noodles with cream or white sauce (mixture)	2.03
Butter	27250040	Crab cake	4.29
Butter	27250260	Lobster with bread stuffing, baked	8.58
Butter	28110220	Sirloin, chopped, with gravy, mashed potatoes, vegetable (frozen meal)	3.92
Butter	28110270	Sirloin beef with gravy, potatoes, vegetable (frozen meal)	0.97
Butter	28110310	Salisbury steak with gravy, potatoes, vegetable (frozen meal)	5.04
Butter	28110390	Salisbury steak, potatoes, vegetable, dessert (diet frozen meal)	0.10
Butter	28110620	Beef short ribs, boneless, with barbecue sauce, potatoes, vegetable (frozen meal)	-
Butter	28110640	Meatballs, Swedish, in sauce, with noodles (frozen meal)	-
Butter	28143010	Chicken and vegetable entrée with rice, Oriental (frozen meal)	-
Butter	28143150	Chicken and vegetable entrée with noodles (frozen meal)	-
Butter	28143170	Chicken in cream sauce with noodles and vegetables (frozen meal)	-
Butter	28143180	Chicken in butter sauce with potatoes and vegetable (diet frozen meal)	-
Butter	28143190	Chicken in mushroom sauce, white and wild rice, vegetable (frozen meal)	-
Butter	28143200	Chicken in soy-based sauce, rice and vegetables (frozen meal)	-
Butter	28143210	Chicken in orange sauce with almond rice (diet frozen meal)	-
Butter	28144100	Chicken and vegetable entrée with noodles and cream sauce (frozen meal)	-
Butter	28145100	Turkey with dressing, gravy, vegetable and fruit (diet frozen meal)	-
Butter	28150210	Haddock with chopped spinach (diet frozen meal)	-
Butter	28150220	Flounder with chopped broccoli (diet frozen meal)	-
Butter	28150510	Fish in lemon-butter sauce with starch item, vegetable (frozen meal)	-
Butter	28152030	Seafood newburg with rice, vegetable (frozen meal)	-
Butter	28154010	Shrimp and vegetables in sauce with noodles (diet frozen meal)	-
Butter	28355140	Clam chowder, New England, canned, reduced sodium, ready-to-serve	-
Butter	28355310	Oyster stew	-
Butter	32101500	Egg, Benedict	-
Butter	51108100	Naan, Indian flatbread	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Butter	51158100	Roll, Mexican, bolillo	-
Butter	51188100	Pannetone (Italian-style sweet bread)	-
Butter	53103550	Cake, butter, without icing	-
Butter	53103600	Cake, butter, with icing	-
Butter	53115600	Cake, poppyseed, without icing	-
Butter	53116350	Cake, pound, Pueto Rican style (Ponque)	-
Butter	53215500	Cookie, coconut	-
Butter	53216000	Cookie, coconut and nut	-
Butter	53341750	Pie, chess	-
Butter	53441110	Baklava	-
Butter	53452170	Pastry, cookie type, fried	-
Butter	53520200	Churros	-
Butter	54403020	Popcorn, popped in oil, buttered	-
Butter	54403040	Popcorn, air-popped, buttered	-
Butter	58120120	Crepe, filled with beef, pork, fish, and/or poultry, no sauce on top	-
Butter	58122220	Gnocchi, potato	-
Butter	58124250	Spanakopitta	-
Butter	58124500	Pastry, filled with potatoes and peas, fried	-
Butter	58127110	Vegetables in pastry	-
Butter	58137210	Pad Thai, NFS	-
Butter	58137230	Pad Thai with chicken	-
Butter	58137250	Pad Thai with meat	-
Butter	58145115	Macaroni or noodles with cheese, from boxed mix with already prepared cheese	-
Butter	58147350	Macaroni, creamed, with vegetables	-
Butter	58149160	Noodle pudding, with milk	-
Butter	58161200	Rice, cooked with coconut milk (Arroz con coco)	-
Butter	58163130	Diry rice	-
Butter	58163380	Flavored rice and pasta mixture	-
Butter	58163400	Flavored rice and pasta mixture, reduced sodium	-
Butter	58304400	Linguini with vegetables and seafood in white wine sauce (diet frozen meal)	-
Butter	71101100	-	-
Butter	71101120	-	-
Butter	71103000	-	-
Butter	71103020	-	-
Butter	71103100	-	-
Butter	71103120	-	-
Butter	71103220	-	-
Butter	71301020	-	-
Butter	71301120	-	-
Butter	71501000	-	-
Butter	71501020	-	-
Butter	71501025	-	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Butter	71501030	-	-
Butter	71501040	-	-
Butter	71501050	-	-
Butter	71501055	-	-
Butter	71501060	-	-
Butter	71501070	-	-
Butter	71501300	-	-
Butter	71501310	-	-
Butter	71507000	-	-
Butter	71507005	-	-
Butter	71507010	-	-
Butter	71507020	-	-
Butter	71507030	-	-
Butter	71507040	-	-
Butter	71507050	-	-
Butter	71508005	-	-
Butter	71508010	-	-
Butter	71508020	-	-
Butter	71508040	-	-
Butter	71508060	-	-
Butter	71508070	-	-
Butter	73301000	-	-
Butter	73301020	-	-
Butter	73303000	-	-
Butter	73303020	-	-
Butter	73305010	-	-
Butter	75460800	Vegetable combinations (including carrots, broccoli, and/or dark-green leafy), cooked, with butter sauce and pasta	-
Butter	75608100	Onion soup, French	-
Butter	75651140	Vegetable soup with chicken broth, Mexican style (Sopa Ranchera)	-
Butter	76102030	Broccoli, carrots and cheese, baby food, junior	-
Butter	81100500	Butter, NFS	-
Butter	81101000	Butter, stick, salted	-
Butter	81101010	Butter, whipped, tub, salted	-
Butter	81101100	Butter, stick, unsalted	-
Butter	81101110	Butter, whipped, tub, unsalted	-
Butter	81101500	Light butter, stick, salted	-
Butter	81101520	Light butter, whipped, tub, salted	-
Butter	81105010	Butter-margarine blend, stick, salted	-
Butter	81302010	Hollandaise sauce	-
Butter	81322000	Honey butter	-
Butter	91301040	Buttered blends syrup	-
Butter	91304010	Topping, butterscotch or caramel	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Butter	91718000	Honey-combed hard candy with peanut butter	-
Butter	91760500	Truffles	-
Cheddar	14010000	Cheese, NFS	-
Cheddar	14010100	Cheese, Cheddar or American type, NS as to natural or processed	-
Cheddar	14100100	Cheese, natural, NFS	-
Cheddar	14104010	Cheese, natural, Cheddar or American type	-
Cheddar	14104015	Cheese, natural, Cheddar or American type, reduced fat	-
Cheddar	14104020	Cheese, Cheddar or American type, dry, grated	-
Cheddar	14110010	Cheese, Cheddar or Colby, low sodium	-
Cheddar	14110030	Cheese, Cheddar or Colby, lowfat	-
Cheddar	14120010	Cheese, Mexican blend	-
Cheddar	14610520	Cheese with nuts	-
Cheddar	14630200	Cheese souffle	-
Cheddar	14630300	Welsh rarebit	-
Cheddar	27111430	Chili con carne, NS as to beans, with cheese	-
Cheddar	27111440	Chili con carne with beans and cheese	-
Cheddar	27212050	Beef and macaroni with cheese sauce (mixture)	-
Cheddar	27213600	Beef and rice with cheese sauce (mixture)	-
Cheddar	27242350	Chicken or turkey tetrazzini	-
Cheddar	27250110	Scallops and noodles with cheese sauce (mixture)	-
Cheddar	27250130	Shrimp and noodles with cheese sauce (mixture)	-
Cheddar	27313310	Beef, noodles and vegetables (including carrots, broccoli, and/or dark-green leafy), (mushroom) soup (mixture)	-
Cheddar	27313320	Beef, noodles and vegetables (excluding carrots, broccoli, and/or dark-green leafy), (mushroom) soup (mixture)	-
Cheddar	27320120	Sausage, potatoes, and vegetables (including carrots, broccoli, and/or dark-green leafy), gravy (mixture)	-
Cheddar	27320130	Sausage, potatoes, and vegetables (excluding carrots, broccoli, and/or dark-green leafy), gravy (mixture)	-
Cheddar	27416300	Beef taco filling, beef, cheese, tomato, taco sauce	-
Cheddar	27446315	Chicken or turkey garden salad with bacon (chicken and/or turkey, bacon, cheese, lettuce, and/or greens, tomato and/or carrots, other vegetables), no dressing	-
Cheddar	27446320	Chicken or turkey (breaded, fried) garden salad with bacon (chicken and/or turkey bacon, cheese, lettuce, and/or greens, tomato and/or carrots, other vegetables), no dressing	-
Cheddar	27460490	Julienne salad (meat, cheese, eggs, vegetables), no dressing	-
Cheddar	27460510	Antipasto with ham, fish, cheese, vegetables	-
Cheddar	27500200	Wrap sandwich, filled with meat, poultry, or fish, vegetables, and cheese	-
Cheddar	27510420	Taco burger, on bun	-
Cheddar	27540210	Wrap sandwich filled with chicken strips (breaded, fried), cheese, lettuce, and spread	-
Cheddar	27540300	Wrap sandwich filled with chicken strips (broiled), cheese, lettuce, and spread	-
Cheddar	27560705	Sausage balls (made with biscuit mix and cheese)	-
Cheddar	28110380	Salisbury steak with gravy, macaroni and cheese, vegetable (frozen meal)	-
Cheddar	28140150	Chicken divan (frozen meal)	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Cheddar	28143220	Veal with peppers in sauce, rice (diet frozen meal)	-
Cheddar	28144100	Chicken and vegetable entrée with noodles and cream sauce (frozen meal)	-
Cheddar	32105010	Egg omelet or scrambled egg, with cheese	-
Cheddar	32105045	Egg omelet or scrambled egg, with cheese and dark-green vegetables	-
Cheddar	32105055	Egg omelet or scrambled egg, with cheese and vegetables other than dark-green	-
Cheddar	32105080	Egg omelet or scrambled egg, with ham or bacon and cheese	-
Cheddar	32105081	Egg omelet or scrambled egg, with ham or bacon, cheese, and dark-green vegetables	-
Cheddar	32105082	Egg omelet or scrambled egg, with ham or bacon, cheese, and vegetables other than dark-green	-
Cheddar	32105085	Egg omelet or scrambled egg, with ham or bacon, cheese, and tomatoes	-
Cheddar	32105119	Egg omelet or scrambled egg, with sausage, cheese, and vegetables other than dark-green	-
Cheddar	32105121	Egg omelet or scrambled egg, with sausage and cheese	-
Cheddar	32105126	Egg omelet or scrambled egg, with hot dog and cheese	-
Cheddar	32105150	Egg omelet or scrambled egg, with cheese, beans, tomatoes, and chili sauce	-
Cheddar	32105161	Egg omelet or scrambled egg, with chorizo and cheese	-
Cheddar	32105190	Egg casserole with bread, cheese, milk and meat	-
Cheddar	32400050	Egg white omelet or scrambled egg, with cheese	-
Cheddar	41205020	Refried beans with cheese	-
Cheddar	51111010	Bread, cheese	-
Cheddar	51111040	Bread, cheese, toasted	-
Cheddar	51154600	Roll, cheese	-
Cheddar	53452450	Cheese pastry puffs	-
Cheddar	54327950	Crackers, cylindrical, peanut-butter filled	-
Cheddar	54328110	Cracker, sandwich-type, peanut butter filled, reduced fat	-
Cheddar	54402500	Salty snacks, wheat- and corn- based chips	-
Cheddar	54408300	Pretzels, cheese-filled	-
Cheddar	54420200	Multigrain mixture, bread sticks, sesame nuggests, pretzel, rye chips	-
Cheddar	58100120	Burrito with beef, beans, and cheese	-
Cheddar	58100130	Burrito with beef and cheese, no beans	-
Cheddar	58100140	Burrito with beef, beans, cheese, and sour cream	-
Cheddar	58100155	Burrito with beef, rice, and cheese	-
Cheddar	58100160	Burrito with beef, beans, rice, and cheese	-
Cheddar	58100220	Burrito with chicken, beans, and cheese	-
Cheddar	58100230	Burrito with chicken and cheese	-
Cheddar	58100245	Burrito with chicken, beans, cheese, and sour cream	-
Cheddar	58100250	Burrito with chicken, rice, and cheese	-
Cheddar	58100255	Burrito with chicken, beans, rice, and cheese	-
Cheddar	58100320	Burrito with beans and cheese, meatless	-
Cheddar	58100330	Burrito with rice, beans, cheese, sour cream, lettuce, tomato and guacamole, meatless	-
Cheddar	58100350	Burrito with eggs and cheese, no beans	-
Cheddar	58100520	Enchilada with beef, beans, and cheese	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Cheddar	58100530	Enchilada with beef and cheese, no beans	-
Cheddar	58100560	Enchilada with ham and cheese, no beans	-
Cheddar	58100620	Enchilada with chicken, beans, and cheese, tomato- based sauce	-
Cheddar	58100630	Enchilada with chicken and cheese, no beans, tomato- based sauce	-
Cheddar	58100720	Enchilada with beans and cheese, meatless	-
Cheddar	58100800	Enchilada with cheese, meatless, no beans	-
Cheddar	58101300	Taco or tostada with beef, cheese and lettuce	-
Cheddar	58101320	Taco or tostada with beef, cheese, lettuce, tomato and salsa	-
Cheddar	58101350	Soft taco with beef, cheese, lettuce, tomato and sour cream	-
Cheddar	58101400	Soft taco with beef, cheese, and lettuce	-
Cheddar	58101450	Soft taco with chicken, cheese, and lettuce	-
Cheddar	58101460	Soft taco with chicken, cheese, lettuce, tomato, and sour cream	-
Cheddar	58101520	Taco or tostada with chicken, cheese, lettuce, tomato and salsa	-
Cheddar	58101530	Soft taco with beef, cheese, lettuce, tomato and salsa	-
Cheddar	58101600	Soft taco with bean, cheese, and lettuce	-
Cheddar	58101610	Soft taco with bean, cheese, lettuce, and tomato and/or salsa	-
Cheddar	58101615	Soft taco with bean, cheese, lettuce, tomato, and/or salsa, and sour cream	-
Cheddar	58101720	Taco or tostada with beans and cheese, meatless, with lettuce, tomato and salsa	-
Cheddar	58101730	Taco or tostada with beans, cheese, meat, lettuce, tomato and salsa	-
Cheddar	58101820	Mexican casserole made with ground beef, beans, tomato sauce, cheese, taco seasonings, and corn chips	-
Cheddar	58101830	Mexican casserole made with ground beef, tomato sauce, cheese, taco seasonings, and corn chips	-
Cheddar	58101910	Taco or tostada salad with beef and cheese, corn chips	-
Cheddar	58101930	Taco or tostada salad with beef, beans and cheese, fried flour tortilla	-
Cheddar	58101940	Taco or tostada salad, meatless, with cheese, fried flour tortilla	-
Cheddar	58104080	Nachos with beef, beans, cheese, and sour cream	-
Cheddar	58104090	Nachos with cheese and sour cream	-
Cheddar	58104120	Nachos with beans and cheese	-
Cheddar	58104130	Nachos with beef, beans, and cheese	-
Cheddar	58104140	Nachos with beef and cheese	-
Cheddar	58104180	Nachos with beef, beans, cheese, tomatoes, sour cream and onions	-
Cheddar	58104250	Nachos with chicken or turkey and cheese	-
Cheddar	58104260	Chalupa with beans, cheese, lettuce and tomato	-
Cheddar	58104280	Chalupa with beef, cheese, lettuce, tomato, and sour cream	-
Cheddar	58104290	Chalupa with beef, cheese, lettuce, tomato, and salsa	-
Cheddar	58104310	Chalupa with beans, chicken, cheese, lettuce and tomato	-
Cheddar	58104320	Chalupa with chicken, cheese, lettuce, tomato and sour cream	-
Cheddar	58104340	Chalupa with chicken, cheese, lettuce, tomato and salsa	-
Cheddar	58104510	Chimichanga with beef, cheese, lettuce and tomato	-
Cheddar	58104520	Chimichanga with beans and cheese, meatless, with lettuce and tomato	-
Cheddar	58104530	Chimichanga with chicken and cheese	-
Cheddar	58104710	Quesadilla with cheese, meatless	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Cheddar	58104730	Quesadilla with meat and cheese	-
Cheddar	58104740	Quesadilla with poultry and cheese	-
Cheddar	58106910	Pizza with seafood, thin crust	-
Cheddar	58106920	Pizza with seafood, thick crust	-
Cheddar	58107220	White pizza, thin crust	-
Cheddar	58107225	White pizza, regular crust	-
Cheddar	58107230	White pizza, thick crust	-
Cheddar	58108000	Calzone, with cheese, meatless	-
Cheddar	58116115	Empanada, Mexican turnover, filled with cheese and vegetables	-
Cheddar	58116310	Empanada, Puerto Rican style (Pastelillo de queso, Empanadilla)	-
Cheddar	58120110	Crepes, filled with meat, fish, or poultry, with sauce	-
Cheddar	58125180	Cheese quiche, meatless	-
Cheddar	58126150	Turnover, meat- and cheese-filled, tomato-based sauce	-
Cheddar	58126270	Turnover, chicken- or turkey-, and cheese-filled, no gravy	-
Cheddar	58126290	Turnover, meat- and cheese-filled, lower in fat	-
Cheddar	58127150	Vegetables and cheese in pastry	-
Cheddar	58130013	Lasagna with meat, canned	-
Cheddar	58131323	Ravioli, meat-filled, with tomato sauce or meat sauce, canned	-
Cheddar	58131523	Ravioli, cheese-filled, with tomato sauce, canned	-
Cheddar	58145115	Macaroni or noodles with cheese, from boxed mix with already prepared cheese sauce	-
Cheddar	58145120	Macaroni or noodles with cheese and tuna	-
Cheddar	58145130	Macaroni or noodles with cheese and beef	-
Cheddar	58146150	Pasta with cheese and tomato sauce, meatless	-
Cheddar	58148180	Macaroni or pasta salad with cheese	-
Cheddar	58161110	Rice casserole with cheese	-
Cheddar	58161120	Brown rice casserole with cheese	-
Cheddar	58162090	Stuffed pepper, with meat	-
Cheddar	58162110	Stuffed pepper, with rice and meat	-
Cheddar	58162120	Stuffed pepper with rice, meatless	-
Cheddar	58302000	Macaroni and cheese (diet frozen meal)	-
Cheddar	58303100	Rice, with broccoli, cheese sauce	-
Cheddar	58304010	Spaghetti and meatballs dinner, NFS (frozen meal)	-
Cheddar	58305250	Pasta with vegetable and cheese sauce (diet frozen meal)	-
Cheddar	58306010	Beef enchilada dinner, NFS (frozen meal)	-
Cheddar	58306020	Beef enchilada, chili gravy, rice, refried beans (frozen meal)	-
Cheddar	58306070	Cheese enchilada (diet frozen meal)	-
Cheddar	58306100	Chicken enchilada (diet frozen meal)	-
Cheddar	71301020	White potato, cooked, with cheese	-
Cheddar	71301120	White potato, cooked, with ham and cheese	-
Cheddar	71405100	White potato, hash brown, with cheese	-
Cheddar	71410500	White potato skins, with adhering flesh, fried, with cheese	-
Cheddar	71411000	White potato skins, with adhering flesh, fried, with cheese and bacon	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Cheddar	71501070	White potato, from dry, mashed, made with milk, fat and egg	-
Cheddar	71507040	White potato, stuffed, baked, peel not eaten, stuffed with broccoli and cheese sauce	-
Cheddar	71508040	White potato, stuffed, baked, peel eaten, stuffed with broccoli and cheese sauce	-
Cheddar	71801100	Potato and cheese soup	-
Cheddar	72125250	Spinach, cooked, NS as to form, with cheese sauce	-
Cheddar	72125251	Spinach, cooked, from fresh, with cheese sauce	-
Cheddar	72125252	Spinach, cooked, from frozen, with cheese sauce	-
Cheddar	72125253	Spinach, cooked from canned, with cheese sauce	-
Cheddar	72201230	Broccoli, cooked, NS as to form, with cheese sauce	-
Cheddar	72201231	Broccoli, cooked, from fresh, with cheese sauce	-
Cheddar	72201232	Broccoli, cooked, from frozen, with cheese sauce	-
Cheddar	73102251	Carrots, cooked, from fresh, with cheese sauce	-
Cheddar	73102252	Carrots, cooked, from frozen, with cheese sauce	-
Cheddar	73305010	Squash, winter, baked with cheese	-
Cheddar	75140500	Broccoli salad with cauliflower, cheese, bacon bits, and dressing	-
Cheddar	75143200	Lettuce, salad with cheese, tomato and/or carrots, with or without other vegetables, no dressing	-
Cheddar	75143350	Lettuce, salad with egg, cheese, tomato, and/or carrots, with or without other vegetables, no dressing	-
Cheddar	75145000	Seven-layer salad (lettuce salad made with a combination of onion, celery, green pepper, peas, mayonnaise, cheese, eggs, and/or bacon)	-
Cheddar	75401010	Asparagus, NS as to form, creamed or with cheese sauce	-
Cheddar	75401011	Asparagus, from flesh, creamed or with cheese sauce	-
Cheddar	75401012	Asparagus, from frozen, creamed or with cheese sauce	-
Cheddar	75403010	Beans, string, green, NS as to form, creamed or with cheese sauce	-
Cheddar	75403011	Beans, string, green, from fresh, creamed or with cheese sauce	-
Cheddar	75403012	Beans, string, green, from frozen, creamed or with cheese sauce	-
Cheddar	75403013	Beans, string, green, from canned, creamed or with cheese sauce	-
Cheddar	75409010	Cauliflower, NS as to form, creamed	-
Cheddar	75409011	Cauliflower, from fresh, creamed	-
Cheddar	75409012	Cauliflower, from frozen, creamed	-
Cheddar	75409020	Cauliflower, batter-dipped, fried	-
Cheddar	75416600	Pea salad with cheese	-
Cheddar	75418040	Squash, summer, casserole with cheese sauce	-
CotCheese	14200100	Cheese, cottage, NFS	-
CotCheese	14201010	Cheese, cottage, creamed, large or small curd	-
CotCheese	14201200	Cottage cheese, farmer's	-
CotCheese	14202010	Cheese, cottage, with fruit	-
CotCheese	14202020	Cheese, cottage, with vegetables	-
CotCheese	14203010	Cheese, cottage, dry curd	-
CotCheese	14203020	Cheese, cottage, salted, dry curd	-
CotCheese	14204010	Cheese, cottage, lowfat (1-2% fat)	-
CotCheese	14204020	Cheese, cottage, lowfat, with fat	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
CotCheese	14204030	Cheese, cottage, lowfat, with vegetables	-
CotCheese	14206010	Cheese, cottage, lowfat, low sodium	-
CotCheese	14207010	Cheese, cottage, lowfat, lactose reduced	-
CotCheese	14610200	Cheese, cottage cheese, with gelatin dessert	-
CotCheese	14610210	Cheese, cottage cheese, with gelatin dessert and fruit	-
CotCheese	14610250	Cheese, cottage cheese, with gelatin dessert and vegetables	-
CotCheese	53104550	Cheesecake with fruit	-
CotCheese	53251100	Cookie, rugelach	-
CotCheese	53400200	Blintz, cheese-filled	-
CotCheese	53400300	Blintz, fruit-filled	-
CotCheese	53511500	Danish pastry, with cheese, fat free, cholesterol free	-
CotCheese	58122320	Knish, cheese (pastry filled with cheese)	-
CreamHeavy	12130100	Cream, heavy, fluid	-
CreamHeavy	12140000	Cream, heavy, whipped, sweetened	-
CreamHeavy	13250000	Mousse, chocolate	-
CreamHeavy	13250100	Mousse, not chocolate	-
CreamHeavy	13252600	Tiramisu	-
CreamHeavy	14650160	Alfredo sauce	-
CreamHeavy	28140730	Chicken patty, breaded, with tomato sauce and cheese, fettuccine alfredo, vegetable (frozen meal)	-
CreamHeavy	28143190	Chicken in mushroom sauce, white and wild rice, vegetable (frozen meal)	-
CreamHeavy	53106500	Cake, cream, without icing or topping	-
CreamHeavy	53118550	Cake, tres leche	-
CreamHeavy	53341750	Pie, chess	-
CreamHeavy	53344300	Dessert pizza	-
CreamHeavy	53347100	Pie, raspberry cream	-
CreamHeavy	53348000	Pie, strawberry cream	-
CreamHeavy	53452420	Pastry, puff, custard or cream filled, iced or not iced	-
CreamHeavy	58146130	Pasta with carbonara sauce	-
CreamHeavy	63402960	Fruit salad (excluding citrus fruits) with cream	-
CreamHeavy	83105000	Fruit dressing, made with fruit juice and cream	-
CreamHeavy	91501040	Gelatin dessert with fruit and whipped cream	-
CreamHeavy	93301400	Irish Coffee	-
EvapConMilk	11210050	Milk, evaporated, NS as to fat content (formerly NS as to dilution, used in coffee or tea, assume undiluted)	-
EvapConMilk	11211050	Milk, evaporated, whole (formerly NS as to dilution, used in coffee or tea)	-
EvapConMilk	11211400	Milk, evaporated, 2% fat (formerly NS as to dilution)	-
EvapConMilk	11212050	Milk, condensed, sweetened (formerly NS as to dilution)	-
EvapConMilk	11220000	Milk, condensed, sweetened, NS as to dilution	-
EvapConMilk	11512500	Spanish-style hot chocolate drink, Puerto Rican style, made with milk	-
EvapConMilk	11512510	Hot chocolate, Puerto Rican style, made with low fat milk	-
EvapConMilk	13210350	Custard, Puerto Rican style (Flan)	-
EvapConMilk	13252100	Coconut custard, Puerto Rican style (Flan de coco)	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
EvapConMilk	13252200	Milk dessert or milk candy, Puerto Rican style (Dulce de leche)	-
EvapConMilk	53115600	Cake, poppyseed, without icing	-
EvapConMilk	53118550	Cake, tres leche	-
EvapConMilk	53205600	Cookie, caramel coated, with nuts	-
EvapConMilk	53211000	Cookie bar, with chocolate, nuts, and graham crackers	-
EvapConMilk	53247500	Cookie, vanilla with caramel, coconut, and chocolate coating	-
EvapConMilk	83112900	Milk, vinegar, and sugar dressing	-
IceCream	11541000	Milk shake, NS as to flavor type	-
IceCream	11541100	Milk shake, homemade or fountain-type, NS as to flavor	-
IceCream	11541110	Milk shake, homemade or fountain-type, chocolate	-
IceCream	11541120	Milk shake, homemade or fountain-type, flavors other than chocolate	-
IceCream	11541400	Milk shake with malt	-
IceCream	11541500	Milk shake, made with skim milk, chocolate	-
IceCream	11541510	Milk shake, made with skim milk, flavors other than chocolate	-
IceCream	11542000	Carry-out milk shake, NS as to flavor	-
IceCream	11542100	Carry-out milk shake, chocolate	-
IceCream	11542200	Carry-out milk shake, flavors other than chocolate	-
IceCream	13110000	Ice cream, NFS	-
IceCream	13110100	Ice cream, regular, flavors other than chocolate	-
IceCream	13110110	Ice cream, regular, chocolate	-
IceCream	13110120	Ice cream, rich, flavors other than chocolate	-
IceCream	13110130	Ice cream, rich, chocolate	-
IceCream	13110140	Ice cream, rich, NS as to flavor	-
IceCream	13110200	Ice cream, soft serve, flavors other than chocolate	-
IceCream	13110210	Ice cream, soft serve, chocolate	-
IceCream	13110220	Ice cream, soft serve, NS as to flavor	-
IceCream	13110310	Ice cream, no sugar added, NS as to flavor	-
IceCream	13110320	Ice cream, no sugar added, flavors other than chocolate	-
IceCream	13110330	Ice cream, no sugar added, chocolate	-
IceCream	13120050	Ice cream bar or stick, not chocolate covered or cake covered	-
IceCream	13120100	Ice cream bar or stick, chocolate covered	-
IceCream	13120110	Ice cream bar or stick, chocolate or caramel covered, with nuts	-
IceCream	13120120	Ice cream bar or stick, rich chocolate ice cream, thick chocolate covering	-
IceCream	13120121	Ice cream bar or stick, rich ice cream, thick chocolate covering	-
IceCream	13120130	Ice cream bar or stick, rich ice cream, chocolate covered, with nuts	-
IceCream	13120140	Ice cream bar or stick, chocolate ice cream, chocolate covered	-
IceCream	13120300	Ice cream bar, cake covered	-
IceCream	13120400	Ice cream bar or stick with fruit	-
IceCream	13120500	Ice cream sandwich	-
IceCream	13120550	Ice cream cookie sandwich	-
IceCream	13120700	Ice cream cone with nuts, flavors other than chocolate	-
IceCream	13120710	Ice cream cone, chocolate covered, with nuts, flavors other than chocolate	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
IceCream	13120720	Ice cream cone, chocolate covered or dipped, flavors other than chocolate	-
IceCream	13120730	Ice cream cone, no topping, flavors other than chocolate	-
IceCream	13120740	Ice cream cone, no topping, NS as to flavor	-
IceCream	13120750	Ice cream cone with nuts, chocolate ice cream	-
IceCream	13120760	Ice cream cone, chocolate covered or dipped, chocolate ice cream	-
IceCream	13120770	Ice cream cone, no topping, chocolate ice cream	-
IceCream	13120780	Ice cream cone, chocolate covered, with nuts, chocolate ice cream	-
IceCream	13120790	Ice cream sundae cone	-
IceCream	13120800	Ice cream soda, flavors other than chocolate	-
IceCream	13120810	Ice cream soda, chocolate	-
IceCream	13121000	Ice cream sundae, NS as to topping, with whipped cream	-
IceCream	13121100	Ice cream sundae, fruit topping, with whipped cream	-
IceCream	13121200	Ice cream sundae, prepackaged type, flavors other than chocolate	-
IceCream	13121300	Ice cream sundae, chocolate or fudge topping, with whipped cream	-
IceCream	13121400	Ice cream sundae, not fruit or chocolate topping, with whipped cream	-
IceCream	13121500	Ice cream sundae, fudge topping, with cake, with whipped cream	-
IceCream	13122100	Ice cream pie, no crust	-
IceCream	13122500	Ice cream pie, with cookie crust, fudge topping, and whipped cream	-
IceCream	13126000	Ice cream, fried	-
IceCream	13130100	Light ice cream, NS as to flavor (formerly ice milk)	-
IceCream	13130300	Light ice cream, flavors other than chocolate (formerly ice milk)	-
IceCream	13130310	Light ice cream, chocolate (formerly ice milk)	-
IceCream	13130320	Light ice cream, no sugar added, NS as to flavor	-
IceCream	13130330	Light ice cream, no sugar added, flavors other than chocolate	-
IceCream	13130340	Light ice cream, no sugar added, chocolate	-
IceCream	13130590	Light ice cream, soft serve, NS as to flavor (formerly ice milk)	-
IceCream	13130600	Light ice cream, soft serve, flavors other than chocolate (formerly ice milk)	-
IceCream	13130610	Light ice cream, soft serve, chocolate (formerly ice milk)	-
IceCream	13130620	Light ice cream, soft serve cone, flavors other than chocolate (formerly ice milk)	-
IceCream	13130630	Light ice cream, soft serve cone, chocolate (formerly ice milk)	-
IceCream	13130640	Light ice cream, soft serve cone, NS as to flavor (formerly ice milk)	-
IceCream	13130700	Light ice cream, soft serve, blended with candy or cookies	-
IceCream	13135000	Ice cream sandwich, made with light ice cream, flavors other than chocolate	-
IceCream	13135010	Ice cream sandwich, made with light chocolate ice cream	-
IceCream	13136000	Ice cream sandwich, made with light, no sugar added ice cream	-
IceCream	13140100	Light ice cream, bar or stick, chocolate-coated (formerly ice milk)	-
IceCream	13140110	Light ice cream, bar or stick, chocolate covered, with nuts (formerly ice milk)	-
IceCream	13140450	Light ice cream, cone, NFS (formerly ice milk)	-
IceCream	13140500	Light ice cream, cone, flavors other than chocolate (formerly ice milk)	-
IceCream	13140550	Light ice cream, cone, chocolate (formerly ice milk)	-
IceCream	13140600	Light ice cream, sundae, soft serve, chocolate or fudge topping, with whipped cream (formerly ice milk)	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
IceCream	13140630	Light ice cream, sundae, soft serve, fruit topping, with whipped cream (formerly ice milk)	-
IceCream	13140650	Light ice cream, sundae, soft serve, not fruit or chocolate topping, with whipped cream (formerly ice milk)	-
IceCream	13140660	Light ice cream, sundae, soft serve, chocolate or fudge topping (without whipped cream) (formerly ice milk)	-
IceCream	13140670	Light ice cream, sundae, soft serve, fruit topping (without whipped cream) (formerly ice milk)	-
IceCream	13140680	Light ice cream, sundae, soft serve, not fruit or chocolate topping (without whipped cream) (formerly ice milk)	-
IceCream	13140700	Light ice cream, creamsicle or dreamsicle (formerly ice milk)	-
IceCream	13140900	Light ice cream, fudgesicle (formerly ice milk)	-
IceCream	13142000	Milk dessert bar or stick, frozen, with coconut	-
IceCream	13160150	Fat free ice cream, no sugar added, chocolate	-
IceCream	13160160	Fat free ice cream, no sugar added, flavors other than chocolate	-
IceCream	13160400	Fat free ice cream, flavors other than chocolate	-
IceCream	13160410	Fat free ice cream, chocolate	-
IceCream	13160420	Fat free ice cream, NS as to flavor	-
IceCream	13161000	Milk dessert bar, frozen, made from lowfat milk	-
IceCream	13161500	Milk dessert sandwich bar, frozen, made from lowfat milk	-
IceCream	13161520	Milk dessert sandwich bar, frozen, with low-calorie sweetener, made from lowfat milk	-
IceCream	13161600	Milk dessert bar, frozen, made from lowfat milk and low calorie sweetener	-
IceCream	13161630	Light ice cream, bar or stick, with low-calorie sweetener, chocolate-coated (formerly ice milk)	-
IceCream	13170000	Baked Alaska	-
IceCream	53112000	Cake, ice cream and cake roll, chocolate	-
IceCream	53112100	Cake, ice cream and cake roll, not chocolate	-
IceCream	53430300	Crepe, dessert type, ice cream-filled	-
IceCream	91611050	Ice pop filled with ice cream, all flavor varieties	-
MilkFluid	11100000	Milk, NFS	-
MilkFluid	11111000	Milk, cow's, fluid, whole	-
MilkFluid	11111100	Milk, cow's, fluid, whole, low-sodium	-
MilkFluid	11111150	Milk, calcium fortified, cow's, fluid, whole	-
MilkFluid	11111160	Milk, calcium fortified, cow's, fluid, 1% fat	-
MilkFluid	11111170	Milk, calcium fortified, cow's, fluid, skim or nonfat	-
MilkFluid	11112000	Milk, cow's, fluid, other than whole, NS as to 2%, 1%, or skim	-
MilkFluid	11112110	Milk, cow's, fluid, 2% fat	-
MilkFluid	11112120	Milk, cow's, fluid, acidophilus, 1% fat	-
MilkFluid	11112130	Milk, cow's, fluid, acidophilus, 2% fat	-
MilkFluid	11112210	Milk, cow's, fluid, 1% fat	-
MilkFluid	11113000	Milk, cow's, fluid, skim or nonfat, 0.5% or less butterfat	-
MilkFluid	11114000	Milk, cow's, fluid, filled with vegetable oil, NS as to percent fat	-
MilkFluid	11114100	Milk, cow's, fluid, filled with vegetable oil, whole	-
MilkFluid	11114200	Milk, cow's, fluid, filled with vegetable oil, lowfat	-
MilkFluid	11114300	Milk, cow's, fluid, lactose reduced, 1% fat	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	11114310	Milk, cow's, fluid, lactose reduced, 1% fat, fortified with calcium	-
MilkFluid	11114320	Milk, cow's, fluid, lactose reduced, nonfat	-
MilkFluid	11114321	Milk, cow's, fluid, lactose reduced, nonfat, fortified with calcium	-
MilkFluid	11114330	Milk, cow's, fluid, lactose reduced, 2% fat	-
MilkFluid	11114350	Milk, cow's, fluid, lactose reduced, whole	-
MilkFluid	11115000	Buttermilk, fluid, nonfat	-
MilkFluid	11115100	Buttermilk, fluid, 1% fat	-
MilkFluid	11115200	Buttermilk, fluid, 2% fat	-
MilkFluid	11115300	Buttermilk, fluid, whole	-
MilkFluid	11511000	Milk, chocolate, NFS	-
MilkFluid	11511100	Milk, chocolate, whole milk-based	-
MilkFluid	11511200	Milk, chocolate, reduced fat milk-based, 2% (formerly "lowfat")	-
MilkFluid	11511300	Milk, chocolate, skim milk-based	-
MilkFluid	11511400	Milk, chocolate, lowfat milk-based	-
MilkFluid	11512000	Cocoa, hot chocolate, not from dry mix, made with whole milk	-
MilkFluid	11513000	Cocoa and sugar mixture, milk added, NS as to type of milk	-
MilkFluid	11513100	Cocoa and sugar mixture, whole milk added	-
MilkFluid	11513150	Cocoa and sugar mixture, reduced fat milk added	-
MilkFluid	11513200	Cocoa and sugar mixture, lowfat milk added	-
MilkFluid	11513300	Cocoa and sugar mixture, skim milk added	-
MilkFluid	11513400	Chocolate syrup, milk added, NS as to type of milk	-
MilkFluid	11513500	Chocolate syrup, whole milk added	-
MilkFluid	11513550	Chocolate syrup, reduced fat milk added	-
MilkFluid	11513600	Chocolate syrup, lowfat milk added	-
MilkFluid	11513700	Chocolate syrup, skim milk added	-
MilkFluid	11516000	Cocoa, whey, and low-calorie sweetener mixture, lowfat milk added	-
MilkFluid	11519000	Milk beverage, made with whole milk, flavors other than chocolate	-
MilkFluid	11519040	Milk, flavors other than chocolate, NFS	-
MilkFluid	11519050	Milk, flavors other than chocolate, whole milk-based	-
MilkFluid	11519105	Milk, flavors other than chocolate, reduced fat milk-based	-
MilkFluid	11519200	Milk, flavors other than chocolate, lowfat milk-based	-
MilkFluid	11519205	Milk, flavors other than chocolate, skim-milk based	-
MilkFluid	11525000	Milk, malted, fortified, natural flavor, made with milk	-
MilkFluid	11526000	Milk, malted, fortified, chocolate, made with milk	-
MilkFluid	11531000	Eggnog, made with whole milk	-
MilkFluid	11531500	Eggnog, made with 2% reduced fat milk (formerly eggnog, made with "2% lowfat" milk)	-
MilkFluid	11541000	Milk shake, NS as to flavor or type	-
MilkFluid	11541110	Milk shake, homemade or fountain-type, chocolate	-
MilkFluid	11541120	Milk shake, homemade or fountain-type, flavors other than chocolate	-
MilkFluid	11541400	Milk shake with malt	-
MilkFluid	11551050	Milk fruit drink	-
MilkFluid	11560000	Chocolate-flavored drink, whey- and milk-based	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	11560020	Flavored milk drink, whey- and milk-based, flavors other than chocolate	-
MilkFluid	11561000	Cafe con leche	-
MilkFluid	11561010	Cafe con leche prepared with sugar	-
MilkFluid	11611000	Instant breakfast, fluid, canned	-
MilkFluid	11612000	Instant breakfast, powder, milk added	-
MilkFluid	11641000	Meal supplement or replacement, milk-based, high protein, liquid	-
MilkFluid	11641020	Meal replacement or supplement, milk based, ready-to-drink	-
MilkFluid	13200110	Pudding, NFS	-
MilkFluid	13210110	Pudding, bread	-
MilkFluid	13210220	Pudding, chocolate, ready-to-eat, NS as to from dry mix or canned	-
MilkFluid	13210250	Pudding, chocolate, ready-to-eat, low calorie, containing artificial sweetener, NS as to from dry mix or canned	-
MilkFluid	13210270	Custard, Puerto Rican style (Maicena, Natilla)	-
MilkFluid	13210280	Pudding, flavors other than chocolate, ready-to-eat, NS as to from dry mix or canned	-
MilkFluid	13210290	Pudding, flavors other than chocolate, ready-to-eat, low calorie, containing articifial sweetener, NS as to from dry mix or canned	-
MilkFluid	13210300	Custard	-
MilkFluid	13210410	Pudding, rice	-
MilkFluid	13210450	Pudding, rice flour, with nuts (Indian dessert)	-
MilkFluid	13210500	Pudding, tapioca, made from home recipe, made with milk	-
MilkFluid	13210520	Pudding, tapioca, made from dry mix, made with milk	-
MilkFluid	13210710	Pudding, Indian (milk, molasses and cornmeal-based pudding)	-
MilkFluid	13210750	Pudding, pumpkin	-
MilkFluid	13210810	Puerto Rican pumpkin pudding (Flan de calabaza)	-
MilkFluid	13220110	Pudding, flavors other than chocolate, prepared from dry mix, milk added	-
MilkFluid	13220120	Pudding, chocolate, prepared from dry mix, milk added	-
MilkFluid	13220210	Pudding, flavors other than chocolate, prepared from dry mix, low calorie, containing artificial sweetener, milk added	-
MilkFluid	13220220	Pudding, chocolate, prepared from dry mix, low calorie, containing artificial sweetener, milk added	-
MilkFluid	13241000	Pudding, with fruit and vanilla wafers	-
MilkFluid	13250000	Mousse, chocolate	-
MilkFluid	13411000	White sauce, milk sauce	-
MilkFluid	13412000	Milk gravy, quick gravy	-
MilkFluid	14630200	Cheese souffle	-
MilkFluid	14630300	Welsh rarebit	-
MilkFluid	14660200	Cheese, nuggets or pieces, breaded, fried	-
MilkFluid	14710100	Cheddar cheese soup	-
MilkFluid	14710200	Beer soup, made with milk	-
MilkFluid	21103110	Beef steak, breaded or floured, baked or fried, NS as to fat eaten	-
MilkFluid	21103120	Beef steak, breaded or floured, baked or fried, lean and fat eaten	-
MilkFluid	21103130	Beef steak, breaded or floured, baked or fried, lean only eaten	-
MilkFluid	21500200	Ground beef or patty, breaded, cooked	-
MilkFluid	22002100	Pork, ground or patty, breaded, cooked	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	22101400	Pork chop, battered, fried, NS as to fat eaten	-
MilkFluid	22101410	Pork chop, battered, fried, lean and fat eaten	-
MilkFluid	22101420	Pork chop, battered, fried, lean only eaten	-
MilkFluid	22201050	Pork steak or cutlet, battered, fried, NS as to fat eaten	-
MilkFluid	22201060	Pork steak or cutlet, battered, fried, lean and fat eaten	-
MilkFluid	22201070	Pork steak or cutlet, battered, fried, lean only eaten	-
MilkFluid	22210450	Pork, tenderloin, battered, fried	-
MilkFluid	26100130	Fish, NS as to type, breaded or battered, baked	-
MilkFluid	26107130	Catfish, breaded or battered, baked	-
MilkFluid	26109130	Cod, breaded or battered, baked	-
MilkFluid	26111130	Croaker, breaded or battered, baked	-
MilkFluid	26115130	Flounder, breaded or battered, baked	-
MilkFluid	26117130	Haddock, breaded or battered, baked	-
MilkFluid	26127130	Perch, breaded or battered, baked	-
MilkFluid	26141130	Sea bass, breaded or battered, baked	-
MilkFluid	26151130	Trout, breaded or battered, baked	-
MilkFluid	26157130	Whiting, breaded or battered, baked	-
MilkFluid	26158020	Tilapia, breaded or battered, baked	-
MilkFluid	27113000	Beef with cream or white sauce (mixture)	-
MilkFluid	27113200	Creamed chipped or dried beef	-
MilkFluid	27113300	Swedish meatballs with cream or white sauce (mixture)	-
MilkFluid	27114000	Beef with (mushroom) soup (mixture)	-
MilkFluid	27116300	Beef with sweet and sour sauce (mixture)	-
MilkFluid	27120060	Sweet and sour pork	-
MilkFluid	27120090	Ham or pork with (mushroom) soup (mixture)	-
MilkFluid	27120120	Sausage gravy	-
MilkFluid	27143000	Chicken or turkey with cream sauce (mixture)	-
MilkFluid	27144000	Chicken or turkey with (mushroom) soup (mixture)	-
MilkFluid	27146100	Sweet and sour chicken or turkey	-
MilkFluid	27150030	Crab imperial	-
MilkFluid	27150100	Shrimp curry	-
MilkFluid	27150170	Sweet and sour shrimp	-
MilkFluid	27211190	Lobster sauce (broth-based)	-
MilkFluid	27211500	Beef and potatoes with cheese sauce (mixture)	-
MilkFluid	27212050	Beef and macaroni with cheese sauce (mixture)	-
MilkFluid	27212300	Beef and noodles with cream or white sauce (mixture)	-
MilkFluid	27212400	Beef and noodles with (mushroom) soup (mixture)	-
MilkFluid	27213300	Beef and rice with cream sauce (mixture)	-
MilkFluid	27213400	Beef and rice with (mushroom) soup (mixture)	-
MilkFluid	27214100	Meat loaf made with beef	-
MilkFluid	27214110	Meat loaf made with beef, with tomato-based sauce	-
MilkFluid	27220010	Meat loaf made with ham (not luncheon meat)	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	27220030	Ham and rice with (mushroom) soup (mixture)	-
MilkFluid	27220080	Ham croquette	-
MilkFluid	27220150	Sausage and rice with (mushroom) soup (mixture)	-
MilkFluid	27220190	Sausage and noodles with cream or white sauce (mixture)	-
MilkFluid	27220520	Ham or pork and potatoes with cheese sauce (mixture)	-
MilkFluid	27230010	Lamb or mutton loaf	-
MilkFluid	27235000	Meat loaf made with venison/deer	-
MilkFluid	27236000	Venison/deer and noodles with cream or white sauce (mixture)	-
MilkFluid	27242250	Chicken or turkey and noodles with (mushroom) soup (mixture)	-
MilkFluid	27242300	Chicken or turkey and noodles with cream or white sauce (mixture)	-
MilkFluid	27243300	Chicken or turkey and rice with cream sauce (mixture)	-
MilkFluid	27246100	Chicken or turkey with dumplings (mixture)	-
MilkFluid	27246300	Chicken or turkey cake, patty, or croquette	-
MilkFluid	27246400	Chicken or turkey souffle	-
MilkFluid	27246500	Meat loaf made with chicken or turkey	-
MilkFluid	27246505	Meat loaf made with chicken or turkey, with tomato-based sauce	-
MilkFluid	27250110	Scallops and noodles with cheese sauce (mixture)	-
MilkFluid	27250124	Shrimp and noodles with (mushroom) soup (mixture)	-
MilkFluid	27250126	Shrimp and noodles with cream or white sauce (mixture)	-
MilkFluid	27250130	Shrimp and noodles with cheese sauce (mixture)	-
MilkFluid	27250250	Flounder with crab stuffing	-
MilkFluid	27250610	Tuna noodle casserole with cream or white sauce	-
MilkFluid	27250630	Tuna noodle casserole with (mushroom) soup	-
MilkFluid	27250810	Fish and rice with tomato-based sauce	-
MilkFluid	27250820	Fish and rice with cream sauce	-
MilkFluid	27250830	Fish and rice with (mushroom) soup	-
MilkFluid	27250900	Fish and noodles with (mushroom) soup	-
MilkFluid	27260010	Meat loaf, NS as to type of meat	-
MilkFluid	27260050	Meatballs, with breading, NS as to type of meat, with gravy	-
MilkFluid	27260080	Meat loaf made with beef and pork	-
MilkFluid	27260090	Meat loaf made with beef, veal and pork	-
MilkFluid	27260100	Meat loaf made with beef and pork, with tomato-based sauce	-
MilkFluid	27311510	Shepherd's pie with beef	-
MilkFluid	27313310	Beef, noodles, and vegetables (including carrots, broccoli, and/or dark-green leafy), (mushroom) soup (mixture)	-
MilkFluid	27320030	Ham or pork, noodles and vegetables (excluding carrots, broccoli, and dark-green leafy), cheese sauce (mixture)	-
MilkFluid	27320120	Sausage, potatoes, and vegetables (including carrots, broccoli, and/or dark-green leafy), gravy (mixture)	-
MilkFluid	27320130	Sausage, potatoes, and vegetables (excluding carrots, broccoli, and dark-green leafy), gravy (mixture)	-
MilkFluid	27330010	Shepherd's pie with lamb	-
MilkFluid	27341035	Chicken or turkey, potatoes, and vegetables (including carrots, broccoli, and/or dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	27341040	Chicken or turkey, potatoes, and vegetables (excluding carrots, broccoli, and dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	-
MilkFluid	27343470	Chicken or turkey, noodles, and vegetables (including carrots, broccoli, and/or dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	-
MilkFluid	27343480	Chicken or turkey, noodles, and vegetables (excluding carrots, broccoli, and/or dark-green leafy), cream sauce, white sauce, or mushroom soup-based sauce (mixture)	-
MilkFluid	27343950	Chicken or turkey, noodles, and vegetables (including carrots, broccoli, and/or dark-green leafy), cheese sauce (mixture)	-
MilkFluid	27343960	Chicken or turkey, noodles, and vegetables (excluding carrots, broccoli, and dark-green leafy), cheese sauce (mixture)	-
MilkFluid	27347240	Chicken or turkey, dumplings, and vegetables (including carrots, broccoli, and/or dark green leafy), gravy (mixture)	-
MilkFluid	27347250	Chicken or turkey, dumplings, and vegetables (excluding carrots, broccoli, and dark green leaft), gravy (mixture)	-
MilkFluid	27350410	Tuna noodle casserole with vegetables and (mushroom) soup	-
MilkFluid	27443110	Chicken or turkey a la king with vegetables (including carrots, broccoli, and/or dark-green leafy (no potatoes)), cream, white, or soup-based sauce	-
MilkFluid	27443120	Chicken or turkey a la king with vegetables (excluding carrots, broccoli, and dark-green leafy (no potatoes)), cream, white, or soup-based sauce	-
MilkFluid	27443150	Chicken or turkey divan	-
MilkFluid	27450510	Tuna casserole with vegetables and (mushroom) soup, no noodles	-
MilkFluid	27515080	Steak sandwich, plain, on biscuit	-
MilkFluid	27550000	Fish sandwich, on bun, with spread	-
MilkFluid	27560300	Corn dog (frankfurter or hot dog with cornbread coating)	-
MilkFluid	27560350	Pig in a blanket (frankfurter or hot dog wrapped in dough)	-
MilkFluid	28110330	Salisbury steak with gravy, whipped potatoes, vegetable, dessert (frozen meal)	-
MilkFluid	28110370	Salisbury steak with gravy, macaroni and cheese, vegetable (frozen meal)	-
MilkFluid	28110380	Salisbury steak with gravy, macaroni and cheese (frozen meal)	-
MilkFluid	28140100	Chicken dinner, NFS (frozen meal)	-
MilkFluid	28140150	Chicken divan (frozen meal)	-
MilkFluid	28140810	Chicken, fried, with potatoes, vegetable, dessert (frozen meal)	-
MilkFluid	28141600	Chicken a la king with rice (frozen meal)	-
MilkFluid	28141610	Chicken and vegetables in cream or white sauce (diet frozen meal)	-
MilkFluid	28143180	Chicken in butter sauce with potatoes and vegetable (diet frozen meal)	-
MilkFluid	28144100	Chicken and vegetable entrée with noodles and cream sauce (frozen meal)	-
MilkFluid	28145710	Turkey tetrazzini (frozen meal)	-
MilkFluid	28150210	Haddock with chopped spinach (diet frozen meal)	-
MilkFluid	28150220	Flounder with chopped broccoli (diet frozen meal)	-
MilkFluid	28160300	Meat loaf dinner, NFS (frozen meal)	-
MilkFluid	28160310	Meat loaf with potatoes, vegetable (frozen meal)	-
MilkFluid	28340590	Chicken corn soup with noodles, home recipe	-
MilkFluid	28345010	Chicken or turkey soup, cream of, canned, reduced sodium, NS as to made with milk or water	-
MilkFluid	28345020	Chicken or turkey soup, cream of, canned, reduced sodium, made with milk	-
MilkFluid	28345110	Chicken or turkey soup, cream of, NS as to prepared with milk or water	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	28345120	Chicken or turkey soup, cream of, prepared with milk	-
MilkFluid	28345160	Chicken and mushroom soup, cream of, prepared with milk	-
MilkFluid	28350050	Fish chowder	-
MilkFluid	28350110	Crab soup, NS as to tomato-base or cream style	-
MilkFluid	28350210	Clam chowder, NS as to Manhattan or New England style	-
MilkFluid	28355110	Clam chowder, New England, NS as to prepared with water or milk	-
MilkFluid	28355120	Clam chowder, New England, prepared with milk	-
MilkFluid	28355210	Crab soup, cream of, prepared with milk	-
MilkFluid	28355250	Lobster bisque	-
MilkFluid	28355310	Oyster stew	-
MilkFluid	28355410	Shrimp soup, cream of, NS as to prepared with milk or water	-
MilkFluid	28355420	Shrimp soup, cream of, prepared with milk	-
MilkFluid	32104900	Egg omelet or scrambled egg, NS as to fat added in cooking	-
MilkFluid	32104950	Egg omelet or scrambled egg, fat not added in cooking	-
MilkFluid	32105000	Egg omelet or scrambled egg, fat added in cooking	-
MilkFluid	32105010	Egg omelet or scrambled egg, with cheese	-
MilkFluid	32105013	Egg omelet or scrambled egg, with seafood	-
MilkFluid	32105020	Egg omelet or scrambled egg, with fish	-
MilkFluid	32105030	Egg omelet or scrambed egg, with ham or bacon	-
MilkFluid	32105040	Egg omelet or scrambed egg, with dark-green vegetables	-
MilkFluid	32105045	Egg omelet or scrambled egg, with cheese and dark-green vegetables	-
MilkFluid	32105048	Egg omelet or scrambled egg, with mushrooms	-
MilkFluid	32105050	Egg omelet or scrambled egg, with vegetables other than dark-green	-
MilkFluid	32105055	Egg omelet or scrambled egg, with cheese and vegetables other than dark-green	-
MilkFluid	32105060	Egg omelet or scrambled egg, with ham or bacon and vegetables other than dark-green	-
MilkFluid	32105070	Egg omelet or scrambled egg, with mushrooms	-
MilkFluid	32105080	Egg omelet or scrambled egg, with ham or bacon and cheese	-
MilkFluid	32105081	Egg omelet or scrambled egg, with ham or bacon, cheese, and dark-green vegetables	-
MilkFluid	32105082	Egg omelet or scrambled egg, with ham or bacon, cheese, and vegetables other than dark-green	-
MilkFluid	32105085	Egg omelet or scrambled egg, with ham or bacon, cheese, and tomatoes	-
MilkFluid	32105100	Egg omelet or scrambled egg, with potatoes and/or onions (Tortilla Espanola, traditional style Spanish omelet)	-
MilkFluid	32105110	Egg omelet or scrambled egg, with beef	-
MilkFluid	32105118	Egg omelet or scrambled egg, with sausage and vegetables other than dark-green	-
MilkFluid	32105119	Egg omelet or scrambled egg, with sausage, cheese, and vegetables other than dark-green	-
MilkFluid	32105121	Egg omelet or scrambled egg, with sausage and cheese	-
MilkFluid	32105122	Egg omelet or scrambled egg, with sausage, cheese, and mushrooms	-
MilkFluid	32105125	Egg omelet or scrambled egg, with hot dogs	-
MilkFluid	32105126	Egg omelet or scrambled egg, with hot dog and cheese	-
MilkFluid	32105130	Egg omelet or scrambled egg, Spanish omelet, made with onions, peppers, tomatoes, and mushrooms	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	32105150	Egg omelet or scrambled egg, with cheese, beans, tomatoes, and chili sauce	-
MilkFluid	32105160	Egg omelet or scrambled egg, with chorizo	-
MilkFluid	32105161	Egg omelet or scrambled egg, with chorizo and cheese	-
MilkFluid	32105170	Egg omelet or scrambled egg, with chicken or turkey	-
MilkFluid	32105190	Egg casserole with bread, cheese, milk and meat	-
MilkFluid	32400010	Egg white omelet or scrambled egg, NS as to fat added in cooking	-
MilkFluid	32400011	Egg white omelet or scrambled egg, fat not added in cooking	-
MilkFluid	32400012	Egg white omelet or scrambled egg, fat added in cooking	-
MilkFluid	32400050	Egg white omelet or scrambled egg, with cheese	-
MilkFluid	33201010	Scrambled egg, made from cholesterol-free frozen mixture	-
MilkFluid	33201110	Scrambled egg, made from cholesterol-free frozen mixture with cheese	-
MilkFluid	33201500	Scrambled egg, made from cholesterol-free frozen mixture with vegetables	-
MilkFluid	33202010	Scrambled egg, made from frozen mixture	-
MilkFluid	33301010	Scrambled egg, made from packaged liquid mixture	-
MilkFluid	41436000	Nutritional supplement for people with diabetes, liquid	-
MilkFluid	51000180	Bread, made from home recipe or purchased at a bakery, NS as to major flour	-
MilkFluid	51000190	Bread, made from home recipe or purchased at a bakery, toasted, NS as to major flour	-
MilkFluid	51000250	Roll, made from home recipe or purchased at a bakery, NS as to major flour	-
MilkFluid	51101050	Bread, white, made from home recipe or purchased at a bakery	-
MilkFluid	51101060	Bread, white, made from home recipe or purchased at a bakery, toasted	-
MilkFluid	51115010	Bread, cornmeal and molasses	-
MilkFluid	51115020	bread, cornmeal and molasses, toasted	-
MilkFluid	51140100	Bread, dough, fried	-
MilkFluid	51161030	Roll, sweet, with fruit, frosted, diet	-
MilkFluid	51161050	Roll, sweet, with nuts, frosted	-
MilkFluid	51161070	Roll, sweet, with fruit, frosted, fat free	-
MilkFluid	51165060	Coffee cake, yeast type, made from home recipe or purchased at a bakery	-
MilkFluid	51165100	Coffee cake, yeast type, fat free, cholesterol free, with fruit	-
MilkFluid	51167000	Brioche	-
MilkFluid	51188100	Pannetone (Italian-style sweet bread)	-
MilkFluid	51201060	Bread, whole wheat, 100%, made from home recipe or purchased at bakery	-
MilkFluid	51300140	Bread, whole wheat, NS as to 100%, made from home recipe or purchased at bakery	-
MilkFluid	51300150	Bread, whole wheat, NS as to 100%, made from home recipe or purchased at bakery, toasted	-
MilkFluid	51502010	Roll, oatmeal	-
MilkFluid	51801010	Bread, barley	-
MilkFluid	51804010	Bread, soy	-
MilkFluid	51804020	Bread, soy, toasted	-
MilkFluid	51805010	Bread, sunflower meal	-
MilkFluid	51805020	Bread, sunflower meal, toasted	-
MilkFluid	52101000	Biscuit, baking powder or buttermilk type, NS as to made from mix, refrigerated dough, or home recipe	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	52101100	Biscuit, baking powder or buttermilk type, made from mix	-
MilkFluid	52104010	Biscuit, baking powder or buttermilk type, made from home recipe	-
MilkFluid	52104040	Biscuit, whole wheat	-
MilkFluid	52104100	Biscuit, cheese	-
MilkFluid	52104200	Biscuit, cinnamon-raisin	-
MilkFluid	52201000	Cornbread, prepared from mix	-
MilkFluid	52202060	Cornbread, made from home recipe	-
MilkFluid	52206060	Cornbread muffin, stick, round, made from home recipe	-
MilkFluid	52220110	Cornmeal bread, Dominican style (Arepa Dominicana)	-
MilkFluid	52302100	Muffin, fruit, fat free, cholesterol free	-
MilkFluid	52302500	Muffin, chocolate chip	-
MilkFluid	52302600	Muffin, chocolate	-
MilkFluid	52302610	Muffin, chocolate, lowfat	-
MilkFluid	52303010	Muffin, whole wheat	-
MilkFluid	52303500	Muffin, wheat	-
MilkFluid	52304060	Muffin, bran with fruit, no fat, no cholesterol	-
MilkFluid	52304100	Muffin, oatmeal	-
MilkFluid	52306010	Muffin, plain	-
MilkFluid	52306300	Muffin, cheese	-
MilkFluid	52306700	Muffin, carrot	-
MilkFluid	52307120	Muffin, multigrain, with fruit	-
MilkFluid	52311010	Popover	-
MilkFluid	52403000	Bread, nut	-
MilkFluid	52405010	Bread, fruit, without nuts	-
MilkFluid	52406010	Bread, whole wheat, with nuts	-
MilkFluid	52408000	Bread, Irish soda	-
MilkFluid	53100100	Cake, NS as to type, with or without icing	-
MilkFluid	53102000	Cake, applesauce, NS as to icing	-
MilkFluid	53102200	Cake, applesauce, without icing	-
MilkFluid	53102600	Cake, banana, without icing	-
MilkFluid	53102700	Cake, banana, with icing	-
MilkFluid	53103550	Cake, butter, without icing	-
MilkFluid	53103600	Cake, butter, with icing	-
MilkFluid	53104580	Cheesecake -type dessert, made with yogurt, with fruit	-
MilkFluid	53105050	Cake, chocolate, devil's food, or fudge, made from home recipe or purchased ready-to-eat, NS as to icing	-
MilkFluid	53105160	Cake, chocolate, devil's food, or fudge, without icing or filling, made from home recipe or purchased ready-to-eat	-
MilkFluid	53105200	Cake, chocolate, devil's food, or fudge, standard-type mix (eggs and water added to dry mix), with icing, coating, or filling	-
MilkFluid	53105260	Cake, chocolate, devil's food, or fudge, with icin, coating, or filling, made from home recipe or purchased ready-to-eat	-
MilkFluid	53105600	Cake, chocolate, devil's food, or fudge, pudding-type mix, made by "Lite" recipe (eggs and water added to mix, no oil added to dry mix), with icing, coating, or filling	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	53107000	Cake, cupcake, NS as to type or icing	-
MilkFluid	53107200	Cake, cupcake, NS as to type, with icing	-
MilkFluid	53108000	Cake, cupcake, chocolate, NS as to icing	-
MilkFluid	53109210	Cake, cupcake, not chocolate, with icing or filling, lowfat, cholesterol free	-
MilkFluid	53111500	Cake, graham cracker, without icing	-
MilkFluid	53112000	Cake, ice cream and cake roll, chocolate	-
MilkFluid	53112100	Cake, ice cream and cake roll, not chocolate	-
MilkFluid	53115200	Cake, marble, with icing	-
MilkFluid	53115320	Cake, nut, with icing	-
MilkFluid	53115410	Cake, oatmeal, with icing	-
MilkFluid	53116000	Cake, pound, without icing	-
MilkFluid	53116020	Cake, pound, with icing	-
MilkFluid	53116270	Cake, pound, chocolate	-
MilkFluid	53116390	Cake, pound, reduced fat, cholesterol free	-
MilkFluid	53116560	Cake, raisin-nut, with icing	-
MilkFluid	53117200	Cake, spice, with icing	-
MilkFluid	53118310	Cake, sponge, chocolate, with icing	-
MilkFluid	53118350	Cake, sweetpotato, with icing	-
MilkFluid	53118500	Cake, torte	-
MilkFluid	53119000	Cake, upside down (all fruits)	-
MilkFluid	53120060	Cake, white, made from home recipe or purchased ready-to-eat, NS as to icing	-
MilkFluid	53120160	Cake, white, without icing, made from home recipe or purchased ready-to-eat	-
MilkFluid	53120200	Cake, white, standard-type mix (egg whites and water added to mix), with icing	-
MilkFluid	53120260	Cake, white, with icing, made from home recipe or purchased ready-to-eat	-
MilkFluid	53120350	Cake, white, pudding-type mix (oil, egg whites, and water added to dry mix), with icing	-
MilkFluid	53120400	Cake, white, eggless, lowfat	-
MilkFluid	53121060	cake, yellow, made from home recipe or purchased ready-to-eat, NS as to icing	-
MilkFluid	53121160	Cake, yellow, without icing, made from home recipe or purchased ready-to-eat	-
MilkFluid	53121200	Cake, yellow, standard-type mix (eggs and water added to dry mix), with icing	-
MilkFluid	53121260	Cake, yellow, with icing, made from home recipe or purchased ready-to-eat	-
MilkFluid	53121330	Cake, yellow, pudding-type mix (oil, eggs, and water added to dry mix), with icing	-
MilkFluid	53122070	Cake, shortcake, biscuit type, with whipped cream and fruit	-
MilkFluid	53122080	Cake, shortcake, biscuit type, with fruit	-
MilkFluid	53124120	Cake, zucchini, with icing	-
MilkFluid	53204850	Cake, brownie, fat free, cholesterol free, with icing	-
MilkFluid	53206550	Cookie, chocolate, made with oatmeal and coconut (no-bake)	-
MilkFluid	53210900	Cookie, graham cracker sandwich with chocolate and marshmallow filling	-
MilkFluid	53233000	Cookie, oatmeal	-
MilkFluid	53233050	Cookie, oatmeal sandwich, with crème filling	-
MilkFluid	53233100	Cookie, oatmeal, with chocolate and peanut butter (no-bake)	-
MilkFluid	53241600	Cookie, butter or sugar cookie, with fruit and/or nuts	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	53244010	Cookie, butter or sugar, with chocolate icing or filling	-
MilkFluid	53341500	Pie, buttermilk	-
MilkFluid	53342000	Pie, chocolate cream	-
MilkFluid	53342070	Pie, chocolate cream, individual size or tart	-
MilkFluid	53343070	Pie, coconut cream, individual size or tart	-
MilkFluid	53345000	Pie, lemon cream	-
MilkFluid	53345070	Pie, lemon cream, individual size or tart	-
MilkFluid	53346000	Pie, peanut butter cream	-
MilkFluid	53346500	Pie, pineapple cream	-
MilkFluid	53360000	Pie, sweetpotato	-
MilkFluid	53382000	Pie, chocolate-marshmallow	-
MilkFluid	53400200	Blintz, cheese-filled	-
MilkFluid	53400300	Blintz, fruit-filled	-
MilkFluid	53410100	Cobbler, apple	-
MilkFluid	53410300	Cobbler, berry	-
MilkFluid	53410500	Cobbler, cherry	-
MilkFluid	53410800	Cobbler, peach	-
MilkFluid	53410850	Cobbler, pear	-
MilkFluid	53410860	Cobbler, pineapple	-
MilkFluid	53410900	Cobbler, rhubarb	-
MilkFluid	53415120	Fritter, apple	-
MilkFluid	53415200	Fritter, banana	-
MilkFluid	53430000	Crepe, dessert type, NS as to filling	-
MilkFluid	53430100	Crepe, dessert type, chocolate-filled	-
MilkFluid	53430200	Crepe, dessert type, fruit-filled	-
MilkFluid	53441210	Basbousa (semolina dessert dish)	-
MilkFluid	53452170	Pastry, cookie type, fried	-
MilkFluid	53452420	Pastry, puff, custard or cream filled, iced or not iced	-
MilkFluid	53511500	Danish pastry, with cheese, fat free, cholesterol free	-
MilkFluid	53520150	Doughnut, cake type, chocolate covered, dipped in peanuts	-
MilkFluid	53520160	Doughnut, chocolate, cake type, with chocolate icing	-
MilkFluid	53520500	Doughnut, oriental	-
MilkFluid	53521100	Doughnut, chocolate, raised or yeast, with chocolate icing	-
MilkFluid	53521130	Doughnut, raised or yeast, chocolate covered	-
MilkFluid	55103000	Pancakes, with fruit	-
MilkFluid	55103100	Pancakes, with chocolate chips	-
MilkFluid	55105000	Pancakes, buckwheat	-
MilkFluid	55105100	Pancakes, cornmeal	-
MilkFluid	55105200	Pancakes, whole wheat	-
MilkFluid	55202000	Waffle, wheat, bran, or multigrain	-
MilkFluid	55203500	Waffle, nut and honey	-
MilkFluid	55204000	Waffle, cornmeal	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	55205000	Waffle, 100% whole wheat or 100% whole grain	-
MilkFluid	55211050	Waffle, plain, lowfat	-
MilkFluid	55301000	French toast, plain	-
MilkFluid	55401000	Crepe, plain	-
MilkFluid	55610300	Dumpling, plain	-
MilkFluid	55801000	Funnel cake	-
MilkFluid	56201300	Grits, cooked, corn or hominy, NS as to regular, quick, or instant, NS as to fat added in cooking, made with milk	-
MilkFluid	56201530	Cornmeal mush, made with milk	-
MilkFluid	56201540	Cornmeal, made with milk and sugar, Puerto Rican style (Harina de maiz)	-
MilkFluid	56201550	Cornmeal dumpling	-
MilkFluid	56201700	Cornstarch with milk, eaten as cereal (2 tbsp cornstarch in 2-1/2 cups milk)	-
MilkFluid	56203210	Oatmeal, NS as to regular, quick, or instant, made with milk, fat not added in cooking	-
MilkFluid	56203211	Oatmeal , cooked, regular, made with milk, fat not added in cooking	-
MilkFluid	56203212	Oatmeal, cooked, quick (1 or 3 minutes), made with milk, fat not added in cooking	-
MilkFluid	56203213	Oatmeal, cooked, instant, made with milk, fat not added in cooking	-
MilkFluid	56203220	Oatmeal, NS as to regular, quick, or instant, made with milk, fat added in cooking	-
MilkFluid	56203221	Oatmeal, cooked regular, made with milk, fat added in cooking	-
MilkFluid	56203222	Oatmeal, cooked, quick (1 or 3 minutes), made with milk, fat added in cooking	-
MilkFluid	56203223	Oatmeal, cooked, instant, made with milk, fat added in cooking	-
MilkFluid	56203230	Oatmeal, NS as to regular, quick, or instant, made with milk, NS as to fat added in cooking	-
MilkFluid	56203231	Oatmeal, cooked, regular, made with milk, NS as to fat added in cooking	-
MilkFluid	56203232	Oatmeal, cooked, quick (1 or 3 minutes), made with milk, NS as to fat added in cooking	-
MilkFluid	56203233	Oatmeal, cooked, instant, made with milk, NS as to fat added in cooking	-
MilkFluid	56205060	Rice, cooked with milk	-
MilkFluid	56205080	Rice, creamed, made with milk and sugar, Puerto Rican style	-
MilkFluid	56207040	Wheat, cream of, cooked, made with milk	-
MilkFluid	56208530	Oat bran cereal, cooked, made with milk, fat not added in cooking	-
MilkFluid	58100160	Burrito with beef, beans, rice, and cheese	-
MilkFluid	58101800	Ground beef with tomato sauce and taco seasonings on a cornbread crust	-
MilkFluid	58120110	Crepes, filled with meat, fish, or poultry, with sauce	-
MilkFluid	58120120	Crepe, filled with beef, pork, fish and/or poultry, no sauce on top	-
MilkFluid	58122220	Gnocchi, potato	-
MilkFluid	58124210	Pastry, cheese-filled	-
MilkFluid	58127110	Vegetables in pastry	-
MilkFluid	58127150	Vegetables and cheese in pastry	-
MilkFluid	58127210	Croissant sandwich, filled with ham and cheese	-
MilkFluid	58128000	Biscuit with gravy	-
MilkFluid	58128120	Cornmeal dressing with chicken or turkey and vegetables	-
MilkFluid	58131120	Ravioli, NS as to filling, with cream sauce	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	58131330	Ravioli, meat-filled, with cream sauce	-
MilkFluid	58131535	Ravioli, cheese-filled, with cream sauce	-
MilkFluid	58131600	Ravioli, cheese and spinach-filled, with cream sauce	-
MilkFluid	58132310	Spaghetti with tomato sauce and meatballs or spaghetti with meat sauce or spaghetti with meat sauce and meatballs	-
MilkFluid	58132360	Spaghetti with tomato sauce and meatballs, whole wheat noodles or spaghetti with meat sauce, whole wheat noodles or spaghetti with meat sauce and meatballs, whole wheat noodles	-
MilkFluid	58132460	Spaghetti with tomato sauce and meatballs made with spinach noodles, or spaghetti with meat sauce made with spinach noodles	-
MilkFluid	58145110	Macaroni or noodles with cheese	-
MilkFluid	58145114	Macaroni or noodles with cheese, made from dry mix	-
MilkFluid	58145115	Macaroni or noodles with cheese, from boxed mix with already prepared cheese sauce	-
MilkFluid	58145120	Macaroni or noodles with cheese and tuna	-
MilkFluid	58145150	Macaroni or noodles with cheese and pork or ham	-
MilkFluid	58145160	Macaroni or noodles with cheese and frankfurters or hot dogs	-
MilkFluid	58145170	Macaroni and cheese with egg	-
MilkFluid	58145190	Macaroni or noodles with cheese and chicken or turkey	-
MilkFluid	58147310	Macaroni, creamed	-
MilkFluid	58149160	Noodle pudding, with milk	-
MilkFluid	58155610	Rice meal fritter, Puerto Rican style (Almojabana)	-
MilkFluid	58161110	Rice casserole with cheese	-
MilkFluid	58161120	Brown rice casserole with cheese	-
MilkFluid	58301110	Vegetable lasagna (frozen meal)	-
MilkFluid	58302000	Macaroni and cheese (diet frozen meal)	-
MilkFluid	58304010	Spaghetti and meatballs dinner, NFS (frozen meal)	-
MilkFluid	58305250	Pasta with vegetable and cheese sauce (diet frozen meal)	-
MilkFluid	58306100	Chicken enchilada (diet frozen meal)	-
MilkFluid	58403050	Chicken noodle soup, cream of	-
MilkFluid	58450300	Noodle soup, made with milk	-
MilkFluid	63402990	Fruit salad (including citrus fruits) with pudding	-
MilkFluid	63403000	Fruit salad (excluding citrus fruits) with pudding	-
MilkFluid	71301000	White potato, cooked, with sauce, NS as to sauce	-
MilkFluid	71301020	White potato, cooked, with cheese	-
MilkFluid	71301120	White potato, cooked, with ham and cheese	-
MilkFluid	71305010	White potato, scalloped	-
MilkFluid	71305110	White potato, scalloped, with ham	-
MilkFluid	71501000	White potato, mashed, NFS	-
MilkFluid	71501010	White potato, from fresh, mashed, made with milk	-
MilkFluid	71501015	White potato, from fresh, mashed, made with milk, sour cream and/or cream cheese	-
MilkFluid	71501020	White potato, from fresh, mashed, made with milk and fat	-
MilkFluid	71501025	White potato, from fresh, mashed, made with milk, sour cream and/or cream cheese and fat	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	71501040	White potato, from dry, mashed, made with milk and fat	-
MilkFluid	71501050	White potato, from fresh, mashed, made with milk, fat, and cheese	-
MilkFluid	71501060	White potato, from dry, mashed, made with milk, fat, and egg	-
MilkFluid	71501090	White potato, from dry, mashed, made with milk, no fat	-
MilkFluid	71501300	White potato, from dry, mashed, NS as to milk or fat	-
MilkFluid	71501310	White potato, from fresh, mashed, NS as to milk or fat	-
MilkFluid	71508120	White potato, stuffed with ham, broccoli and cheese sauce, baked, peel eaten	-
MilkFluid	71801000	Potato soup, NS as to made with milk or water	-
MilkFluid	71801010	Potato soup, cream of, prepared with milk	-
MilkFluid	71801100	Potato and cheese soup	-
MilkFluid	71802010	Macaroni and potato soup	-
MilkFluid	71803010	Potato chowder	-
MilkFluid	72125240	Spinach souffle	-
MilkFluid	72201240	Broccoli, cooked, NS as to form, with mushroom sauce	-
MilkFluid	72201242	Broccoli, cooked, from frozen, with mushroom sauce	-
MilkFluid	72202020	Broccoli casserole (broccoli, rice, cheese, and mushroom sauce)	-
MilkFluid	72202030	Broccoli, batter-dipped and fried	-
MilkFluid	72302000	Broccoli soup	-
MilkFluid	72302100	Broccoli cheese soup, prepared with milk	-
MilkFluid	73305020	Squash, winter, souffle	-
MilkFluid	73409000	Sweetpotato, casserole or mashed	-
MilkFluid	73501000	Carrot soup, cream of, prepared with milk	-
MilkFluid	73501010	Carrot with rice soup, cream of, prepared with milk	-
MilkFluid	74202050	Tomatoes, red, NS as to form, fried	-
MilkFluid	74202051	Tomatoes, red, from fresh, fried	-
MilkFluid	74205010	Tomatoes, green, cooked, NS as to form	-
MilkFluid	74205011	Tomatoes, green, cooked, from fresh	-
MilkFluid	74601010	Tomato soup, cream of, prepared with milk	-
MilkFluid	74602300	Tomato soup, canned, reduced sodium, prepared with milk	-
MilkFluid	75216070	Corn, dried, cooked	-
MilkFluid	75340160	Vegetable and pasta combinations with cream or cheese sauce (broccoli, pasta, carrots, corn, zucchini, peppers, cauliflower, peas, etc), cooked	-
MilkFluid	75402020	Beans, lima, immature, cooked, NS as to form, with mushroom sauce	-
MilkFluid	75403020	Beans, string, green, cooked, NS as to form, with mushroom sauce	-
MilkFluid	75403022	Beans, string, green, cooked, from frozen, with mushroom sauce	-
MilkFluid	75403023	Beans, string, green, cooked, from canned, with mushroom sauce	-
MilkFluid	75411010	Corn, scalloped or pudding	-
MilkFluid	75411020	Corn fritter	-
MilkFluid	75418060	Squash, summer, souffle	-
MilkFluid	75601000	Asparagus soup, cream of, NS as to made with milk or water	-
MilkFluid	75601010	Asparagus soup, cream of, prepared with milk	-
MilkFluid	75602010	Cauliflower soup, cream of, prepared with milk	-
MilkFluid	75603000	Celery soup, cream of, NS as to made with milk or water	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
MilkFluid	75603010	Celery soup, cream of, prepared with milk	-
MilkFluid	75604010	Corn soup, cream of, prepared with milk	-
MilkFluid	75604020	Corn soup, cream of, prepared with water	-
MilkFluid	75605010	Leek soup, cream of, prepared with milk	-
MilkFluid	75607010	Mushroom soup, cream of, prepared with milk	-
MilkFluid	75607060	Mushroom soup, cream of, NS as to made with milk or water	-
MilkFluid	75607080	Mushroom with chicken soup, cream of, prepared with milk	-
MilkFluid	75607090	Mushroom soup, cream of, canned, reduced sodium, NS as to made with milk or water	-
MilkFluid	75609010	Pea soup, prepared with milk	-
MilkFluid	75611010	Vegetable soup, cream of, prepared with milk	-
MilkFluid	75612010	Zucchini soup, cream of, prepared with milk	-
MilkFluid	75652030	Vegetable beef soup, prepared with milk	-
MilkFluid	77230210	Cassava Pasteles, Puerto Rican style (Pasteles de yuca)	-
MilkFluid	77272010	Puerto Rican pasteles (Pasteles de masa)	-
MilkFluid	77316600	Eggplant and meat casserole	-
MilkFluid	91304010	Topping, butterscotch or caramel	-
MilkFluid	91305010	Icing, chocolate	-
MilkFluid	91735000	Pralines	-
MilkFluid	92101900	Coffee, latte	-
MilkFluid	92101910	Coffee, latte, decaffeinated	-
MilkFluid	92101920	Blended coffee beverage, made with regular coffee, milk, and ice, sweetened	-
MilkFluid	92101930	Blended coffee beverage, made with decaffeinated coffee, milk, and ice, sweetened	-
MilkFluid	92101950	Coffee, mocha	-
MilkFluid	92161000	Cappuccino	-
MilkFluid	92162000	Cappuccino, decaffeinated	-
MilkFluid	92611100	Oatmeal beverage with milk (Atole de avena)	-
MilkFluid	92613010	Atole (corn meal beverage)	-
MilkFluid	92613510	Corn beverage with chocolate and milk (Champurrado, Atole de Chocolate)	-
MilkFluid	93301550	Eggnog, alcoholic	-
Mozzarella	14010000	Cheese, NFS	-
Mozzarella	14100100	Cheese, natural, NFS	-
Mozzarella	14107010	Cheese, Mozzarella, NFS	-
Mozzarella	14107020	Cheese, Mozzarella, whole milk	-
Mozzarella	14107030	Cheese, Mozzarella, part skim	-
Mozzarella	14107040	Cheese, Mozzarella, low sodium	-
Mozzarella	14107060	Cheese, Mozzarella, nonfat or fat free	-
Mozzarella	14610520	Cheese with nuts	-
Mozzarella	14620300	Topping from cheese pizza	-
Mozzarella	14620310	Topping from vegetable pizza	-
Mozzarella	14620320	Topping from meat pizza	-
Mozzarella	14620330	Topping from meat and vegetable pizza	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Mozzarella	14660200	Cheese, nuggets or pieces, breaded, baked, or fried	-
Mozzarella	27135110	Veal parmigiana	-
Mozzarella	27146300	Chicken or turkey parmigiana	-
Mozzarella	27460510	Antipasto with ham, fish, cheese, vegetables	-
Mozzarella	27500200	Wrap sandwich, filled with meat, poultry, or fish, vegetables, and cheese	-
Mozzarella	27510700	Meatball and spaghetti sauce submarine sandwich	-
Mozzarella	27510710	Pizzaburger (hamburger, cheese, sauce) on 1/2 bun	-
Mozzarella	28113110	Veal, breaded, with spaghetti, in tomato sauce (frozen meal)	-
Mozzarella	28140730	Chicken patty, breaded, with tomato sauce and cheese, fettuccine alfredo, vegetable (frozen meal)	-
Mozzarella	28141050	Chicken patty parmigiana, breaded, with vegetable (diet frozen meal)	-
Mozzarella	58100160	Burrito with beef, beans, rice, and cheese	-
Mozzarella	58100255	Burrito with chicken, beans, rice, and cheese	-
Mozzarella	58106200	Pizza, cheese, prepared from frozen, thin crust	-
Mozzarella	58106205	Pizza, cheese, prepared from frozen, thick crust	-
Mozzarella	58106210	Pizza, cheese, NS as to type of crust	-
Mozzarella	58106220	Pizza, cheese, thin crust	-
Mozzarella	58106225	Pizza, cheese, regular crust	-
Mozzarella	58106230	Pizza, cheese, thick crust	-
Mozzarella	58106240	Pizza, extra cheese, NS as to type of crust	-
Mozzarella	58106250	Pizza, extra cheese, thin crust	-
Mozzarella	58106255	Pizza, extra cheese, regular crust	-
Mozzarella	58106260	Pizza, extra cheese, thick crust	-
Mozzarella	58106300	Pizza, cheese, with vegetables, prepared from frozen, thin crust	-
Mozzarella	58106305	Pizza, cheese with vegetables, prepared from frozen, thick crust	-
Mozzarella	58106310	Pizza, cheese, with vegetables, NS as to type of crust	-
Mozzarella	58106320	Pizza, cheese, with vegetables, thin crust	-
Mozzarella	58106325	Pizza, cheese, with vegetables, regular crust	-
Mozzarella	58106330	Pizza, cheese, with vegetables, thick crust	-
Mozzarella	58106340	Pizza, with cheese and extra vegetables, NS as to type of crust	-
Mozzarella	58106345	Pizza with cheese and extra vegetables, thin crust	-
Mozzarella	58106347	Pizza with cheese and extra vegetables, regular crust	-
Mozzarella	58106350	Pizza with cheese and extra vegetables, thick crust	-
Mozzarella	58106357	Pizza, cheese, with fruit, NS as to type of crust	-
Mozzarella	58106358	Pizza, cheese, with fruit, thin crust	-
Mozzarella	58106359	Pizza, cheese, with fruit, regular crust	-
Mozzarella	58106360	Pizza, cheese, with fruit, thick crust	-
Mozzarella	58106410	Pizza with chicken, NS as to type of crust	-
Mozzarella	58106411	Pizza with chicken, thin crust	-
Mozzarella	58106412	Pizza with chicken, regular crust	-
Mozzarella	58106413	Pizza with chicken, thick crust	-
Mozzarella	58106440	Pizza with chicken and vegetables, NS as to type of crust	-
Mozzarella	58106441	Pizza with chicken and vegetables, thin crust	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Mozzarella	58106442	Pizza with chicken and vegetables, regular crust	-
Mozzarella	58106443	Pizza with chicken and vegetables, thick crust	-
Mozzarella	58106460	Pizza with chicken and fruit, NS as to type of crust	-
Mozzarella	58106461	Pizza with chicken and fruit, thin crust	-
Mozzarella	58106462	Pizza with chicken and fruit, regular crust	-
Mozzarella	58106463	Pizza with chicken and fruit, thick crust	-
Mozzarella	58106500	Pizza with meat, prepared from frozen, thin crust	-
Mozzarella	58106505	Pizza with meat, prepared from frozen, thick crust	-
Mozzarella	58106540	Pizza with pepperoni, NS as to type of crust	-
Mozzarella	58106550	Pizza with pepperoni, thin crust	-
Mozzarella	58106555	Pizza with pepperoni, regular crust	-
Mozzarella	58106560	Pizza with pepperoni, thick crust	-
Mozzarella	58106610	Pizza with meat other than pepperoni, NS as to type of crust	-
Mozzarella	58106620	Pizza with meat other than pepperoni, thin crust	-
Mozzarella	58106625	Pizza with meat other than pepperoni, regular crust	-
Mozzarella	58106630	Pizza with meat other than pepperoni, thick crust	-
Mozzarella	58106640	Pizza with extra meat, NS as to type of crust	-
Mozzarella	58106650	Pizza with extra meat, thin crust	-
Mozzarella	58106655	Pizza with extra meat, regular crust	-
Mozzarella	58106660	Pizza with extra meat, thick crust	-
Mozzarella	58106700	Pizza with meat and vegetables, prepared from frozen, thin crust	-
Mozzarella	58106705	Pizza with meat and vegetables, prepared from frozen, thick crust	-
Mozzarella	58106710	Pizza with meat and vegetables, NS as to type of crust	-
Mozzarella	58106720	Pizza with meat and vegetables, thin crust	-
Mozzarella	58106725	Pizza with meat and vegetables, regular crust	-
Mozzarella	58106730	Pizza with meat and vegetables, thick crust	-
Mozzarella	58106733	Pizza with extra meat and extra vegetables, prepared from frozen, thin crust	-
Mozzarella	58106734	Pizza with extra meat and extra vegetables, prepared from frozen, thick crust	-
Mozzarella	58106735	Pizza with extra meat and extra vegetables, NS as to type of crust	-
Mozzarella	58106736	Pizza with extra meat and extra vegetables, thin crust	-
Mozzarella	58106737	Pizza with extra meat and extra vegetables, thick crust	-
Mozzarella	58106738	Pizza with extra meat and extra vegetables, regular crust	-
Mozzarella	58106740	Pizza with meat and fruit, NS as to type of crust	-
Mozzarella	58106750	Pizza with meat and fruit, thin crust	-
Mozzarella	58106755	Pizza with meat and fruit, regular crust	-
Mozzarella	58106760	Pizza with meat and fruit, thick crust	-
Mozzarella	58106780	Pizza with meat and vegetables, prepared from frozen, lowfat, thin crust	-
Mozzarella	58106810	Pizza with beans and vegetables, NS as to type of crust	-
Mozzarella	58106820	Pizza with beans and vegetables, thin crust	-
Mozzarella	58106825	Pizza with beans and vegetables, regular crust	-
Mozzarella	58106830	Pizza with beans and vegetables, thick crust	-
Mozzarella	58106900	Pizza with seafood, NS as to type of crust	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Mozzarella	58106910	Pizza with seafood, thin crust	-
Mozzarella	58106915	Pizza with seafood, regular crust	-
Mozzarella	58106920	Pizza with seafood, thick crust	-
Mozzarella	58107210	White pizza, NS as to type of crust	-
Mozzarella	58107220	White pizza, thin crust	-
Mozzarella	58107225	White pizza, regular crust	-
Mozzarella	58107230	White pizza, thick crust	-
Mozzarella	58108000	Calzone, with cheese, meatless	-
Mozzarella	58108010	Calzone, with meat and cheese	-
Mozzarella	58108030	Panzerotti, with meat, vegetables, and cheese	-
Mozzarella	58108040	Panzerotti, with vegetables and cheese	-
Mozzarella	58108050	Pizza rolls	-
Mozzarella	58109000	Italian pie, meatless	-
Mozzarella	58109010	Italian pie with meat	-
Mozzarella	58126300	Turnover, meat- and cheese-filled, tomato-based sauce, lower in fat	-
Mozzarella	58126400	Turnover, filled with egg, meat and cheese	-
Mozzarella	58130011	Lasagna with meat	-
Mozzarella	58130020	Lasagna with meat and spinach	-
Mozzarella	58130140	Lasagna with chicken or turkey	-
Mozzarella	58130150	Lasagna, with chicken or turkey, and spinach	-
Mozzarella	58130310	Lasagna, meatless	-
Mozzarella	58130320	Lasagna, meatless, with vegetables	-
Mozzarella	58133110	Manicotti, cheese-filled, no sauce	-
Mozzarella	58133120	Manicotti, cheese-filled, with tomato sauce, meatless	-
Mozzarella	58133130	Manicotti, cheese-filled, with meat sauce	-
Mozzarella	58133140	Manicotti, vegetable- and cheese-filled, with tomato sauce, meatless	-
Mozzarella	58134110	Stuffed shells, cheese-filled, no sauce	-
Mozzarella	58134120	Stuffed shells, cheese-filled, with tomato sauce, meatless	-
Mozzarella	58134130	Stuffed shells, cheese-filled, with meat sauce	-
Mozzarella	58134160	Stuffed shells, cheese- and spinach- filled, no sauce	-
Mozzarella	58301020	Lasagna with cheese and sauce (diet frozen meal)	-
Mozzarella	58301030	Veal lasagna (diet frozen meal)	-
Mozzarella	58301110	Vegetable lasagna (frozen meal)	-
Mozzarella	58301150	Zucchini lasagna (diet frozen meal)	-
Mozzarella	58302050	Beef and noodles with meat sauce and cheese (diet frozen meal)	-
Mozzarella	58304200	Ravioli, cheese-filled, with tomato sauce (diet frozen meal)	-
Mozzarella	58304220	Rigatoni with meat sauce and cheese (diet frozen meal)	-
Mozzarella	58304250	Manicotti, cheese-filled, with tomato sauce (diet frozen meal)	-
Mozzarella	75412060	Eggplant parmesan casserole, regular	-
Mozzarella	75412070	Eggplant with cheese and tomato sauce	-
NFDM	11120000	Milk, dry, reconstituted, NFS	-
NFDM	11121210	Milk, dry, reconstituted, lowfat	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
NFDM	11121300	Milk, dry, reconstituted, nonfat	-
NFDM	11541000	Milk shake, NS as to flavor or type	-
NFDM	11541500	Milk shake, made with skim milk, chocolate	-
NFDM	11541510	Milk shake, made with skim milk, flavors other than chocolate	-
NFDM	11552200	Orange Julius	-
NFDM	11810000	Milk, dry, not reconstituted, NS as to whole, lowfat, or nonfat	-
NFDM	11812000	Milk, dry, lowfat, not reconstituted	-
NFDM	11813000	Milk, dry, nonfat, not reconstituted	-
NFDM	13250200	Mousse, chocolate, lowfat, reduced calorie, prepared from dry mix, water added	-
NFDM	27540180	Chicken patty sandwich or biscuit	-
NFDM	51105010	Bread, Cuban	-
NFDM	51105040	Bread, Cuban, toasted	-
NFDM	51301040	Bread, wheat or cracked wheat, made from home recipe or purchased at bakery	-
NFDM	51301050	Bread, wheat or cracked wheat, made from home recipe or purchased at bakery, toasted	-
NFDM	51301540	Bread, French or Vienna, whole wheat, NS as to 100%, made from home reciped or purchased at bakery	-
NFDM	51320040	Roll, wheat or cracked wheat, made from home recipe or purchased at bakery	-
NFDM	51320530	Roll, whole wheat, NS as to 100%, made from home recipe or purchased at bakery	-
NFDM	52304040	Muffin, bran with fruit, lowfat	-
NFDM	53102300	Cake, applesauce, diet, without icing	-
NFDM	53104300	Cake, carrot, diet	-
NFDM	53105500	Cake, chocolate, with icing, diet	-
NFDM	53109270	Cake, cupcake, chocolate, with or without icing, fruit filling or cream filling, lowfat, cholesterol free	-
NFDM	55101010	Pancakes, reduced calorie, high fiber	-
NFDM	55610200	Dumpling, fried, Puerto Rican style	-
NFDM	58127210	Croissant sandwich, filled with ham and cheese	-
NFDM	58163330	Flavored rice mixture with cheese	-
NFDM	58163380	Flavored rice and pasta mixture	-
NFDM	58163400	Flavored rice and pasta mixture, reduced sodium	-
NFDM	58310210	Sausage and french toast (frozen meal)	-
NFDM	58310310	Pancakes and sausage (frozen meal)	-
NFDM	71402040	White potato, french fries, breaded or battered	-
NFDM	75415020	Onion rings, NS as to form, batter-dipped, baked or fried	-
NFDM	75415022	Onion rings, from frozen, batter-dipped, baked or fried	-
NFDM	75649100	Vegetable soup, cream of, made from dry mix, low sodium, prepared with water	-
NFDM	91304070	Topping, peanut butter, thick, fudge type	-
ProcessedCheese	13252600	Tiramisu	-
ProcessedCheese	14010000	Cheese, NFS	-
ProcessedCheese	14010100	Cheese, Cheddar or American type, NS as to natural or processed	-
ProcessedCheese	14301010	Cheese, cream	-
ProcessedCheese	14303010	Cheese, cream, light or lite (formerly called Cream Cheese Lowfat)	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
ProcessedCheese	14410100	Cheese, processed, American and Swiss blends	-
ProcessedCheese	14410200	Cheese, processed, American or Cheddar type	-
ProcessedCheese	14410210	Cheese, processed, American or Cheddar type, low sodium	-
ProcessedCheese	14410300	Cheese, processed, American or Cheddar type, lowfat	-
ProcessedCheese	14410330	Cheese, processed cheese product, American or Cheddar type, reduced fat	-
ProcessedCheese	14410350	Cheese, processed, American or Cheddar type, nonfat or fat free	-
ProcessedCheese	14410380	Cheese, processed cream cheese product, nonfat or fat free	-
ProcessedCheese	14410400	Cheese, processed, Swiss	-
ProcessedCheese	14410420	Cheese, processed, Swiss, lowfat	-
ProcessedCheese	14410500	Cheese, processed cheese food	-
ProcessedCheese	14410600	Cheese, processed, with vegetables	-
ProcessedCheese	14410620	Cheese, processed, with wine	-
ProcessedCheese	14420000	Cheese spread, NFS	-
ProcessedCheese	14420100	Cheese spread, American or Cheddar cheese base	-
ProcessedCheese	14420160	Cheese spread, Swiss cheese base	-
ProcessedCheese	14420200	Cheese spread, cream cheese, regular	-
ProcessedCheese	14420210	Cheese spread, cream cheese, light or lite	-
ProcessedCheese	14420300	Cheese spread, pressurized can	-
ProcessedCheese	14620100	Dip, cream cheese base	-
ProcessedCheese	14620120	Shrimp dip, cream cheese base	-
ProcessedCheese	14620150	Dip, cheese with chili pepper (chili con queso)	-
ProcessedCheese	14620200	Dip, cheese base other than cream cheese	-
ProcessedCheese	14640000	Cheese sandwich	-
ProcessedCheese	14640100	Cheese sandwich, grilled	-
ProcessedCheese	14650100	Cheese sauce	-
ProcessedCheese	25220150	Beef sausage with cheese, smoked	-
ProcessedCheese	25220360	Bratwurst, with cheese	-
ProcessedCheese	27146200	Chicken or turkey with cheese sauce (mixture)	-
ProcessedCheese	27150510	Scallops with cheese sauce (mixture)	-
ProcessedCheese	27211500	Beef and potatoes with cheese sauce (mixture)	-
ProcessedCheese	27220170	Sausage and rice with cheese sauce (mixture)	-
ProcessedCheese	27220190	Sausage and noodles with cream or white sauce (mixture)	-
ProcessedCheese	27220520	Ham or pork and potatoes with cheese sauce (mixture)	-
ProcessedCheese	27242310	Chicken or turkey and noodles with cheese sauce (mixture)	-
ProcessedCheese	27311635	Beef, potatoes, and vegetables (including carrots, broccoli, and/or dark-green leafy), cheese sauce (mixture)	-
ProcessedCheese	27311640	Beef, potatoes, and vegetables (excluding carrots, broccoli, and dark-green leafy) cheese sauce (mixture)	-
ProcessedCheese	27315340	Beef, rice, and vegetables (excluding carrots, broccoli, and/or dark green leafy), cheese sauce (mixture)	-
ProcessedCheese	27320030	Ham or pork, noodles and vegetables (excluding carrots, broccoli, and dark-green leaft), cheese sauce (mixture)	-
ProcessedCheese	27320070	Ham or pork, noodles, and vegetables (including carrots, broccoli, and/or dark-green leafy) tomato-based sauce (mixture)	-
ProcessedCheese	27341000	Chicken or turkey, potatoes, corn, and cheese, with gravy	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
ProcessedCheese	27341050	Chicken or turkey, potatoes, and vegetables (excluding carrots, broccoli, and dark-green leafy), cheese sauce (mixture)	-
ProcessedCheese	27343950	Chicken or turkey, noodles, and vegetables (including carrots, broccoli, and/or dark-green leafy), cheese sauce (mixture)	-
ProcessedCheese	27343960	Chicken or turkey, noodles, and vegetables (excluding carrots, broccoli, and dark-green leafy), cheese sauce (mixture)	-
ProcessedCheese	27345440	Chicken or turkey, rice, and vegetables (including carrots, broccoli, and/or dark-green leafy) cheese sauce (mixture)	-
ProcessedCheese	27345450	Chicken or turkey, rice, and vegetables (excluding carrots, broccoli, and dark-green leafy) cheese sauce (mixture)	-
ProcessedCheese	27446400	Chicken or turkey and vegetables (including carrots, broccoli, and/or dark-green leafy (no potatoes)), cheese sauce (mixture)	-
ProcessedCheese	27446410	Chicken or turkey and vegetables (excluding carrots, broccoli, and dark-green leaft (no potatoes)), cheese sauce (mixture)	-
ProcessedCheese	27450090	Tuna salad with cheese	-
ProcessedCheese	27460510	Antipasto with ham, fish, cheese, vegetables	-
ProcessedCheese	27500200	Wrap sandwich, filled with meat, poultry, or fish, vegetables, and cheese	-
ProcessedCheese	27500300	Wrap sandwich, filled with meat, poultry, or fish, and vegetables	-
ProcessedCheese	27510210	Cheeseburger, plain, on bun	-
ProcessedCheese	27510220	Cheeseburger, with mayonnaise or salad dressing, on bun	-
ProcessedCheese	27510230	Cheeseburger, with mayonnaise or salad dressing and tomatoes, on bun	-
ProcessedCheese	27510250	Cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing, on bun	-
ProcessedCheese	27510260	Cheeseburger, 1/4 lb meat, with mushrooms in sauce, on bun	-
ProcessedCheese	27510280	Double cheeseburger (2 patties), with mayonnaise or salad dressing, on bun	-
ProcessedCheese	27510300	Double cheeseburger (2 patties), with mayonnaise or salad dressing, on double-decker bun	-
ProcessedCheese	27510310	Cheeseburger with tomato and/or catsup, on bun	-
ProcessedCheese	27510311	Cheeseburger, 1 oz meat, plain, on miniature bun	-
ProcessedCheese	27510320	Cheeseburger, 1/4 lb meat, with tomato and/or catsup, on bun	-
ProcessedCheese	27510330	Double cheeseburger (2 patties), with tomato and/or catsup, on bun	-
ProcessedCheese	27510340	Double cheeseburger (2 patties), with mayonnaise or salad dressing and tomatoes, on bun	-
ProcessedCheese	27510350	Cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun	-
ProcessedCheese	27510355	Cheeseburger, 1/3 lb meat, with mayonniase or salad dressing, tomato and/or catsup on bun	-
ProcessedCheese	27510360	Bacon cheeseburger, with mayonnaise or salad dressing, tomato and/or catsup, on bun	-
ProcessedCheese	27510370	Double cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, on bun	-
ProcessedCheese	27510375	Double cheeseburger (2 patties, 1/4 lb meat each), with tomato and/or catsup, on bun	-
ProcessedCheese	27510380	Triple cheeseburger (3 patties, 1/4 lb meat each), with mayonnais or salad dressing and tomatoes, on bun	-
ProcessedCheese	27510390	Double bacon cheeseburger (2 patties, 1/4 lb meat each), on bun	-
ProcessedCheese	27510400	Bacon cheeseburger, 1/4 lb meat, with tomato and/or catsup, on bun	-
ProcessedCheese	27510420	Taco burger, on bun	-
ProcessedCheese	27510425	Double bacon cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, on bun	-
ProcessedCheese	27510430	Double bacon cheeseburger (2 patties, 1/4 lb meat each), with mayonnaise or salad dressing, and tomato and/or catsup, on bun	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
ProcessedCheese	27510435	Double bacon cheeseburger (2 patties, 1/3 lb meat each), with mayonnaise or salad dressing, on bun	-
ProcessedCheese	27510440	Bacon cheeseburger, 1/4 lb meat, with mayonnaise or salad dressing and tomatoes, on bun	-
ProcessedCheese	27510450	Cheeseburger, 1/4 lb meat, with ham, on bun	-
ProcessedCheese	27510480	Cheeseburger (hamburger with cheese sauce), 1/4 lb meat, with grilled onions, on rye bun	-
ProcessedCheese	27510700	Meatball and spaghetti sauce submarine sandwich	-
ProcessedCheese	27513041	Roast beef submarine sandwich, with cheese, lettuce, tomato and spread	-
ProcessedCheese	27513050	Roast beef sandwich with cheese	-
ProcessedCheese	27515020	Steak and cheese submarine sandwich, with lettuce and tomato	-
ProcessedCheese	27515040	Steak and cheese submarine sandwich, plain, on roll	-
ProcessedCheese	27520135	Bacon, chicken, and tomato club sandwich, with cheese, lettuce and spread	-
ProcessedCheese	27520166	Bacon, chicken fillet (breaded, fried), and tomato club sandwich with cheese, lettuce and spread	-
ProcessedCheese	27520320	Ham and cheese sandwich, with lettuce and spread	-
ProcessedCheese	27520350	Ham and cheese sandwich, with spread, grilled	-
ProcessedCheese	27520360	Ham and cheese sandwich, on bun, with lettuce and spread	-
ProcessedCheese	27520370	Hot ham and cheese sandwich, on bun	-
ProcessedCheese	27520390	Ham and cheese submarine sandwich, with lettuce, tomato and spread	-
ProcessedCheese	27540230	Chicken patty sandwich with cheese, on wheat bun, with lettuce, tomato and spread	-
ProcessedCheese	27540250	Chicken fillet, broiled, sandwich with cheese, on whole wheat roll, with lettuce, tomato and non-mayonnaise type spread	-
ProcessedCheese	27540280	Chicken fillet, broiled, sandwich with cheese, on bun, with lettuce, tomato and spread	-
ProcessedCheese	27540291	Chicken submarine sandwich, with cheese, lettuce, tomato, and spread	-
ProcessedCheese	27540350	Turkey submarine sandwich, with cheese, lettuce, tomato and spread	-
ProcessedCheese	27541001	Turkey, ham, and roast beefclub sandwich with cheese, lettuce, tomato, and spread	-
ProcessedCheese	27550100	Fish sandwich, on bun, with cheese and spread	-
ProcessedCheese	27550751	Tuna salad submarine, with cheese, lettuce, and tomato	-
ProcessedCheese	27560330	Frankfurter or hot dog, with cheese, plain, on bun	-
ProcessedCheese	27560370	Frankfurter or hot dog with chili and cheese, on bun	-
ProcessedCheese	27560670	Sausage and cheese on English muffin	-
ProcessedCheese	27560910	Cold cut submarine sandwich, with cheese, lettuce, tomato, and spread	-
ProcessedCheese	28110370	Salisbury steak with gravy, macaroni and cheese, vegetable (frozen meal)	-
ProcessedCheese	32105010	Egg omelet or scrambled egg, with cheese	-
ProcessedCheese	32105080	Egg omelet or scrambled egg, with ham or bacon and cheese	-
ProcessedCheese	32105085	Egg omelet or scrambled egg, with ham or bacon, cheese, and tomatoes	-
ProcessedCheese	32202000	Egg, cheese, ham, and bacon on bun	-
ProcessedCheese	32202010	Egg, cheese, and ham on English muffin	-
ProcessedCheese	32202020	Egg, cheese, and ham on biscuit	-
ProcessedCheese	32202025	Egg, cheese, and ham on bagel	-
ProcessedCheese	32202030	Egg, cheese, and sausage on English muffin	-
ProcessedCheese	32202035	Egg, extra cheese (2 slices), and extra sausage (2 patties) on bun	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
ProcessedCheese	32202045	Egg, cheese, and steak on bagel	-
ProcessedCheese	32202050	Egg, cheese, and sausage on biscuit	-
ProcessedCheese	32202055	Egg, cheese, and sausage griddle cake sandwich	-
ProcessedCheese	32202070	Egg, cheese, and bacon on biscuit	-
ProcessedCheese	32202075	Egg, cheese, and bacon griddle cake sandwich	-
ProcessedCheese	32202080	Egg, cheese, and bacon on English muffin	-
ProcessedCheese	32202085	Egg, cheese and bacon on bagel	-
ProcessedCheese	32202120	Egg, cheese, and sausage on bagel	-
ProcessedCheese	32202200	Egg and cheese on biscuit	-
ProcessedCheese	52104100	Biscuit, cheese	-
ProcessedCheese	52306300	Muffin, cheese	-
ProcessedCheese	53104000	Cake, carrot, NS as to icing	-
ProcessedCheese	53104260	Cake, carrot, with icing	-
ProcessedCheese	53104520	Cheesecake, diet	-
ProcessedCheese	53104550	Cheesecake with fruit	-
ProcessedCheese	53104600	Cheesecake, chocolate	-
ProcessedCheese	53124120	Cake, zucchini, with icing	-
ProcessedCheese	53204500	Cookie, brownie, with cream cheese filling, without icing	-
ProcessedCheese	53340500	Pie, cherry, made with cream cheese and sour cream	-
ProcessedCheese	53344200	Mixed tart filled with custard or cream cheese	-
ProcessedCheese	54304000	Cracker, cheese, regular	-
ProcessedCheese	54304100	Cracker, cheese, reduced fat	-
ProcessedCheese	56201060	Grits, cooked, corn or hominy, with cheese, NS as to regular, quick, or instant, NS as to fat added cooking	-
ProcessedCheese	56201061	Grits, cooked, corn or hominy, with cheese, NS as to regular, quick, or instant, fat not added in cooking	-
ProcessedCheese	56201071	Grits, cooked, corn or hominy, with cheese, regular, fat not added in cooking	-
ProcessedCheese	56201072	Grits, cooked, corn or hominy, with cheese, regular, fat added in cooking	-
ProcessedCheese	56201081	Grits, cooked, corn or hominy, with cheese, quick, fat not added in cooking	-
ProcessedCheese	56201082	Grits, cooked, corn or hominy, with cheese, quick, fat added in cooking	-
ProcessedCheese	56201091	Grits, cooked, corn or hominy, with cheese, instant, fat not added in cooking	-
ProcessedCheese	56201092	Grits, cooked, corn or hominy, with cheese, instant, fat added in cooking	-
ProcessedCheese	58100255	Burrito with chicken, beans, rice, and cheese	-
ProcessedCheese	58100340	Burrito with eggs, sausage, cheese, and vegetables	-
ProcessedCheese	58100410	Burrito with beef, cheese, and sour cream	-
ProcessedCheese	58104100	Nachos with cheese, meatless, no beans	-
ProcessedCheese	58111200	Puffs, fried, crab meat and cream cheese filled	-
ProcessedCheese	58121610	Dumpling, potato- or cheese-filled	-
ProcessedCheese	58126130	Turnover, meat- and cheese-filled, no gravy	-
ProcessedCheese	58126270	Turnover, chicken- or turkey-, and cheese-filled, no gravy	-
ProcessedCheese	58127210	Croissant sandwich, filled with ham and cheese	-
ProcessedCheese	58127310	Croissant sandwich with ham, egg, and cheese	-
ProcessedCheese	58127330	Croissant sandwich with sausage, egg, and cheese	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
ProcessedCheese	58127350	Croissant sandwich with bacon, egg, and cheese	-
ProcessedCheese	58145110	Macaroni or noodles with cheese	-
ProcessedCheese	58145113	Macaroni or noodles with cheese, canned	-
ProcessedCheese	58145114	Macaroni or noodles with cheese, made from dry mix	-
ProcessedCheese	58145120	Macaroni or noodles with cheese and tuna	-
ProcessedCheese	58145130	Macaroni or noodles with cheese and beef	-
ProcessedCheese	58145140	Macaroni or noodles with cheese and tomato	-
ProcessedCheese	58145150	Macaroni or noodles with cheese and pork or ham	-
ProcessedCheese	58145160	Macaroni or noodles with cheese and frankfurters or hot dogs	-
ProcessedCheese	58145170	Macaroni and cheese with egg	-
ProcessedCheese	58145190	Macaroni or noodles with cheese and chicken or turkey	-
ProcessedCheese	58146115	Macaroni or noodles with cheese, from boxed mix with already prepared cheese	-
ProcessedCheese	58200100	Wrap sandwich, filled with meat, poultry, or fish, vegetables, and rice	-
ProcessedCheese	58200250	Wrap sandwich, filled with vegetables	-
ProcessedCheese	58200300	Wrap sandwich, filled with meat, poultry, or fish, vegetables, rice, and cheese	-
ProcessedCheese	58306100	Chicken enchilada (diet frozen meal)	-
ProcessedCheese	71204000	Potato puffs, cheese-filled	-
ProcessedCheese	71402500	White potato, french fries, with cheese	-
ProcessedCheese	71402505	White potato, french fries, with cheese and bacon	-
ProcessedCheese	71402510	White potato, french fries, with chili and cheese	-
ProcessedCheese	71501015	White potato, from fresh, mashed, made with milk, and sour cream and/or cream cheese	-
ProcessedCheese	71501025	White potato, from fresh, mashed, made with milk, and sour cream and/or cream cheese and fat	-
ProcessedCheese	71501050	White potato, from fresh, mashed, made with milk, fat, and cheese	-
ProcessedCheese	71501055	White potato, from fresh, mashed, made with sour cream and/or cream cheese and fat	-
ProcessedCheese	71507020	White potato, stuffed, baked, peel not eaten, stuffed with cheese	-
ProcessedCheese	71508020	White potato, stuffed, baked, peel eaten, stuffed with cheese	-
ProcessedCheese	71508060	White potato, stuffed, baked, peel eaten, stuffed with bacon and cheese	-
ProcessedCheese	71508070	White potato, stuffed, baked, peel not eaten, stuffed with chicken, broccoli, and cheese sauce	-
ProcessedCheese	72125260	Spinach and cheese casserole	-
ProcessedCheese	72202020	Broccoli casserole (broccoli, rice, cheese, and mushroom sauce)	-
ProcessedCheese	75340160	Vegetable and pasta combinations with cream or cheese sauce (broccoli, pasta, carrots, corn, zucchini, peppers, cauliflower, peas, etc), cooked	-
ProcessedCheese	75410550	Jalapeno pepper, stuffed with cheese, breaded or battered, fried	-
ProcessedCheese	75418020	Squash, summer, casserole with tomato, and cheese	-
ProcessedCheese	75440500	Vegetable combinations (including carrots, broccoli, and/or dark-green leafy), cooked, with cheese sauce	-
ProcessedCheese	75440510	Vegetable combinations (excluding carrots, broccoli, and dark-green leafy), cooked, with cheese sauce	-
ProcessedCheese	83112600	Cream cheese dressing	-
ProcessedCheese	91501050	Gelatin dessert with cream cheese	-
ProcessedCheese	91501080	Gelatin dessert with fruit and cream cheese	-
SourCream	12310100	Sour cream	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
SourCream	12310200	Sour cream, half and half	-
SourCream	12310300	Sour cream, reduced fat	-
SourCream	12310350	Sour cream, light	-
SourCream	12310370	Sour cream, fat free	-
SourCream	12320200	Sour cream, filled, sour dressing, nonbutterfat	-
SourCream	12350000	Dip, sour cream base	-
SourCream	12350020	Dip, sour cream base, reduced calorie	-
SourCream	12350100	Spinach dip	-
SourCream	13252600	Tiramisu	-
SourCream	26119160	Herring, pickled, in cream sauce	-
SourCream	27113100	Beef stroganoff	-
SourCream	27120080	Ham stroganoff	-
SourCream	27212350	Beef stroganoff with noodles	-
SourCream	27213600	Beef and rice with cheese sauce (mixture)	-
SourCream	28110660	Meatballs, Swedish, in gravy, with noodles (diet frozen meal)	-
SourCream	28144100	Chicken and vegetable entree with noodles and cream sauce (frozen meal)	-
SourCream	53104580	Cheesecake -type dessert, made with yogurt, with fruit	-
SourCream	53340500	Pie, cherry, made with cream cheese and sour cream	-
SourCream	58100140	Burrito with beef, beans, cheese, and sour cream	-
SourCream	58100245	Burrito with chicken, beans, cheese, and sour cream	-
SourCream	58100330	Burrito with rice, beans, cheese, sour cream, lettuce, tomato and guacamole, meatless	-
SourCream	58100410	Burrito with beef, cheese, and sour cream	-
SourCream	58101350	Soft taco with beef, cheese, lettuce, tomato and sour cream	-
SourCream	58101460	Soft taco with chicken, cheese, lettuce, tomato and sour cream	-
SourCream	58101615	Soft taco with bean, cheese, lettuce, tomato and/or salsa, and sour cream	-
SourCream	58104080	Nachos with beef, beans, cheese, and sour cream	-
SourCream	58104090	Nachos with cheese and sour cream	-
SourCream	58104180	Nachos with beef, beans, cheese, tomatoes, sour cream and onions	-
SourCream	58104280	Chalupa with beef, cheese, lettuce, tomato and sour cream	-
SourCream	58104320	Chalupa with chicken, cheese, lettuce, tomato and sour cream	-
SourCream	58104550	Chimichanga with chicken, sour cream, lettuce and tomato, no cheese	-
SourCream	58306100	Chicken enchilada (diet frozen meal)	-
SourCream	71501015	White potato, from fresh, mashed, made with milk, and sour cream and/or cream cheese	-
SourCream	71501025	White potato, from fresh, mashed, made with milk, and sour cream and/or cream cheese and fat	-
SourCream	71501055	White potato, from fresh, mashed, made with sour cream and/or cream cheese and fat	-
SourCream	71507000	White potato, stuffed, baked, peel not eaten, NS as to topping	-
SourCream	71507010	White potato, stuffed, baked, peel not eaten, stuffed with sour cream	-
SourCream	71508010	White potato, stuffed, baked, peel eaten, stuffed with sour cream	-
SourCream	72202010	Broccoli casserole (broccoli, noodles, and cream sauce)	-
SourCream	75142500	Cucumber salad with creamy dressing	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
SourCream	75601100	Beet soup (borscht)	-
SourCream	81302060	Horseradish sauce	-
SourCream	91501060	Gelatin dessert with sour cream	-
SourCream	91501070	Gelatin dessert with fruit and sour cream	-
Yogurt	11410000	Yogurt, NS as to type of milk or flavor	-
Yogurt	11411010	Yogurt, plain, NS as to type of milk	-
Yogurt	11411100	Yogurt, plain, NS as to type of milk	-
Yogurt	11411200	Yogurt, plain, whole milk	-
Yogurt	11411300	Yogurt, plain, lowfat milk	-
Yogurt	11420000	Yogurt, plain, nonfat milk	-
Yogurt	11421000	Yogurt, vanilla, lemon, or coffee flavor, NS as to type of milk	-
Yogurt	11422000	Yogurt, vanilla, lemon, or coffee flavor, whole milk	-
Yogurt	11422100	Yogurt, vanilla, lemon, maple, or coffee flavor, lowfat milk, sweetened with low calorie sweetener	-
Yogurt	11423000	Yogurt, vanilla, lemon, maple, or coffee flavor, nonfat milk	-
Yogurt	11424000	Yogurt, vanilla, lemon, maple, or coffee flavor, nonfat milk, sweetened with low calorie sweetener	-
Yogurt	11425000	Yogurt, chocolate, NS as to type of milk	-
Yogurt	11426000	Yogurt, chocolate, whole milk	-
Yogurt	11427000	Yogurt, chocolate, nonfat milk	-
Yogurt	11430000	Yogurt, fruit variety, NS as to type of milk	-
Yogurt	11431000	Yogurt, fruit variety, whole milk	-
Yogurt	11432000	Yogurt, fruit variety, lowfat milk	-
Yogurt	11432500	Yogurt, fruit variety, lowfat milk, sweetened with low-calorie sweetener	-
Yogurt	11433000	Yogurt, fruit variety, nonfat milk	-
Yogurt	11433500	Yogurt, fruit variety, nonfat milk sweetened with low-calorie sweetener	-
Yogurt	11445000	Yogurt, fruit and nuts, lowfat milk	-
Yogurt	11446000	Fruit and lowfat yogurt parfait	-
Yogurt	11480010	Yogurt, whole milk, baby food	-
Yogurt	11480040	Yogurt, whole milk, baby food, with fruit and multigrain cereal puree, plus DHA	-
Yogurt	11553000	Fruit smoothie drink, made with fruit or fruit juice and dairy products	-
Yogurt	11553100	Fruit smoothie drink, NFS	-
Yogurt	27516010	Gyro sandwich (pita bread, beef, lamb, onion, condiments), with tomato and spread	-
Yogurt	51108100	Naan, Indian flatbread	-
Yogurt	53104580	Cheesecake -type dessert, made with yogurt, with fruit	-
Yogurt	53441210	Basbousa (semolina dessert dish)	-
Yogurt	63401015	Apple and grade salad with yogurt and walnuts	-
Yogurt	67250100	Banana juice with lowfat yogurt, baby food	-
Yogurt	67250150	Mixed fruit juice with lowfat yogurt, baby food	-
Yogurt	67404070	Apple yogurt dessert, baby food, strained	-
Yogurt	67404500	Mixed fruit yogurt dessert, baby food, strained	-
Yogurt	67408500	Banana yogurt dessert, baby food, strained	-

Dairy Product	WWEIA/ NHANES Food Code	WWEIA/ NHANES Food Description	Dairy Ingredient %
Yogurt	67413700	Peach yogurt dessert, baby food, strained	-
Yogurt	67430500	Yogurt and fruit snack, baby food	-
Yogurt	83115000	Yogurt dressing	-

WWEIA/NHANES: What We Eat In America, National Health and Nutrition Examination Survey, 2005-2010 (CDC, 2011). Dairy product ingredient percentages were determined based on the Food and Nutrient Database for Dietary Surveys (FNDDS) 5.0 (USDA FSIS, 2012a).

APPENDIX 5.17: CRITERION C: DESCRIPTION OF ANALYSIS

We generated the consumption data for the 12 selected milk and milk products by using results of What We Eat In America (WWEIA), the food consumption survey portion of the 2005-2006, 2007-2008, and 2009-2010 National Health and Nutrition Examination Surveys (NHANES, 2013). This dataset includes information provided by survey respondents at his/her initial interview in the NHANES Mobile Exam Center on all foods consumed during the previous 24 hours, and also includes information from an additional 24 hour food recall conducted as part of a telephone interview approximately three to ten days later. Parents provided intake data for young children. Body weights were measured for NHANES participants as part of the examination process.

To characterize milk product ingredient percentages (e.g, the proportion of sour cream present as an ingredient in spinach dip), we used data from the Food and Nutrient Database for Dietary Surveys (FNDDS) v. 5.0 (USDA FSIS, 2012a), adjusted for moisture and fat changes during cooking. See Appendix 5.16 for these ingredient percentages. Intakes of fluid milk and processed dairy products by each survey respondent were estimated as two-day averages, divided by the individual's body weight in kilograms (kg bw).

WWEIA/NHANES data were analyzed to estimate mean dairy product intakes per consumer, percent consumers of each dairy product, and lifetime daily average dairy product intakes. Analyses were performed for eight age groups. WWEIA/NHANES statistical weights were used in all analyses. Estimated mean dairy product intakes by consumers were flagged when based on a sample size of less than 68, the minimum needed for reliable statistical estimates, calculated according to WWEIA/NHANES guidelines (USDA, 2010a; USDA, 2010b; USDA, 2012b).

Sensitivity analyses were performed to determine whether males and females have different consumption patterns for specific dairy products. Potential gender-based differences in amounts of dairy products consumed (per kg bw) were evaluated using linear regression, with the consumption amount as the dependent variable and gender as the independent variable in each age group. Potential gender-based differences in percent consumers of dairy products were evaluated using logistic regression, with consumption (yes/no) as the dependent variable and gender as the independent variable in each age group. Some gender-based difference were found in amounts consumed of fluid milk (ages 6-12 y and 13-19 y), butter (ages 50-59 y), cheddar cheese (6-12 y and 40-49 y), cottage cheese (60-75 y), mozzarella cheese (13-19 y), processed cheese (13-19 y), ice cream (6-12 y and 13-19 y), and yogurt (6-12 y and 60-75 y). Some gender-based difference in percentages of individuals consuming specific products were found for fluid milk (30-39y), butter (13-19y), cheddar cheese (40-49), cottage cheese (6-12 y, 40-49

y), mozzarella cheese (13-19 y), processed cheese (2-5 y), heavy cream (20-29 y), sour cream (13-19 y), ice cream (2-5 y, 40-49 y), evaporated milk (20-29 y), and yogurt (30-39 y, 40-49 y, 50-59 y, 60-75 y).

APPENDIX 6.1: COMPARISON OF HIGHEST-RANKING DRUG CLASSES

The following table is a comparison of the top (top 1/3 of ranking) drugs within each criterion (or sub-criterion or factor), by drug class:

Table A6.1 Comparison of highest-ranking drug classes

Criterion	Aminoglycoside	Amphenicol	Antiparasitic	B-Lactams	Fluoroquinolone	Macrolide	NSAID	Sulfonamide	Tetracycline
A LODA	Dihydrostreptomycin Gentamycin Neomycin	Florfenicol	Amprolium Doramectin Eprinomectin Ivermectin Moxidectin Thiabendazole	*****Ceftiofur *****Cephapirin *****Penicillin Amoxicillin Ampicillin Cloxicillin Hetacillin	-	Erythromycin Tilmicosin Tulathromycin Tylosin	*Flunixin Acetylsalicyclic acid	Sulfabromomethazine Sulfadimethoxine Sulfamethazine	*****Oxytetracycline Tetracycline
A.1 LODA-Ave. of Surveys	-	-	-	*****Ceftiofur *****Cephapirin Amoxicillin Cloxacillin Penicillin	-	-	-	-	*****Oxytetracycline
A.1.1. LODA—APHIS Data	-	-	Doramectin Eprinomectin Ivermectin Moxidectin Thiabendazole	*****Ceftiofur *Cephapirin Amoxicillin Ampicillin Cloxacillin Hetacillin Penicillin	-	-	-	-	*****Oxytetracycline Tetracycline
A.1.2. LODA-Sundlof Data	-	-	-	*Ceftiofur *Penicillin Ampicillin Cephapirin Cloxacillin	-	-	Flunixin	Sulfadimethoxine	*Oxytetracycline
A.1.3. LODA-Expert Elicitation	Dihydrostreptomycin	-	Eprinomectin Moxidectin	*Ceftiofur *Cephapirin Amoxicillin Ampicillin Penicillin	-	-	Flunixin	-	*Oxytetracycline
A.2. Market Status Drugs avail. OTC	*Dihydrostreptomycin *Gentamycin *Neomycin *Streptomycin	-	*Albendazole *Amprolium *Clorsulon *Doramectin *Eprinomectin *Ivermectin *Levamisole *Moxidectin	*Cephapirin *Penicillin	-	*Erythromycin *Tylosin	*Acetylsalicylic Acid	*Sulfabromomethazine *Sulfachlorpyridazine *Sulfadimethoxine *Sulfaquinoxaline *Sulfamethazine *Sulfaquinoxaline	*Oxytetracycline *Tetracycline

Criterion	Aminoglycoside	Amphenicol	Antiparasitic	B-Lactams	Fluoroquinolone	Macrolide	NSAID	Sulfonamide	Tetracycline
			*Oxfendazole *Thiabendazole						
A.3. Approval Status	*Gentamycin	-	*Eprinomectin *Moxidectin *Thiabendazole	*Amoxicillin *Ampicillin *Ceftiofur *Cephapirin *Cloxacillin *Hetacillin *Penicillin	-	*Erythromycin	*Flunixin	*Sulfabromomethazine *Sulfadimethoxine *Sulfaethoxypyridazine	*Oxytetracycline
A.4 Evidence of Use	*Dihydrostreptomycin	Florfenicol	-	*Ceftiofur *Penicillin Ampicillin Cephapirin Cloxacillin	Enrofloxacin	Tilmicosin Tulathromycin Tylosin	*Flunixin Acetylsalicylic acid	Sulfadimethoxine Sulfamethazine	Oxytetracycline
B. LODP	*Gentamycin Amikacin Kanamycin Neomycin Streptomycin	Chloramphenicol Florfenicol	Doramectin Ivermectin Oxfendazole	*Ampicillin *Penicillin Cloxacillin	*Danofloxacin *Enrofloxacin	Erythromycin Gamithromycin Tildipirosin Tilmicosin Tulathromycin	Naproxen Phenylbutazone	*Sulfachlorpyridazine *Sulfaethoxypyridazine *Sulfaquinoxaline Sulfadimethoxine Sulfamethazine	*Tetracycline
B.1. LODP - evidence	*Dihydrostreptomycin *Kanamycin *Neomycin	*Florfenicol *Chloramphenicol	*Albendazole *Clorsulon *Ivermectin *Oxfendazole	*Cephapirin *Penicillin	*Enrofloxacin	*Gamithromycin Tilmicosin *Tulathromycin	*Phenylbutazone	*Sulfadimethoxine *Sulfaethoxypyridazine *Sulfamethazine	*Tetracycline
B.2. LODP—Drug misuse	*Gentamycin *Amikacin	*Chloramphenicol	*Albendazole *Ivermectin *Levamisole *Moxidectin Oxfendazole	*Ampicillin *Ceftiofur *Cehpapirin *Penicillin	*Danofloxacin *Enrofloxacin	*Gamithromycin *Tilmicosin	*Flunixin *Napoxen	*Sulfabromomethazine *Sulfaethoxypyridazine *Sulfamethazine *Sulfachlorpyridazine Sulfaquinoxaline	*Tetracycline
B.3. LODP—Expert Elicitation	-	*Florfenicol	*Albendazole	-	*Enrofloxacin *Danofloxacin	*Tilmicosin *Tulathromycin *Tylosin	*Phenylbutazone	*Sulfaquinoxaline	-
C. Relative Exposure	-	-	*Amprolium *Doramectin *Eprinomectin *Ivermectin *Moxidectin *Oxfendazole *Thiabendazole	-	-	*Gamithromycin *Tulathromycin	-	-	-
C.1. Impact of Processing	-	-	*Amprolium *Doramectin *Eprinomectin *Ivermectin *Moxidectin *Oxfendazole *Thiabendazole	-	-	*Gamithromycin *Tulathromycin	-	-	-
D. Potenti	-	*Chloramphenicol	Doramectin	Amoxicillin Ampicillin	-	-	*Phenylbutazone Flunixin	Sulfabromomethazine Sulfaquinoxaline	-

Criterion	Aminoglycoside	Amphenicol	Antiparasitic	B-Lactams	Fluoroquinolone	Macrolide	NSAID	Sulfonamide	Tetracycline
al for a Human Health Hazard Score				Cloxacillin Hetacillin Penicillin			Meloxicam		
Final Ranking (All Criteria) using Expert Elicitation Weights	*Gentamycin Neomycin	Florfenicol	*Dormectin *Ivermectin *Amprolium *Eprinomectin *Moxidectin *Oxfendazole Thiabendazole	*Penicillin *Ampicillin *Cloxacillin Cephapirin Amoxicillin Hetacillin	Enrofloxacin	*Tulathromycin *Gamithromycin	*Flunixin	*Sulfaquinoxaline Sulfadimethoxine Sulfamethazine Sulfaethoxypyridazine Sulfabromomethazine	Tetracycline

*: Drugs in the top scoring bin.

APPENDIX 6.2: RESULTS: SCORES AND RANKING OF 54 DRUGS BY EACH SUB-CRITERION AND ITS FACTORS

CRITERION A

A1. Likelihood of Drug Administration Score (LODA) based on surveys:

Figure A6.1 illustrates the LODA based on surveys (A1). Figure A6.2 illustrates the LODA scores for each of the three factors (A1.1 – A1.3) that inform A1. The similarity between the scores for A1.1, A1.2, and A1.3 (derived from the USDA, Sundlof *et al*., and the 2014 expert elicitation data sets is striking. This is particularly so in light of the limitations in the data sets mentioned previously. Beta-lactams and oxytetracycline had the highest LODA scores in Factors A1.1,-A1.2, and A1.3. Beta-lactams and oxytetracycline also had the highest LODA scores in the overarching sub-criterion A1.

A2. LODA Based on Drug Marketing Status:

Figure A6.3 illustrates the scores for the marketing status of the drugs. Drugs that are marketed "over-the-counter" (OTC) were given a slightly higher score than drugs available only through a prescription status. Over half of the drugs in this study were available via OTC, including all of the antiparasitics, both tetracycline drugs, and most of the aminoglycosides and sulfonamides. This availability via OTC for these drugs increased the ranking score for these drugs slightly.

A3. LODA Based on Drug Approval Status:

Figure A6.3 also illustrates the scores giving to drugs based on the drugs approval status. With this data set, illegal drugs, such as phenylbutazone, nitrrofurazone, furazolidone, danofloxacin, and chloramphenicol are isolated with an extremely low score.

A4. LODA Based on Evidence of Drug Use on Dairy Farms.

Figure A6.3 also illustrates the scores for the evidence of drug use on dairy farms from 2009-2014 FDA dairy farm inspections. The most frequently identified drugs included the NSAIDs, flunixin and acetylsalicylic acid, the beta-lactam drugs, and the amphenicol, florfenicol.

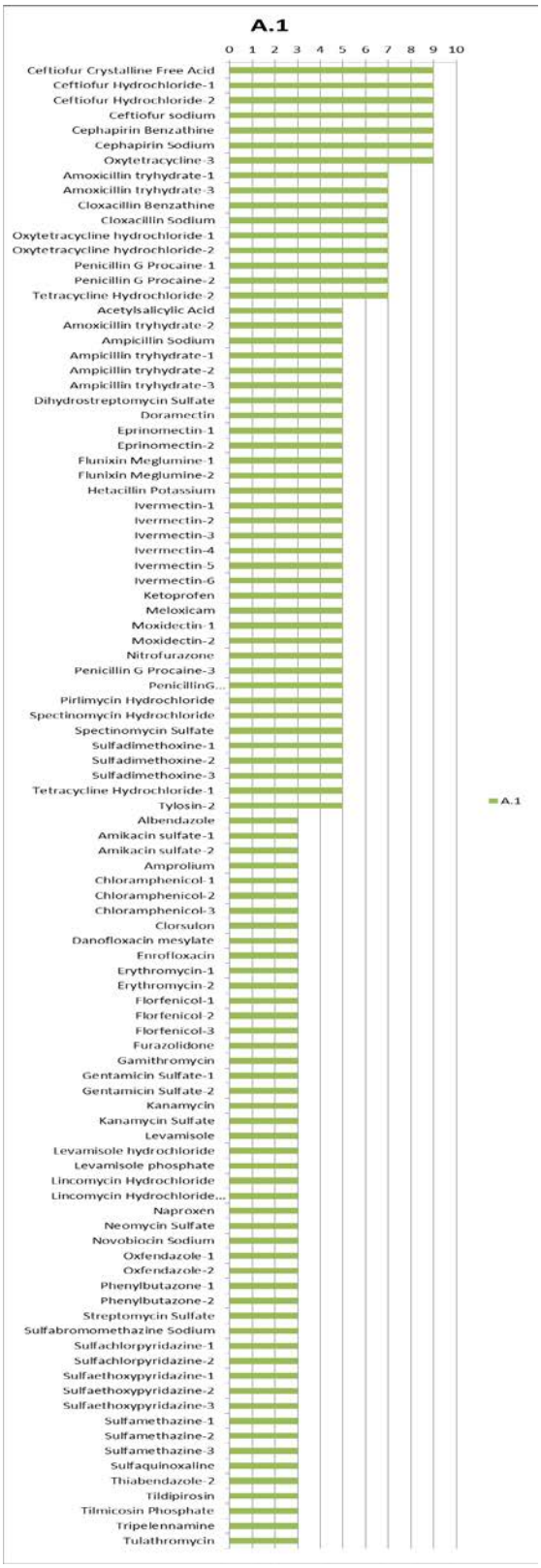


Figure A6.1 Drug scores for A1

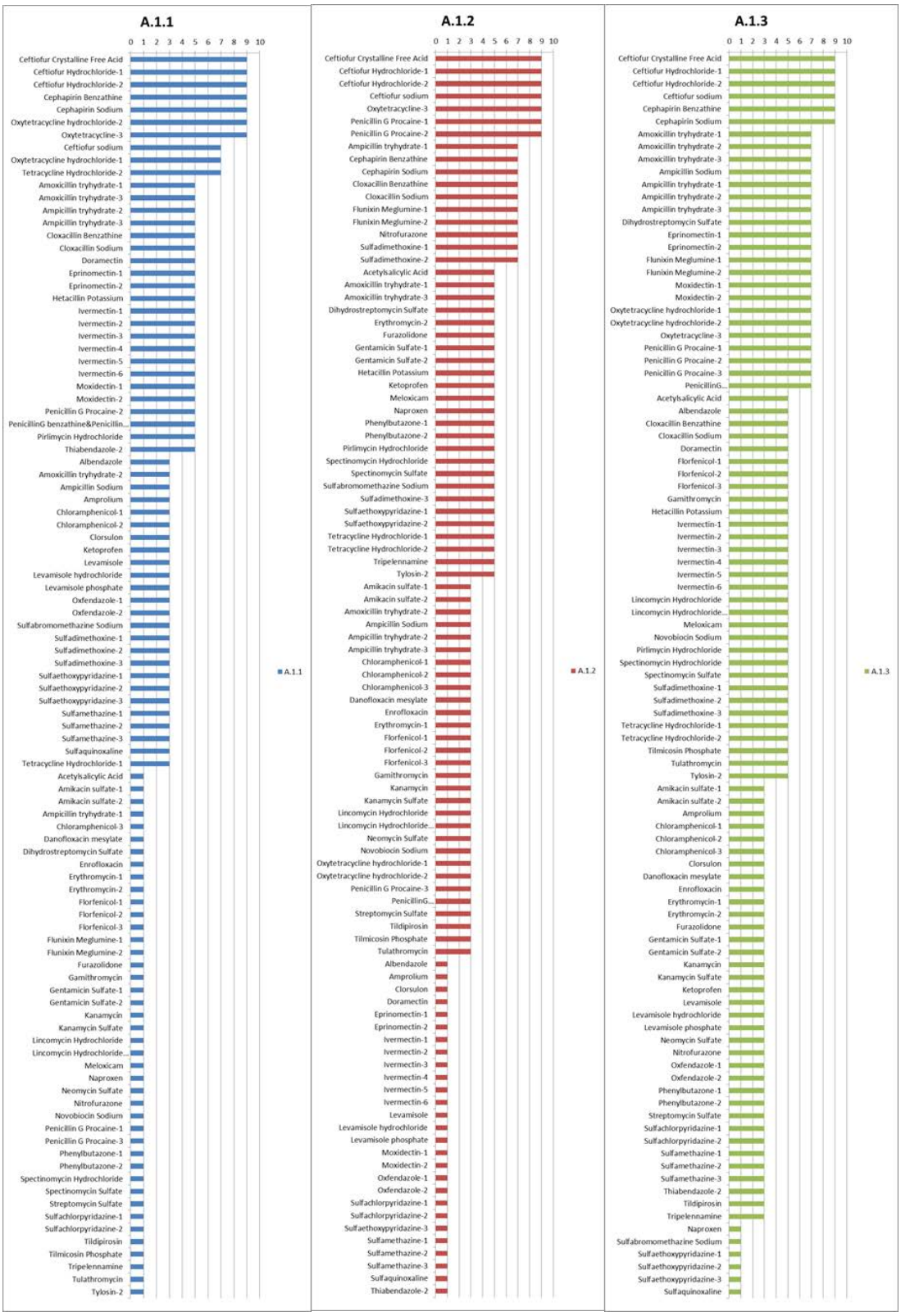


Figure A6.2 Drug scores for A1.1, A1.2, and A1.3

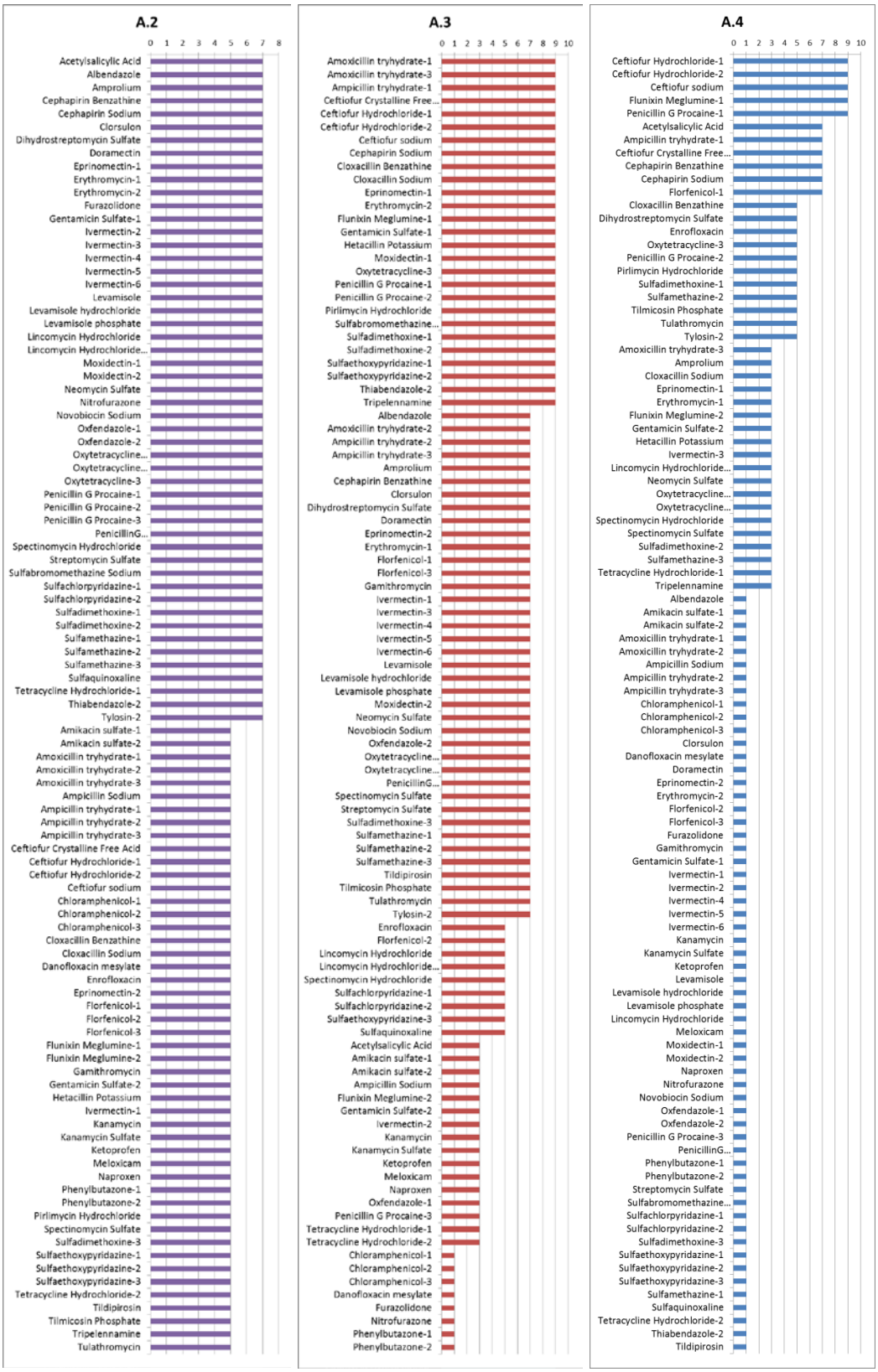


Figure A6.3 Drug scores for A2, A3, and A4

CRITERION B

B1. Likelihood of Drug's Presence (LODP) based on evidence of drug identification in bulk-tank-milk, or bulk-milk-tanker.

Figure A6.4 presents the drug scores for sub-criterion B1, and its factors B1.1 and B1.2
The drugs identified with the highest "evidence" scores were the macrolides (tulathromycin and tilmicosin); the sulfonamides (sulfamethazine and sulfadimethoxine); the aminoglycosides (gentamycin and neomycin); and the following individual drugs from different drug classes: tetracycline, florfenicol, enrofloxacin, doramectin, and cloxacillin.

B2. Likelihood of drug presence (LODP) based on the likelihood and consequence of drug mis-use

Figure A6.5 presents the Drug scores for sub-criterion B2, and its factors B2.1 and B2.2.
Drugs with the highest scores for B2 include tetracycline, the sulfonamides (sulfaquinoxaline, sulfaethoxypyridazine, and sulfachloropyridazine); the beta-lactams (penicillin and ampicillin); the NSAIDs (phenylbutazone and naproxen); the aminoglycosides (gentamycin, kanamycin, and amikacin); the flouroquinolones (enrofloxacin and danofloxacin); the amphenicols (chloramphenicol); the antiparasitics (oxfendazole and ivermectin); and the nitrofuran (nitrofurozone).

B3. Likelihood of drug presence (LODP) based on expert elicited information.

Scores for B3 were assigned here based on an expert panel's evaluation of factor B3.1 (likelihood of drug getting into lactating dairy cow's milk); and factor B3.2 (likelihood of drug getting into milk (bulk-tank or bulk-milk pickup tanker). Figure A6.6 presents the drug scores for sub-criterion B3, and its factors B3.1 and B3.2. The macrolides, tulathromycin, tilmicosin, tildipirosin; the lincosamide, pirlmycin; the tetracycline, oxytetracycline; the fluoroquinolone, enrofloxacin; and the antiparasitics, oxfendazole and doramectin were rated the highest by the experts as most likely to be present in the bulk-tank milk, if in the cow's milk. At the opposite end of the spectrum, the antiparasitic, eprinomectin was rated as least likely to be present in the bulk-tank milk, if in the cow's milk.

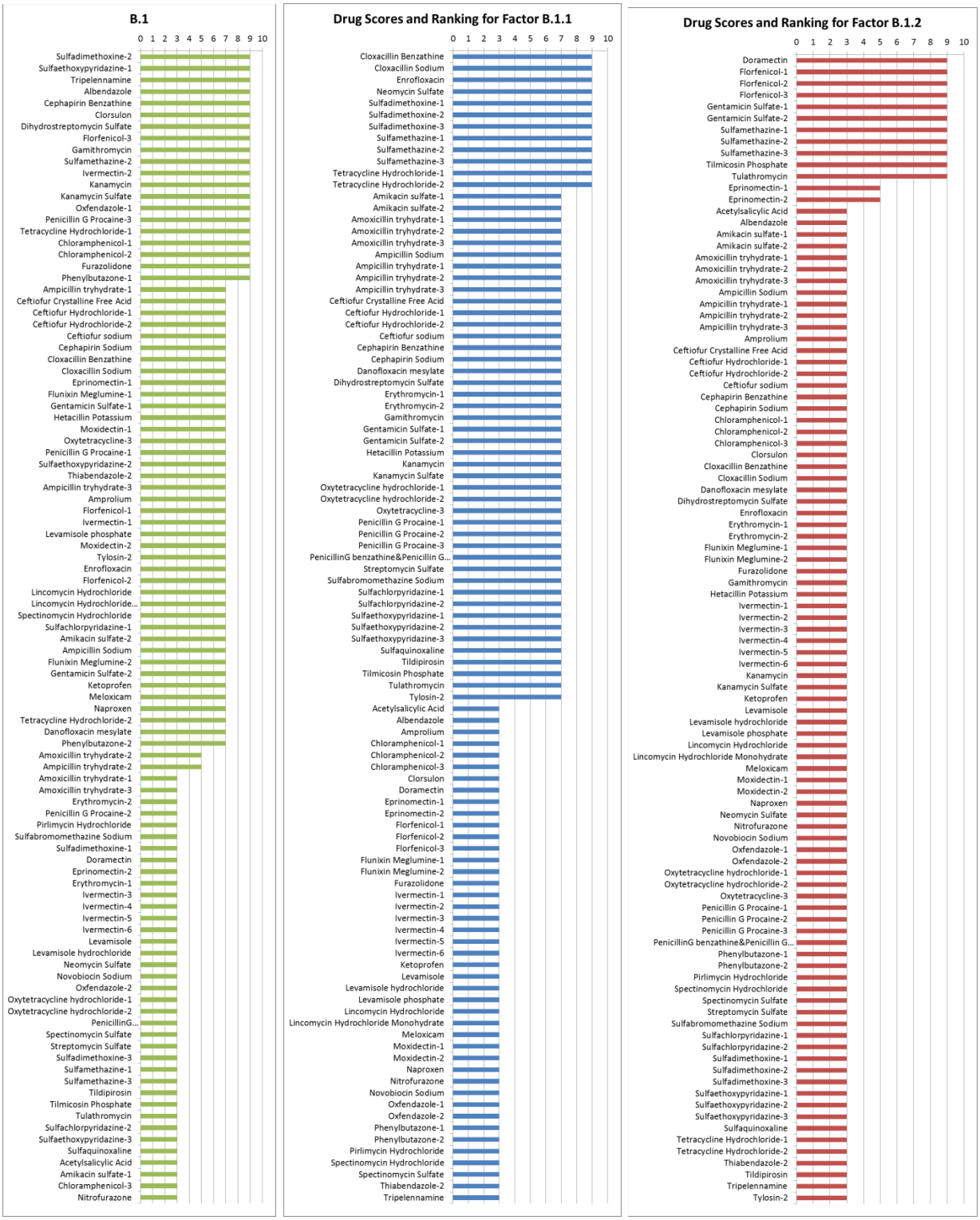


Figure A6.4 Drug scores for sub-criterion B1, and its factors B1.1 and B1.2

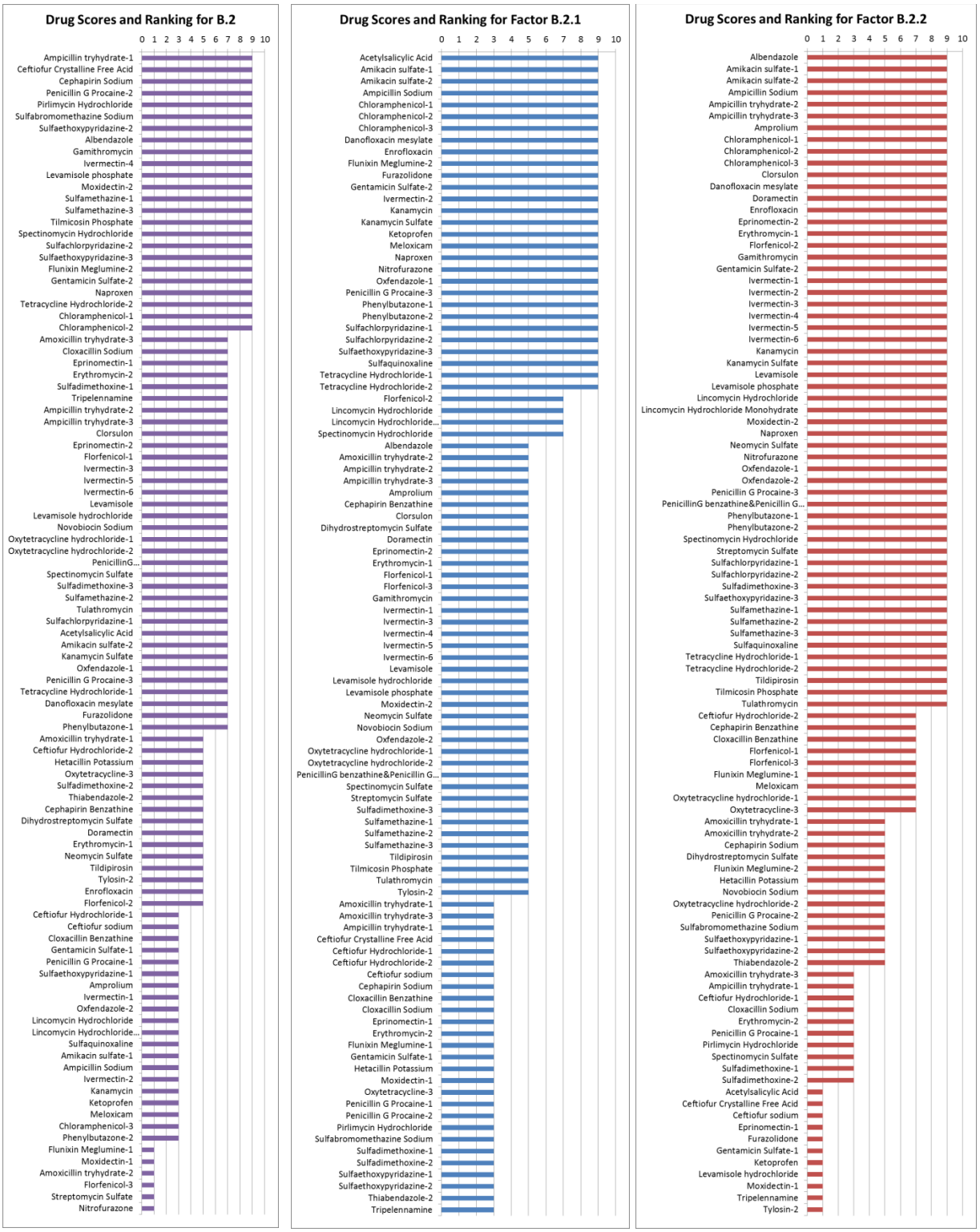


Figure A6.5 Drug scores for sub-criterion B2, and its factors B2.1 and B2.2

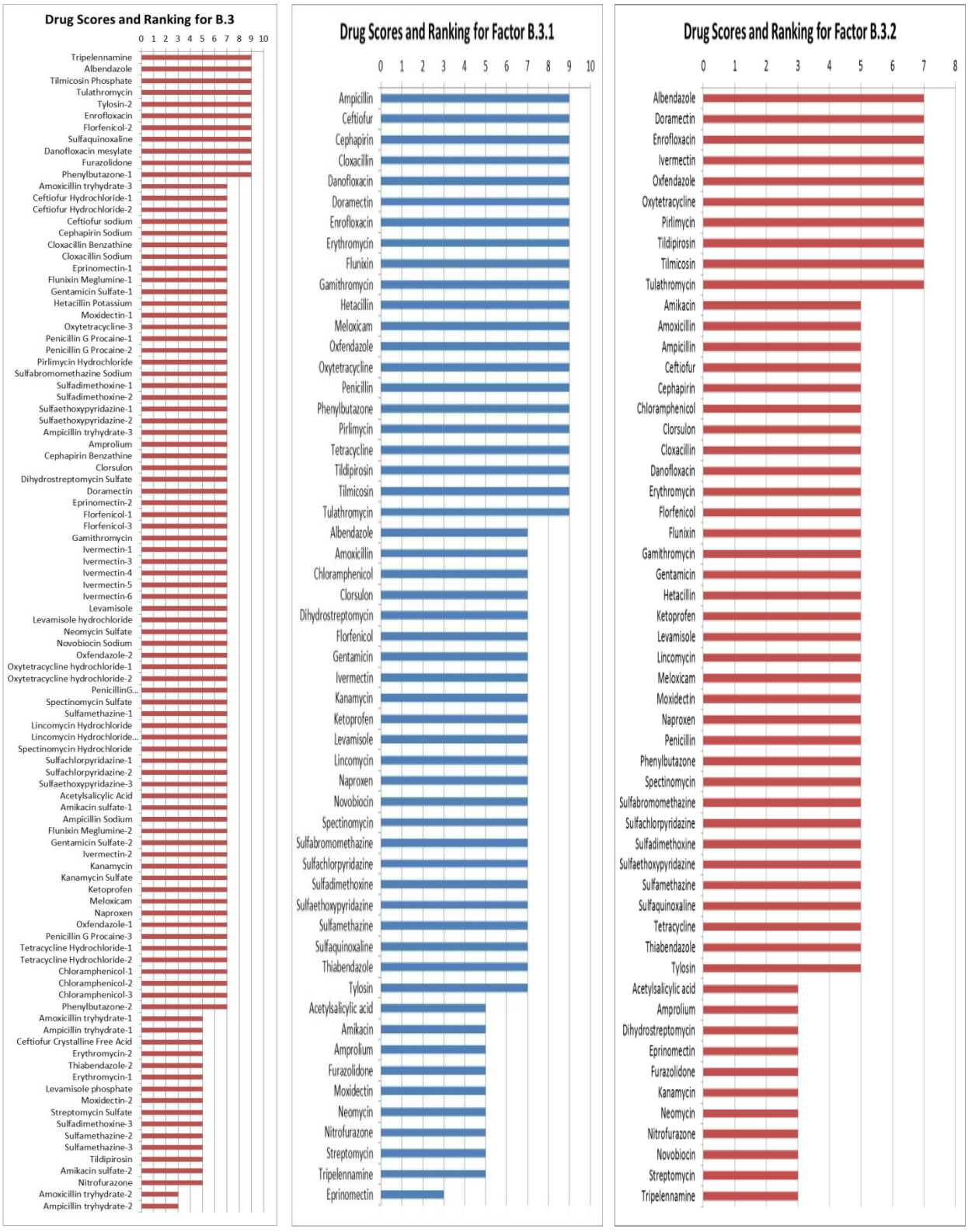


Figure A6.6 Drug scores for sub-criterion B3, and its factors B3.1 and B3.2

CRITERION C

C1. Impact of Processing:

The ranking scores from the impact of processing generate predicted changes in drug concentrations in the final milk products relative to the initial concentration in "raw" milk. The scores varied from a 0.3 (*i.e.,* 3.3-fold decrease) to a 10 (*i.e.,* 10-fold increase). The drug residues with the highest impact of processing consisted of fat-soluble drugs that are not impacted (or reduced) by heat degradation or water removal, and have the additional potential to concentrate in some high-fat dairy products. There is also potential for protein-soluble drug residues to concentrate in dairy products with a high-protein concentration, but this was not addressed in this model because of a lack of data on the protein-binding characteristics of the drug residues or significant metabolites in this study.

Figure A6.6 describes the estimated impact of processing (C1) for each drug residue by dairy product. Figure A6.7 illustrates the impact of processing on drugs in fluid milk, butter, and evaporated milk, respectively. As illustrated in the figures, the fat-soluble drugs, amprolium, dormectin, eprinomectin, ivermectin, moxidectin, oxfendazole, thiabendazole, and tulathromycin have the highest-ranking scores because of the potential to concentrate up to nine times the original concentration in high-fat dairy products, such as butter.

C1.1. Product Composition.

Figure A6.8 describes the estimated impact of product composition on relative drug concentration. Table A6.1 presents the Product Fat Composition value relative to milk. Figure A6.9 graphically illustrates the Product Fat Composition values of milk products relative to milk. Butter is the dairy product with the highest fat content, among the milk and milk products included in this multicriteria-based ranking.

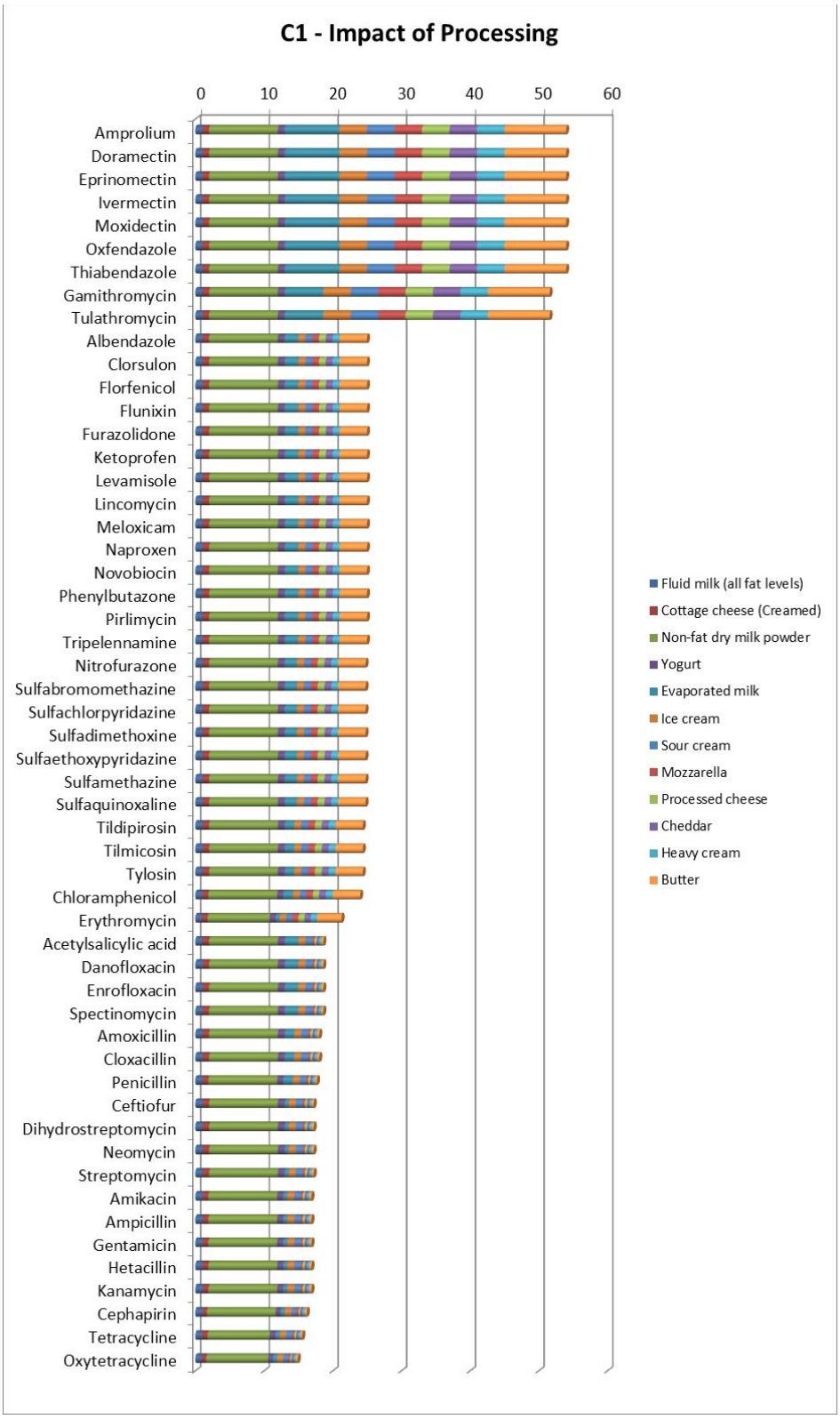


Figure A6.7 Impact of processing

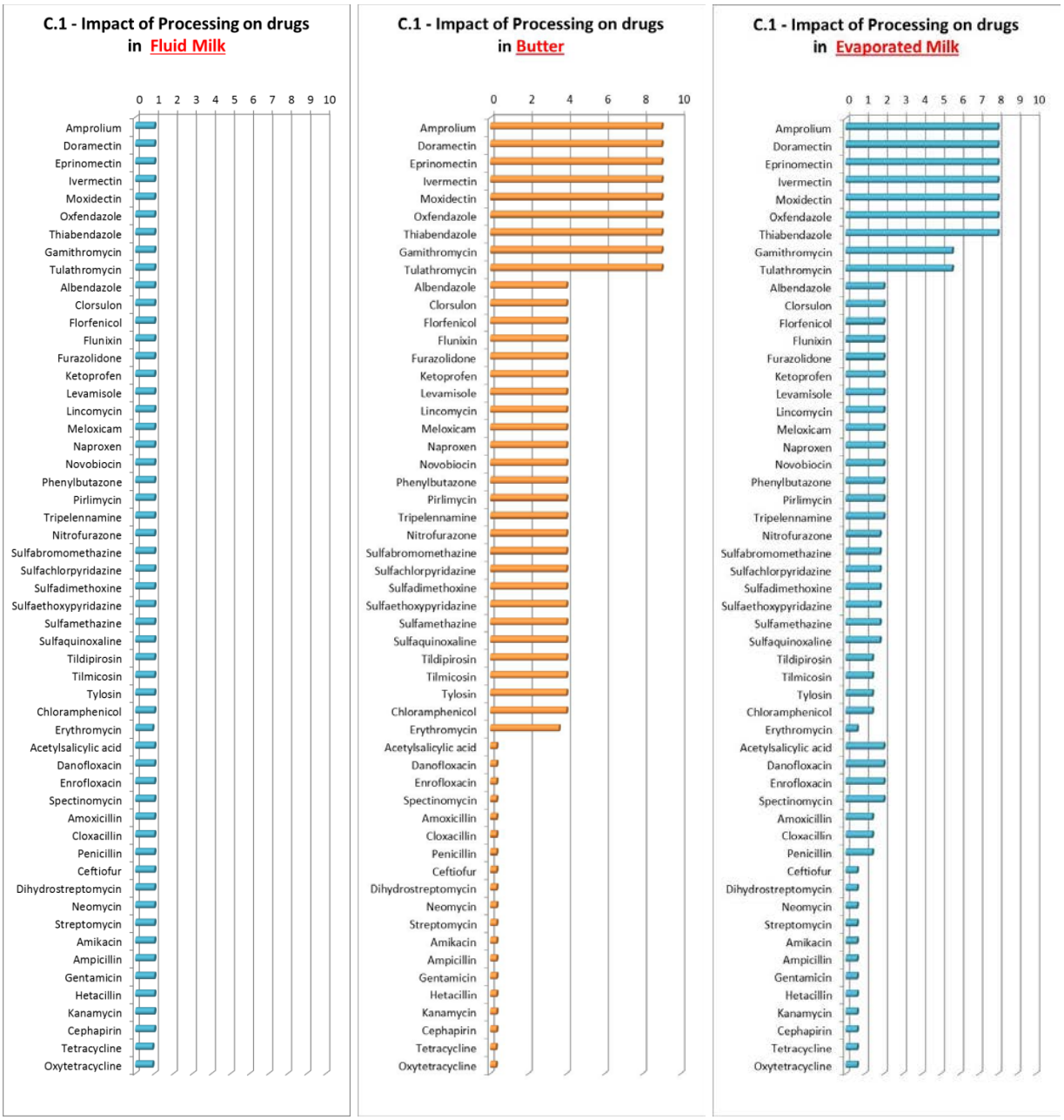
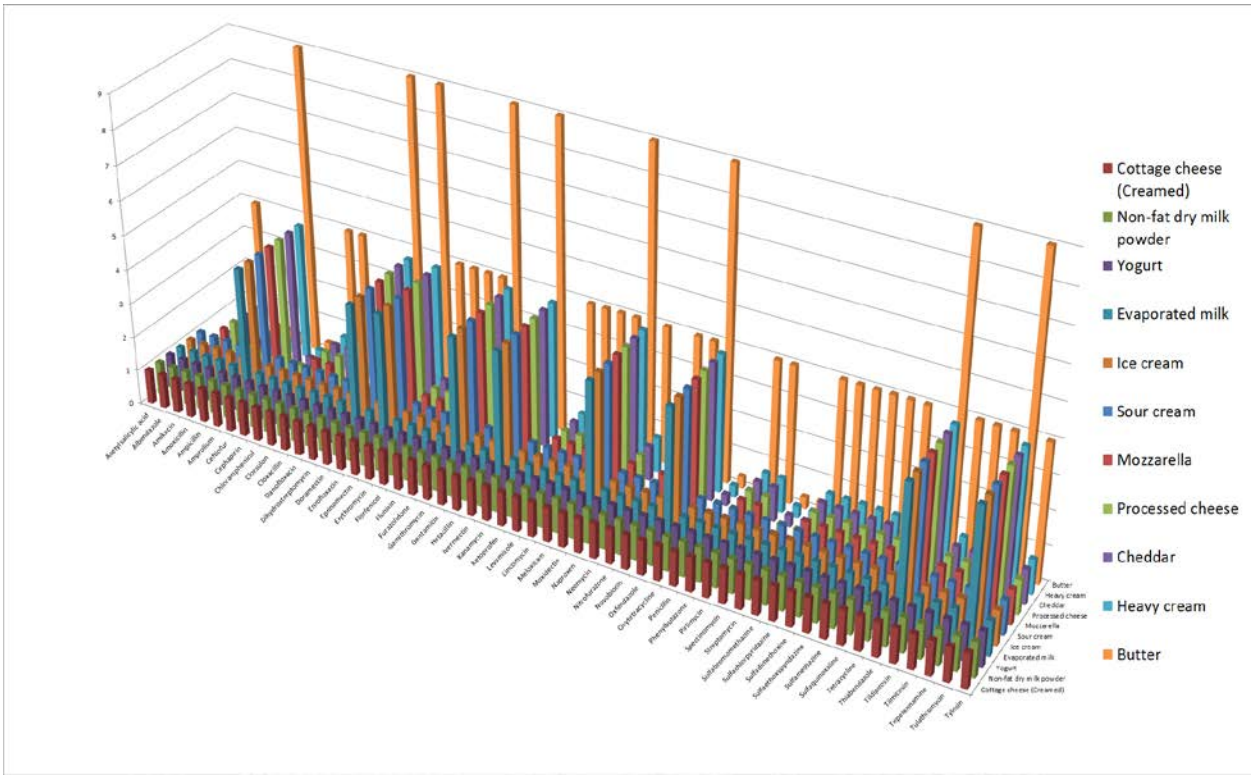


Figure A6.8 Impact of processing on each drug in fluid milk, butter, and evaporated milk

The following figure illustrates the Product Composition value (C.1.1) for each of the drug-product pairs, as described in Tables 5.21 and 5.22. Butter is the dairy product with the highest fat content, among the milk and milk products included in this multicriteria-based ranking.

Figure A6.9 Product Composition value



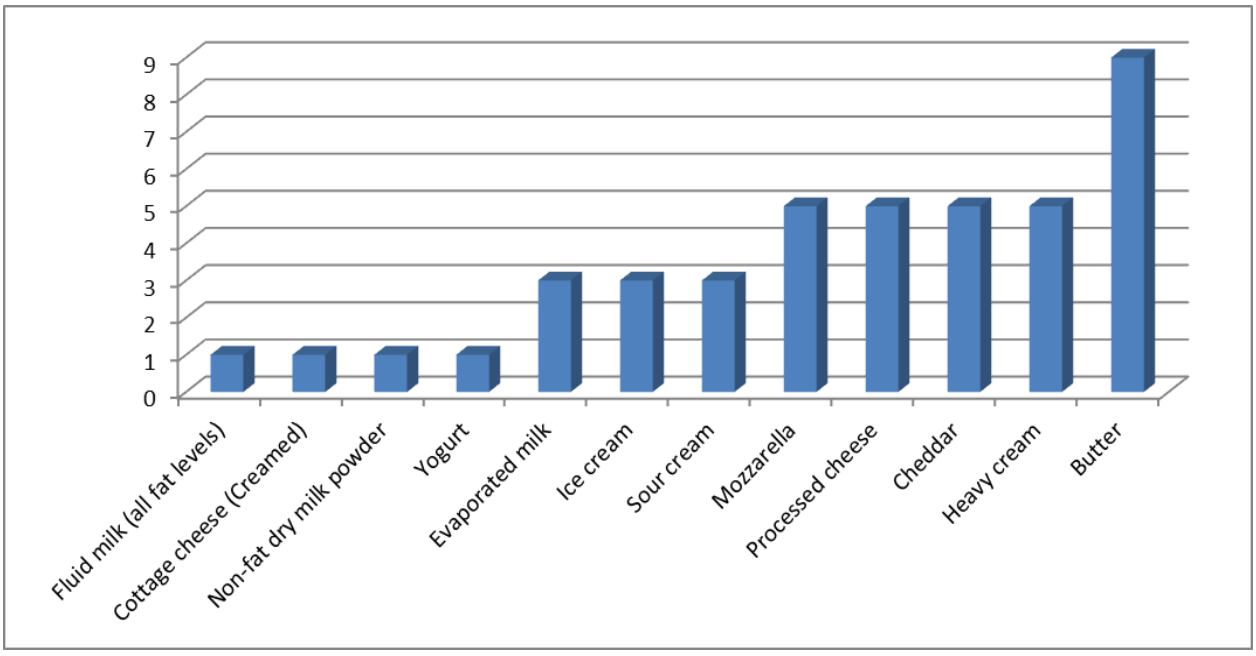


Figure A6.10 Product fat composition categorization

Table A6.2 Product composition score

Milk Product	Product Fat Composition Categorization	Estimated change in drug residue concentration in product relative to milk
Fluid milk (all fat levels)	1 (0-5%)	D-no change
Cottage cheese (Creamed)	1 (0-5%)	D-no change
Non-fat dry milk powder	1 (0-5%)	D-no change
Yogurt	1 (0-5%)	D-no change
Evaporated milk	3 (5.1-20%)	D- no change to E-moderate increase depending on drug
Ice cream	3 (5.1-20%)	D- no change to E-moderate increase depending on drug
Sour cream	3 (5.1-20%)	D- no change to E-moderate increase depending on drug
Mozzarella	5 (20.1-45%)	C- moderate decrease to F-high increase depending on drug
Processed cheese	5 (20.1-45%)	C- moderate decrease to F-high increase depending on drug
Cheddar	5 (20.1-45%)	C- moderate decrease to F-high increase depending on drug
Heavy cream	5 (20.1-45%)	C- moderate decrease to F-high increase depending on drug
Butter	9 (>45%)	C- moderate decrease to G-very high increase depending on drug

The following figure illustrates the expected drug (or major drug metabolite) partitioning/distribution behavior for each of the 54 drugs considered in this multicriteria-based ranking.

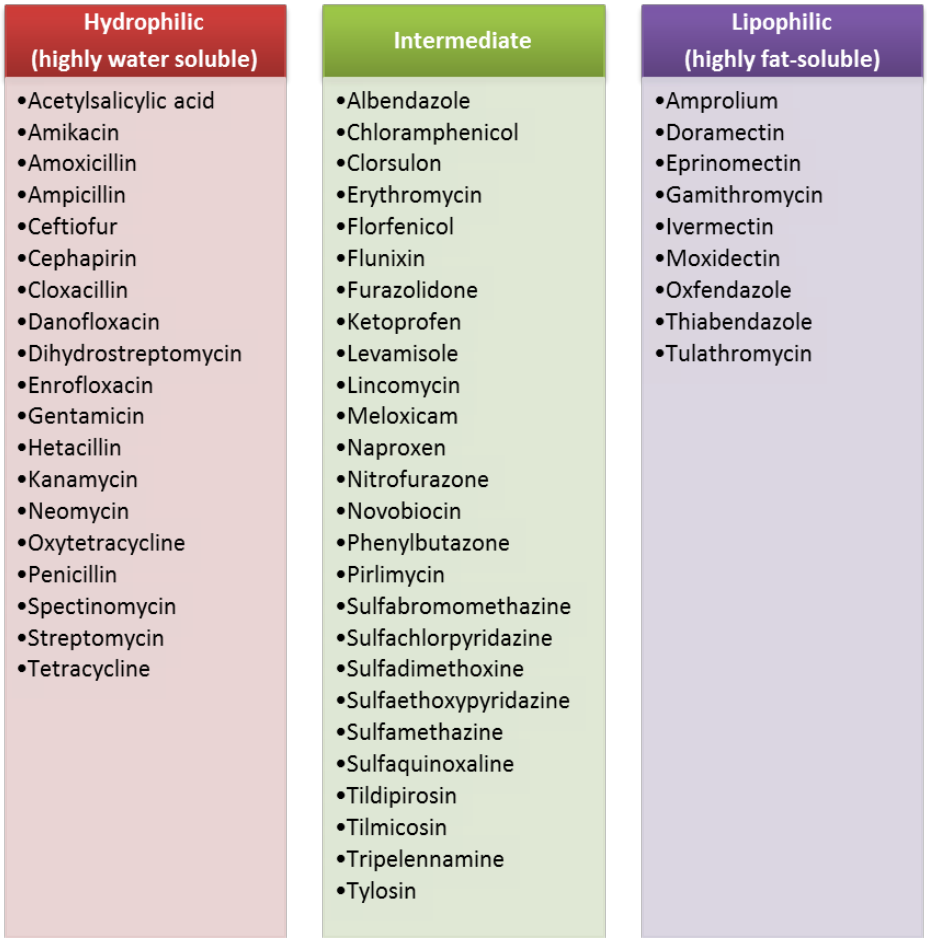
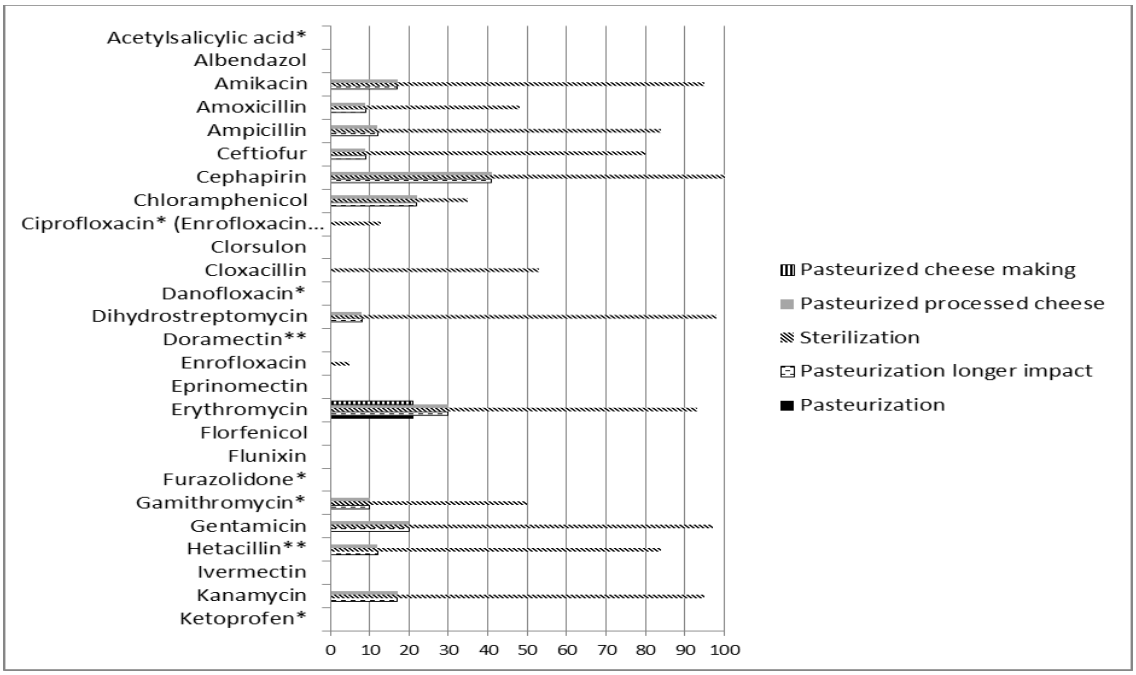


Figure A6.11 Hydrophilic, intermediate, and lipophilic drugs

These general categorical assignments were made on the basis of the value of the apparent partition coefficient and experimental determinations of drug partitioning during milk processing. Lipophilic drugs will concentrate in high fat milk products and as a result, these drugs are expected to result in increased exposure to consumers, based on the lifetime average daily consumption in the U.S.

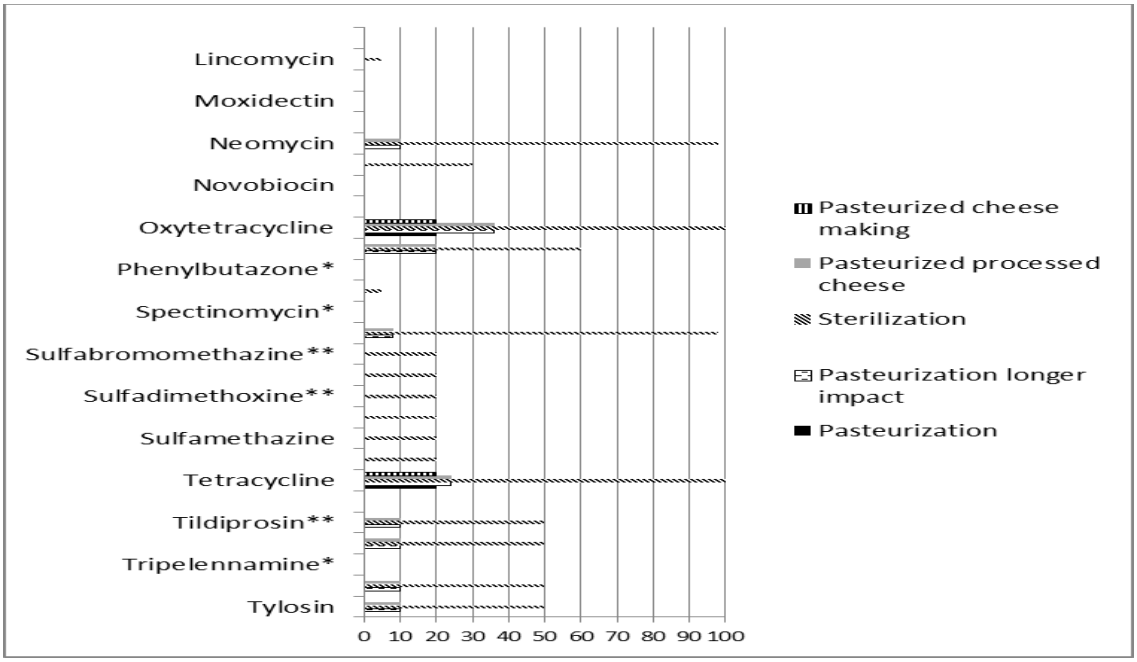
C1.2. Impact of Heat Degradation:

A majority of the drugs in this study is heat stable, but the tetracyclines (tetracycline and oxytetracycline) as well as erythromycin are more heat sensitive and will be impacted by pasteurization. These heat sensitive drugs are expected to decrease in concentration in processed milk and dairy products.



* No data available; but information available on melting point or stability at a temperature level
** No data available; assumed same properties as for similar drugs (see Appendix 5.14)
Note : No data available for the amprolium

Figure A6.12 Impact of heat degradation (Drugs A-K)



* No data available; but information available on melting point or stability at a temperature level
** No data available; assumed same properties as for a similar drugs (see Appendix 5.13)

Figure A6.13 Impact of heat degradation (Drugs L-T)

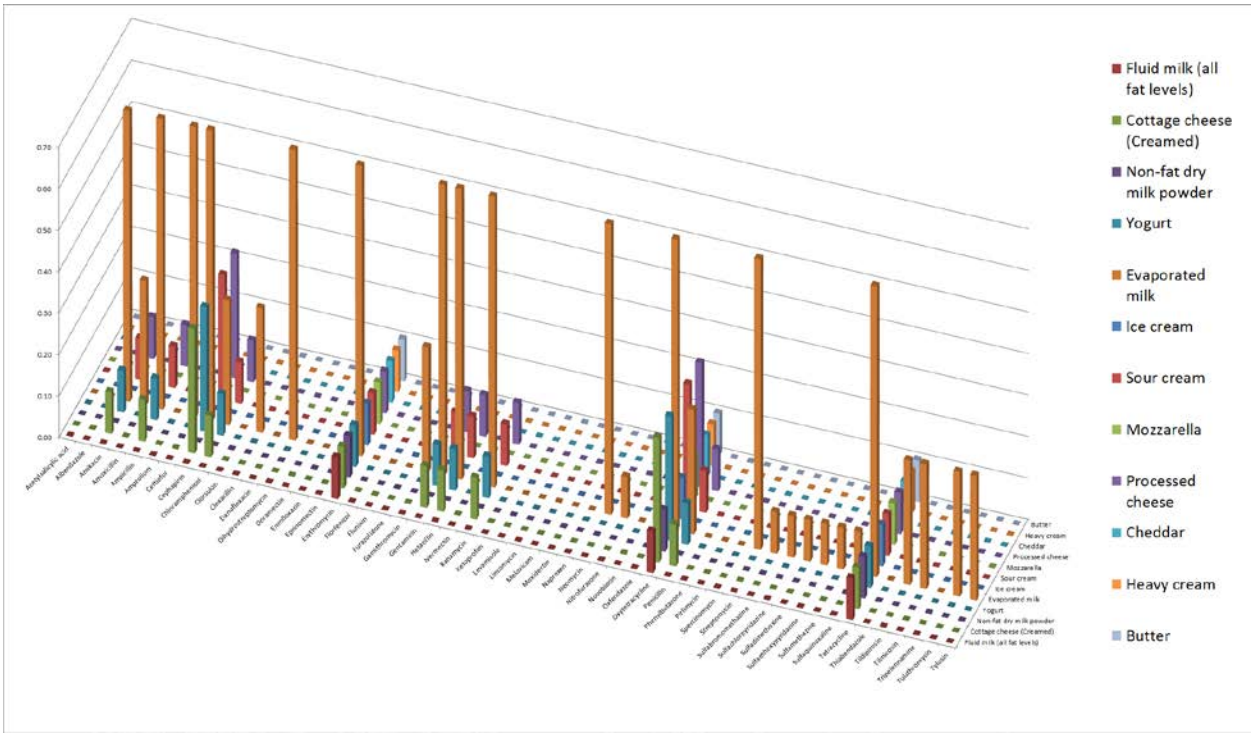


Figure A6.14 Illustration of 1 – "Heat Degradation value" for each of the 54 drug-product pairs.

C1.3. Water Removal Factor Score.

The figure below describes the impact of water removal on drug residue concentrations by product.

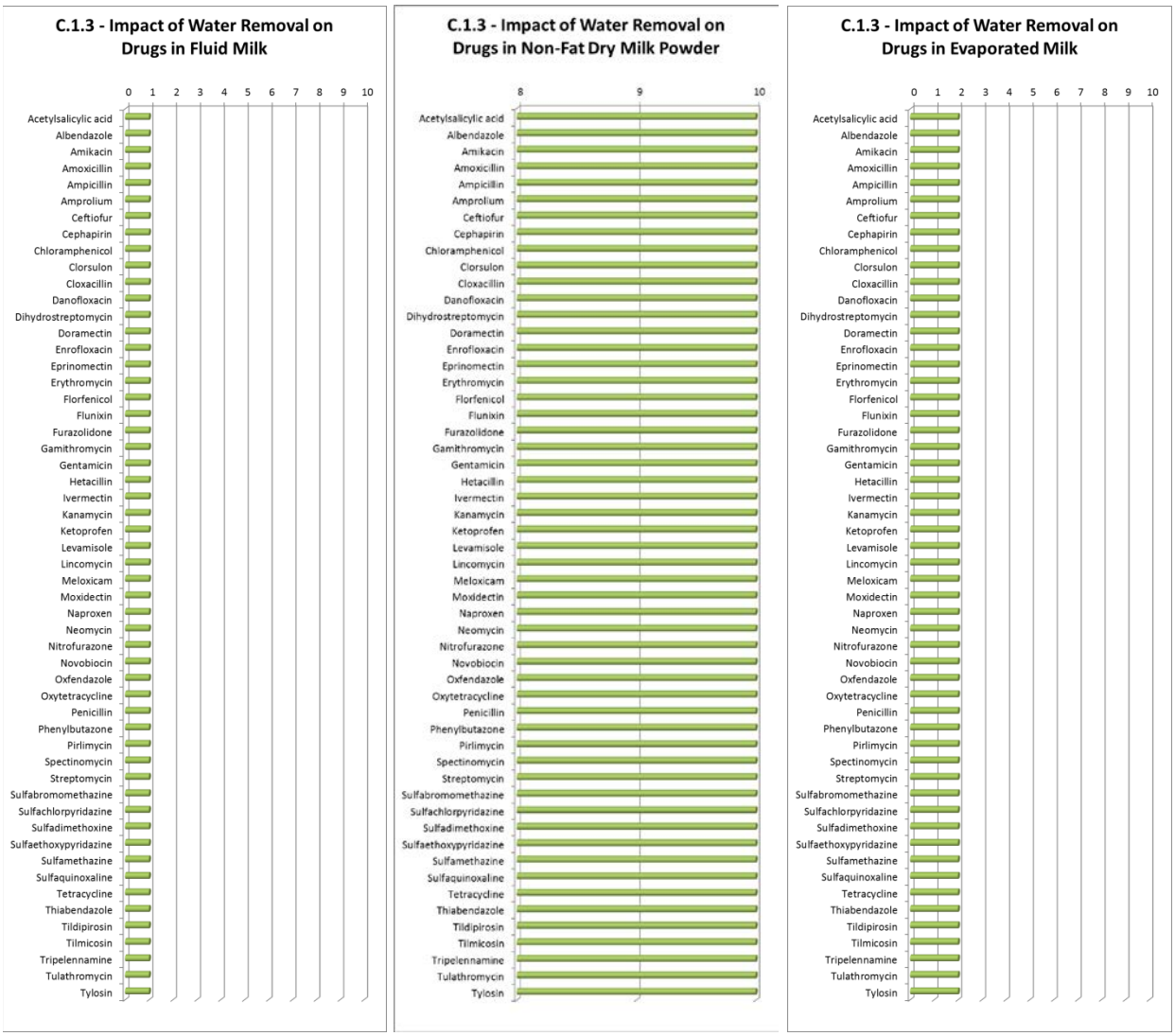


Figure A6.15 Impact of water removal on drugs in fluid milk, non-Fat dry milk powder, and evaporated milk

C2. Magnitude of Consumption of Milk and Milk Products.

C2.1. Magnitude of Consumption of Milk and Dairy Products (LADI-Life –time Ave. daily intake/ kg/bw).

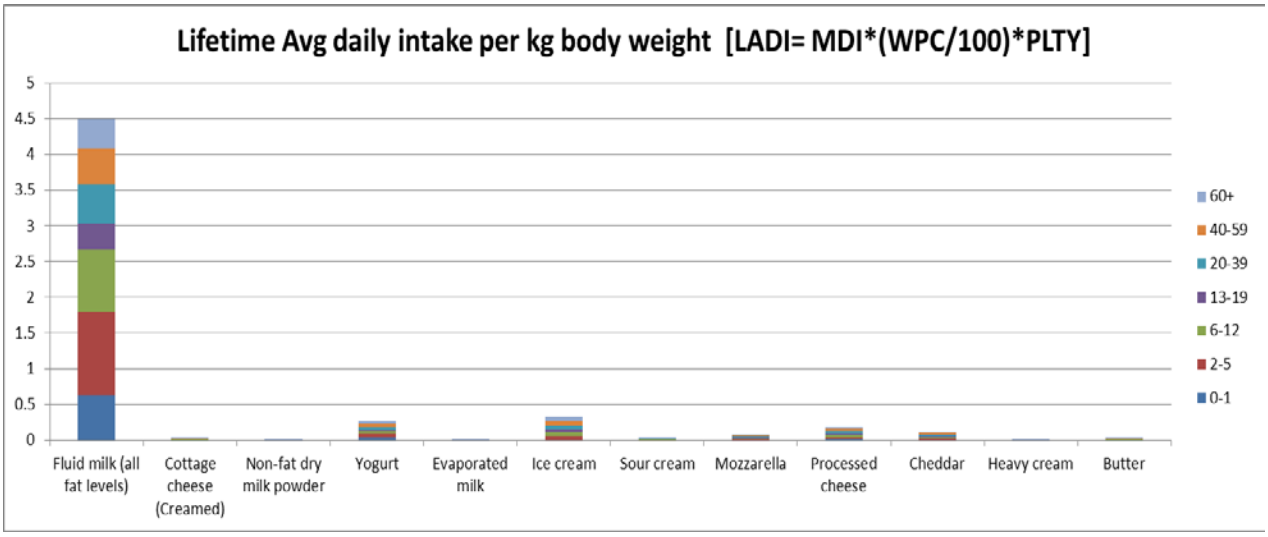


Figure A6.16 Magnitude of consumption of milk & dairy products (LADI - LifetimeAvg daily intake/kg bw)

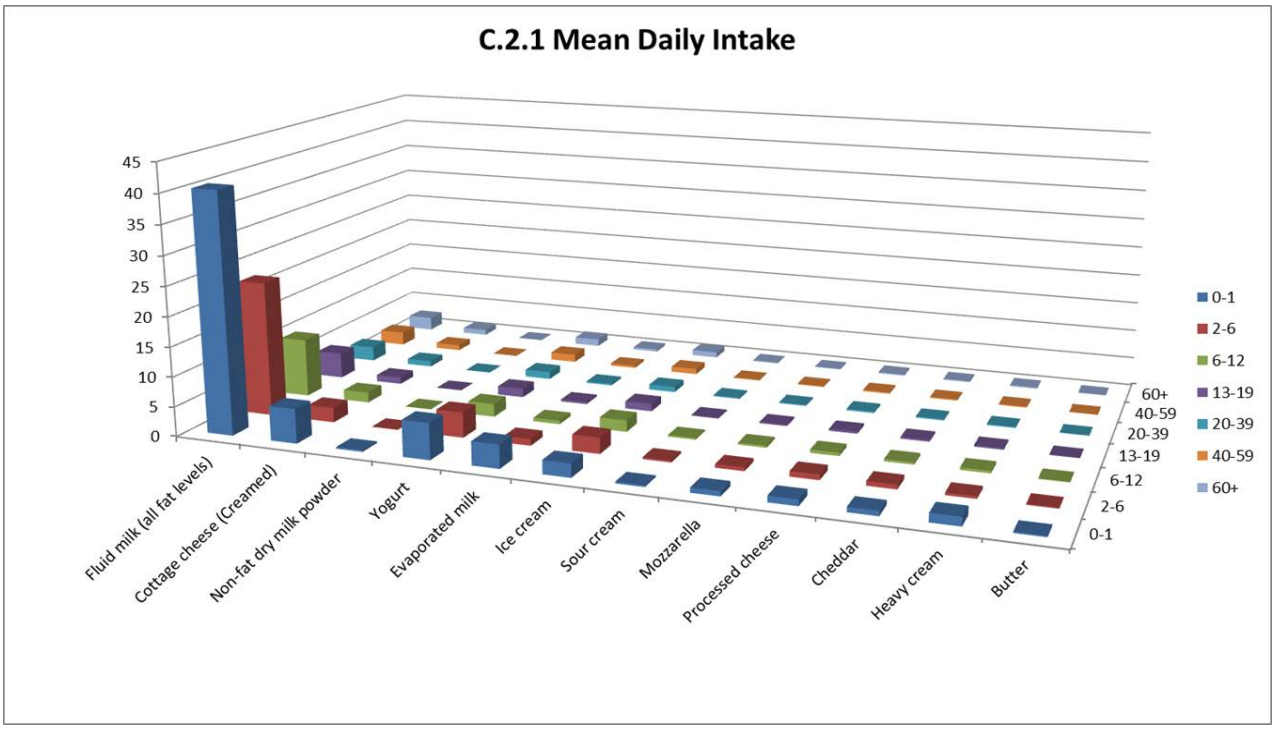
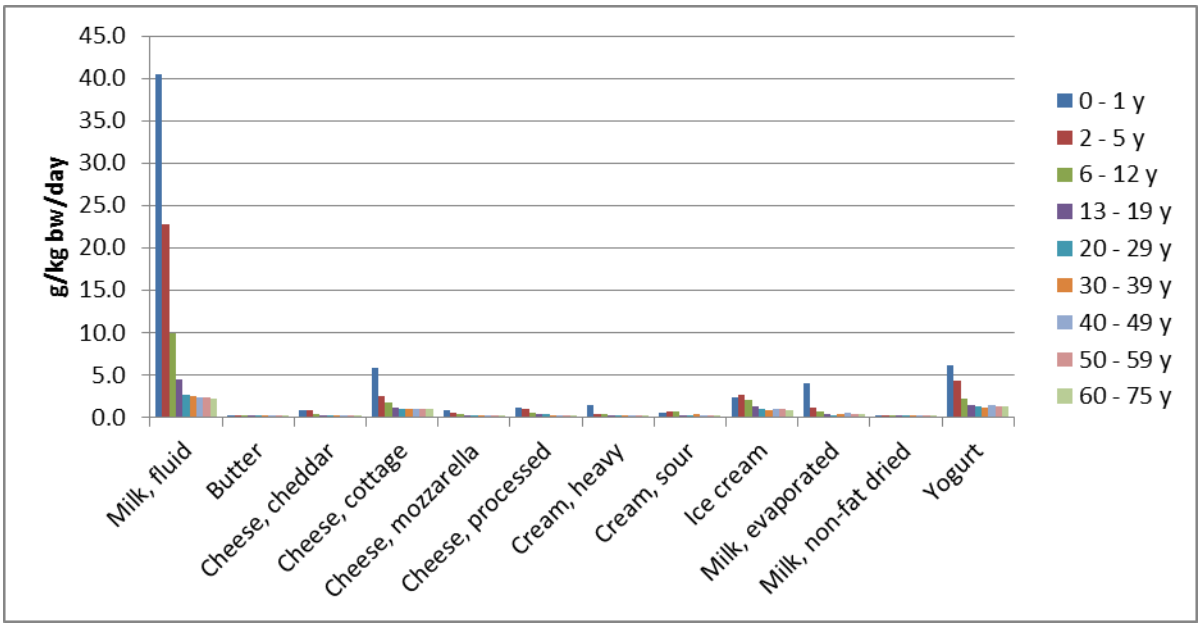
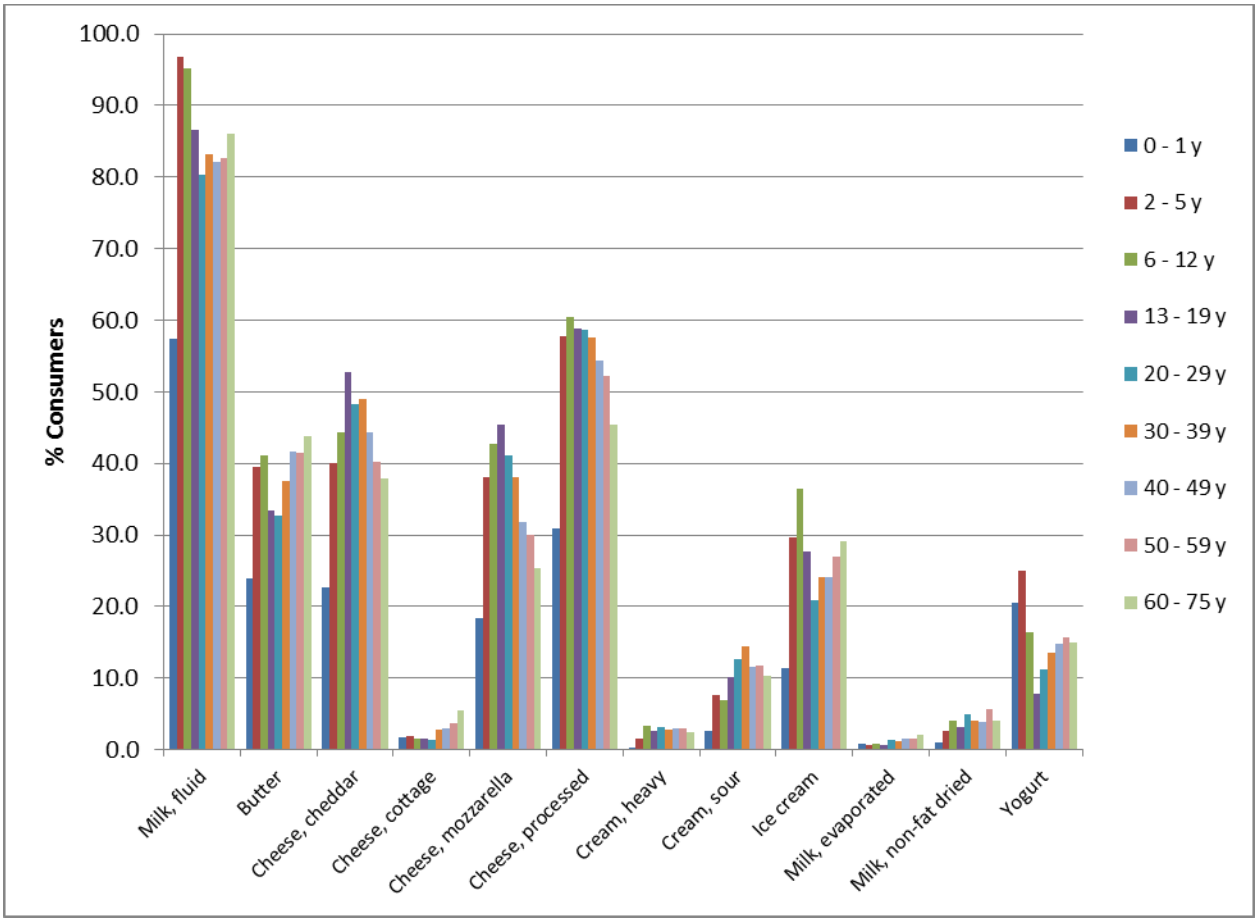


Figure A6.17 Mean daily intake of milk and milk products by age group



Data source: What We Eat In America, National Health and Nutrition Examination Survey (WWEIA/NHANES), 2005-2010 (CDC, 2011). Dairy product ingredient percentages were determined based on the Food and Nutrient Database for Dietary Surveys (FNDDS) 5.0 (USDA FSIS, 2012a). Intake amounts are two-day averages.

Figure A6.18 Mean intakes of the 12 selected milk and milk products (g/kg body weight/day) by consumers



Data source: What We Eat In America, National Health and Nutrition Examination Survey (WWEIA/NHANES), 2005-2010 (CDC, 2011). Dairy product ingredient percentages were determined based on the Food and Nutrient Database for Dietary Surveys (FNDDS) 5.0 (USDA FSIS, 2012b). Percentages reflect the proportion of survey respondents in each age group reporting intake of the dairy product (or a mixture containing the dairy product) at least once during the two-day survey period.

Figure A6.19 Percent of individuals consuming the 12 selected milk and milk products

C2.2. Percentage of Individual Consuming Dairy Products. Figure below illustrates the weighted percent consumption of all dairy products by age groups, as compared fluid milk. The consumption of fluid milk surpassed dairy product consumption for all age groups.

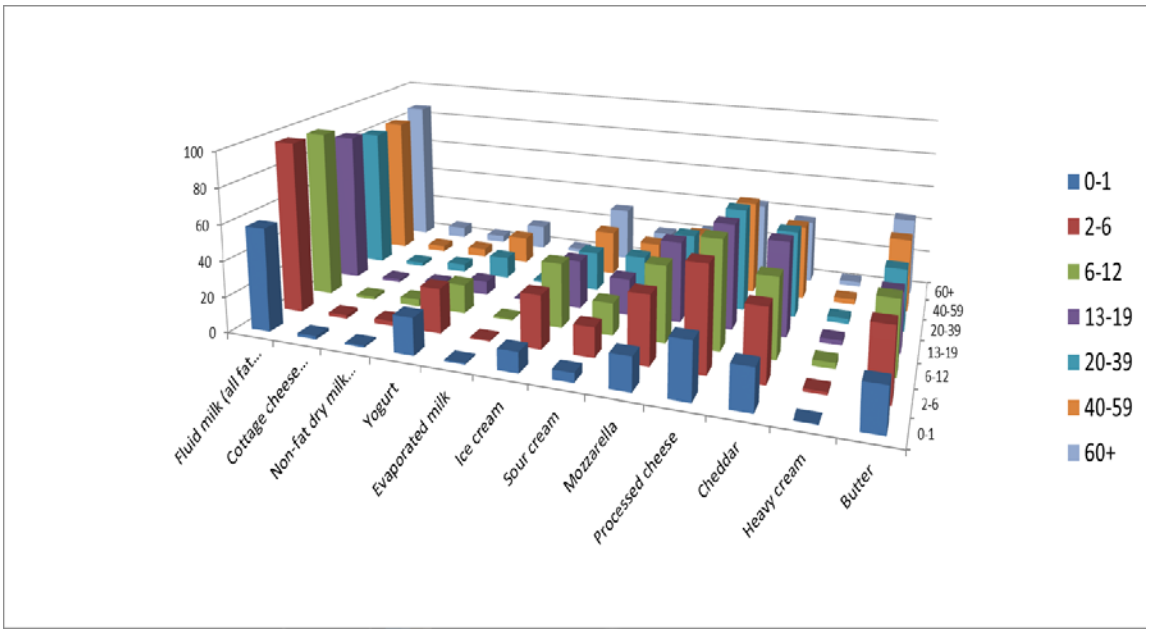


Figure A6.20 Percent consumers

C2.3. Years in Age Group. Proportion of Life-time Years Spent in an Age Group, PLTag

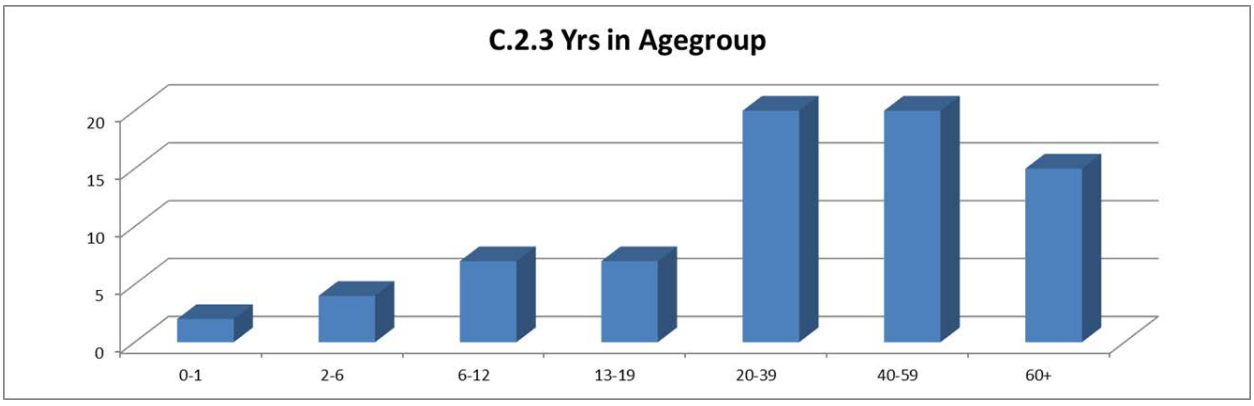


Figure A6.21 Years in population group (YPop)

APPENDIX 6.3: RESULTS: DATA UNCERTAINTY—DETAILED DESCRIPTION OF SCORING

In order to develop a ranking of drugs on the basis of confidence in the data, subject matter experts within the risk assessment team classified their confidence in each datum used in the model as high confidence, medium confidence, or low confidence. In some cases, a more resolved scale was required. Table A6.3 summarizes the level and type of evidence required for each classification category across all data sets and the associated data confidence score. A low confidence score means that the data are relatively uncertain.

Table A6.3 General scheme for characterizing confidence of each datum used in the model

Confidence level	Strength and quality of evidence	Confidence Score
High	Strong evidence/data based on its relevance and reliability as determined from a number of factors. For example, a) Data for specific animal drug of interest b) Data for relevant to milk or milk products c) Data obtained using well documented and accepted methods d) Strong agreement among experts (*e.g.,* data from expert elicitation) e) Data from reliable source (*e.g.,* refereed scientific literature or government report)	9
Medium	Moderate evidence/data based on its relevance and reliability as determined from a number of factors. For example, a) Data for another drug in the same animal drug class or family or only specific to the drug class/family b) Moderate agreement among experts (*e.g.,* data from expert elicitation) c) Data obtained in a matrix other than milk or milk products d) Data obtained using well documented and accepted methods e) Data from reliable source (*e.g.,* refereed scientific literature or government report)	5
Low	Minimal evidence /data based on its relevance and reliability as determined from a number of factors. For example, a) No direct measurements or information available (*e.g.,* data obtained from theoretical estimates only or data	1

Confidence level	Strength and quality of evidence	Confidence Score
	estimated from loosely related data/information) b) Disagreement among experts (*e.g.*, data from expert elicitation) c) No relevant data available	

An overall data confidence score for each drug was derived from the assigned datum scores in a manner parallel to the multicriteria-based ranking model., *i.e.,* each sub-criterion score was generated from the confidence scores of the data sets informing it and each criterion score was derived from the combination of sub-criterion scores. Criterion scores were combined using the same expert weights assigned in the multicriteria-based ranking model, *i.e.,*

Data Uncertainty Score of Each Drug (U_{DRUG})

$U_{DRUG} = ((U_A*W_A) + (U_B*W_B) + (U_C*W_C) + (U_D*W_C))/W$

Where:

U_A, U_B, U_C, U_D = Data uncertainty scores for each drug with respect to criteria A, B, C, and D.
W_A = Weight assigned to criterion A.
W_B= Weight assigned to criterion B.
W_C = Weight assigned to criterion C.
W_D = Weight assigned to criterion D.
$W_{sum} = W_A + W_B + W_C + W_D$

Inclusion of the same weights used in the multicriteria-based ranking model in the development of the data confidence ranking is critical, because these reflect the extent to which information from each criterion contribute to the multicriteria-based ranking model. More specific details related to the classification of data in each data set used in the model and the scoring matrices used are provided below.

A. Animal Drug Data Uncertainty Score for Criterion A

The multicriteria-based ranking score for each animal drug associated with criterion A was derived from scores for each of four sub-criteria: (A1) LODA based on surveys, (A2) LODA based on drug marketing status, (A3) LODA based on drug approval status, and (A4) LODA based on evidence of drug use on dairy farms. Below, we defined data confidence scoring associated with each sub-criterion and then combined these confidence scores to derive an overall data confidence score for criterion A.

- **Animal Drug Data Uncertainty Score for A1**

Three different studies informed the score for A1. We evaluated the data confidence for each drug associated with each study and then combined these scores to provide an overall data confidence score for A1.

A1.1: USDA Study (NAHMS Dairy 2007)
A1.2: Veterinary Survey (Sundlof *et al*., 1995)
A1.3: Expert Elicitation

The animal drug data confidence score for each drug associated with factors A1.1 or A1.2 is defined below.

Table A6.4 Confidence scores for A1.1 or A1.2

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
Survey data available for the animal drug	9
Survey data available for the animal drug class	5
No survey data available for the animal drug or drug class	1

The ranking score for A1.3 was derived from expert responses to each of three questions. Data confidence scores for each drug were also derived from the answers to the three questions, but in this case, scored on the basis of the numbers of experts that provided a quantitative response to each question and the level of agreement among those experts (as measured by the standard deviation of the respondents scores for each drug) (standard deviation confidence).

The standard deviation confidence score (SDC), and the proportion of respondents confidence score (PRC) were summed and used to determine the confidence score for each drug as follows

Table A6.5 Confidence scores for A1.3, Q1 (percentage of dairy cows herds treated with a specific animal drug), Q2 (percentage of lactating dairy cows within a herd that is treated with a specific animal drug as derived from the Expert Elicitation), and Q3 (frequency of treatment with a specific animal drug per year per lactating dairy cow as derived from the Expert Elicitation)

Strength and quality of evidence associated with the datum for a given animal drug	A1.3-Q1 Confidence Score
If (SDC+PRC) > 10	9
If 10 ≥ (SDC+PRC) > 8	5
If 8 ≥ (SDC+PRC)	1

SDC is the standard deviation confidence score,
PRC is the proportion of respondents confidence score.

The data confidence score for A1.3 summarizes our confidence in the data provided by experts for each drug across all three questions.

Table A6.6 Confidence scores for overall A1.3

Level and type of evidence	Confidence Score
Sum of data confidence scores for Q1, Q2, and Q3 ≥ 23	9
Sum of data uncertainty scores for Q1, Q2, and Q3 ≥ 11	5
Sum of data uncertainty scores for Q1, Q2, and Q3 < 11	1

The confidence score for A1 reflects confidence in each of the three data sources (factors) informing the sub-criterion and agreement among the data sets.

Table A6.7 Confidence scores for overall A1

Level and type of evidence	Confidence Score
Sum of data uncertainty scores for A1.1, A1.2, and A1.3 > 15 (*e.g.,* 9+5+5)	9
Sum of data uncertainty scores for A1.1, A1.2, and A1.3 > 9 (*e.g.,* 5+5+1)	5
Sum of data uncertainty scores for A1.1, A1.2, and A1.3 ≤ 9 (*e.g.,* 5+1+1)	1

- **Animal Drug Data Confidence Scores for A2 and A3**

Both animal drug prescription status and drug approval status in the United States are known so the confidence scores assigned to each drug in A2 and A3 was 9.

- **Animal Drug Data Confidence Score for A4**

FDA/CVM farm inspection data informed the score for A4. The data confidence score associated with these data is defined below. If a drug was never observed on farms over at least 5 years of inspection, then there is a relatively high degree of confidence (7) that the zero observation is correct.

Table A6.8 Confidence scores for A4

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
FDA/CVM Farm Inspection observed the animal drug on the farm	9
FDA/CVM Farm Inspection did not observe the animal drug on the farm	7

Data confidence score for Criterion A

The data confidence score for each of the 99 drug formulations considered in the model was derived from the scores for each of the four sub-criteria as follows:

Table A6.9 Confidence scores for overall Criterion A

Level and type of evidence	Confidence Score
Sum of data confidence scores for A1, A2, A3, and A4 > 28 (*e.g.*, 9+9+9+5)	9
Sum of data confidence scores for A1, A2, A3, and A4 > 12 (*e.g.*, 9+9+5+5)	5
Sum of data confidence scores for A1, A2, A3, and A4 ≤ 12 (*e.g.*, 5+5+1+1)	1

B. Animal Drug Data Confidence Score for Criterion B

The ranking score for each animal drugs associated with Criterion B was derived from scores for each of three sub-criteria: (B1) LODP based on evidence of the animal drug having been detected in bulk-tank milk, (B2) LODP based on the likelihood and consequence of drug mis-use, (B3) LODP based on a score derived from the expert elicitation. Below we define data confidence scoring associated with each sub-criterion and then combine these confidence scores to derive an overall data confidence score for criterion B.

- **Animal Drug Data Uncertainty Score for B1**

Two different studies informed the score for B1: data from the National Milk Drug Residue Database for the years 2000-2013 (B1.1) and FDA/CVM sampling survey of bulk-tank milk conducted during part of FY2012 and FY2013 (B1.2). We evaluated the data confidence for drug from each study and then combined these scores to provide an overall data uncertainty score for B1.

Table A6.10 Confidence scores for B1.1

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
One or more bulk tank milk samples examined during the NMDR study period 2000-20013 were found positive for the drug	9
One or more bulk tank milk samples examined during the NMDR study period 2000-20013 were found positive for the drug class and no more specificity with regard to the specific drugs detected was available	5
The animal drug or drug class were not reported as detected in bulk tank milk during the study period 2000-20013	1

Table A6.11 Confidence scores for B1.2

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
One or more bulk tank milk samples examined during the FY2012-FY2013 FDA/CVM drug residue sampling study were found positive for the drug/metabolite and the drug level was above the FDA limit in one or more samples	9
One or more bulk tank milk samples examined during the FY2012-FY2013 FDA/CVM drug residue sampling study were found positive for the drug/metabolite but the drug level was not above the FDA limit in one or more samples	7
The drug/metabolite was not found positive in any of the bulk tank milk samples examined during the FY2012-FY2013 FDA/CVM drug residue sampling study	5
No bulk tank milk samples were examined for the presence/absence of the drug/metabolite during the FY2012-FY2013 FDA/CVM drug residue sampling study	1

The confidence score for B1 reflects confidence in each of the three data sources (factors) informing the sub-criterion and agreement among the data sets.

Table A6.12 Confidence scores for overall B1

Level and type of evidence	Confidence Score
Sum of data confidence scores for B1.1 and B1.2 > 10 (*e.g.,* 9+5)	9
Sum of data confidence scores for B1.1 and B1.2 > 5 (*e.g.,* 5+1)	5
Sum of data confidence scores for B1.1 and B1.2 ≤ 5 (*e.g.,* 1+1)	1

- **Animal Drug Data Uncertainty Score for B2**

The ranking score for B2 was derived from (B2.1) the animal drug approval status in the United States and (B2.2) drug persistence in the milk. The animal drug approval status is known, so the confidence scores assigned to each drug in B2.1 was 9. The B2.2 data confidence score for each drug was determined as below.

Table A6.13 Confidence scores for B2.2

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
Drug persistence estimated by FDA drug persistence data	9
Drug persistence estimated by FARAD drug persistence data	5
Drug persistence data from a source other than FDA or FARAD or drug persistence data not available	1

The confidence score for B2 reflects confidence in each of the two data sources (factors) informing the sub-criterion and agreement among the data sets.

Table A6.14 Confidence scores for overall B2

Level and type of evidence	Confidence Score
Sum of data confidence scores for B2.1 and B2.2 > 10 (*e.g.,* 9+5)	9
Sum of data confidence scores for B2.1 and B2.2 > 5 (*e.g.,* 5+1)	5
Sum of data confidence scores for B2.1 and B2.2 ≤ 5 (*e.g.,* 1+1)	1

- **Animal Drug Data Uncertainty Score for B3**

The risk ranking score for B3 was derived from expert responses to questions evaluating B3.1, the likelihood of the animal drug getting into the lactating dairy cow's milk, and B3.2, the likelihood of the drug getting into the bulk-tank milk.

Data confidence scores for each drug were also derived from the answers to the two questions, but in this case, scored on the basis of the proportion of experts that provided a quantitative response to each question, PRC, and the level of agreement among those experts (as measured by the standard deviation of the respondents scores for each drug), SDC.

The standard deviation confidence score (SDC), and the proportion of respondents confidence score (PRC) were summed and used to determine the confidence score for each drug as follows:

Table A6.15 Confidence scores for B3.1 (likelihood of the animal drug getting into the lactating dairy cow's milk), and B3.2 (likelihood of the drug getting into the bulk-tank milk)

Strength and quality of evidence associated with the datum for a given animal drug	B3.1, B3.2 Confidence Score
If (SDC+PRC) > 10	9
If 10 ≥ (SDC+PRC) > 8	5
If 8 ≥ (SDC+PRC)	1

- SDC is the standard deviation confidence score,
- PRC is the proportion of respondents confidence score.

The confidence score for B3 reflects confidence in each of the two data sources (factors) informing the sub-criterion and agreement among the data sets

Table A6.16 Confidence scores for overall B3

Level and type of evidence	Confidence Score
Sum of data confidence scores for B3.1 and B3.2 > 10 (*e.g.,* 9+5)	9
Sum of data confidence scores for B3.1 and B3.2 > 5 (*e.g.,* 5+1)	5
Sum of data confidence scores for B3.1 and B3.2 ≤ 5 (*e.g.,* 1+1)	1

Overall Animal Drug Data Uncertainty Score for Criterion B

The data confidence score for each of the 99 drug formulations considered in the model were derived from the scores for each of the three sub-criteria as follows

Table A6.17 Confidence scores for overall B

Level and type of evidence	Confidence Score
Sum of data confidence scores for B1, B2, and B3 > 21 (*e.g.,* 9+9+5)	9
Sum of data confidence scores for B1, B2, and B3 > 9 (*e.g.,* 5+5+1)	5
Sum of data confidence scores for B1, B2, and B3 ≤ 9 (*e.g.,* 5+1+1)	1

C. Animal Drug Data Confidence Score for Criterion C

The risk ranking score for each animal drug associated with criterion C was derived from scores for each of two sub-criteria: (C1) the apparent partition coefficient and (C2) magnitude of consumption of dairy products. Below, we describe the uncertainty score assigned to data used in each of these two data sub-criteria and the scoring matrix used to determine an overall data uncertainty score for criterion C.

- **Animal Drug Data Uncertainty Score for C1**

Two different factors informed the uncertainty score for C1: Heat Degradation, and Partitioning Behavior. We are confident with the Product Composition. The data confidence for each drug associated with each of these factors was evaluated and then combined to provide an overall data confidence score for C1.

The factor C1.1 is determined by the partitioning/distribution behavior of the drug and the composition of the milk product. For the purposes of this uncertainty analysis, we assume the milk product composition is constant and known (as it is defined by the CFR) and assign uncertainty associated with this factor to the data describing the partitioning/distribution behavior of the drug.

Partitioning Behavior:

Table A6.18 Confidence scores for partitioning behavior

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
Experimental data available for the animal drug quantitatively describing the partitioning/distribution of the drug among milk components/products produced processing (*e.g.*, separation of cream from skim portion of the milk)	9
Experimental data available for the animal drug class quantitatively describing the partitioning/distribution of the drug among milk components/products produced processing (*e.g.*, separation of cream from skim portion of the milk)	5
No experimental data available for the animal drug or drug class quantitatively describing the partitioning/distribution of the drug among milk components/products produced processing (*e.g.*, separation of cream from skim portion of the milk). Sub-criterion score derived from apparent partition coefficient value calculated from published log P and pKa values.	1

Heat degradation

The confidence score for Heat Degradation is determined by the confidence in the heat stability of each drug, according to the following table.

Table A6.19 Confidence scores for heat degradation

Strength and quality of evidence associated with the datum for a given animal drug	Confidence Score
Experimental data available for the animal drug quantitatively describing the decrease in concentration of the drug during heating	9
Experimental data available for the animal drug class quantitatively describing the decrease in concentration of the drug during heating	5
No experimental data available for the animal drug or drug class quantitatively describing the decrease in concentration of the drug during heating.	1

Confidence scores for C1

The overall confidence score for sub-criterion C1 is calculated as a score derived from the following table:

Table A6.20 Confidence scores for C1

Level and type of evidence	Confidence Score
Sum of data confidence scores for PBC and HDC > 14 (*e.g.*, 9+5)	9
Sum of data confidence scores for PBC and HDC > 6 (*e.g.*, 5+1)	5
Sum of data confidence scores for PBC and HDC ≤ 6 (*e.g.*, 1+1)	1

- PBC is Partitioning Behavior Confidence Score
- HDC is Heat Degradation Confidence Score

- **Animal Drug Data Uncertainty Score for sub-criterion C2**

There is no uncertainty in C2, the Magnitude of consumption of milk and milk products., which is the magnitude of consumption. As such each drug has a confidence score of 9.

- **Animal Drug Data Uncertainty Score for Criterion C**

The overall confidence score for criterion C is calculated as a score derived from summing the confidences for C1 and C2 according to the following table:

Table A6.21 Scoring matrix for overall animal drug data confidence score for criterion C

Level and type of evidence	Confidence Score
Sum of data confidence scores for C1 and C2 > 14 (*e.g.*, 9+5)	9
Sum of data confidence scores for C1 and C2 > 6 (*e.g.*, 5+1)	5
Sum of data confidence scores for C1 and C2 ≤ 6 (*e.g.*, 1+1)	1

D. Animal Drug Data Confidence Score for Criterion D

Drug-related data that are used in criterion D include (1) hazard value and (2) whether the drug is a known carcinogen; data for only (1) is considered to be uncertain so the data uncertainty score for criterion D is assigned the data uncertainty score for the hazard value.

APPENDIX 6.4: RESULTS: MODEL STRUCTURE UNCERTAINTY

To characterize the uncertainty associated with model structure, we compared results for different scenarios that include different model structure choices.

A. Criterion Weights

We evaluated the sensitivity of the results on criterion weights by comparing model results using expert-assigned criterion weights to a scenario using uniform criterion weights. The scores and ranking of drugs derived from this scenario (using uniform criterion weights) are illustrated in Figure A6.23. A major difference between the model results and the uniform weights scenario was resolution; fewer differences in rank among drugs were identified when assigning uniform weights. The reduced resolution arose from the fact that sets of criterion scores that are permutations of one another (*e.g.,* [5,5,9,9] and [9,5,5,9]) were indistinguishable when using uniform weights.

This "uniform criterion weights" scenario also led to a significant increase in score for four drugs: nitrofurazone, chloramphenicol, phenylbutazone, and furazolidone, relative to the scores derived from the model scores determined using expert-assigned criterion weights ("Model Results"). These four drugs were assigned the highest hazard scores among all drugs, because no hazard value could be established. The increase in scores and shift in rank for these drugs in this "uniform criterion weights" scenario compared with the original model, arose from the larger weight given to the score for criterion D (the potential for a health hazard, given exposure) and smaller weights applied to the scores for criterion A and criterion B in this scenario. The increase in score for these drugs resulted in only a small change in the ranking of the 54 drugs; chloramphenicol and phenylbutazone increased in rank with a consequent decrease in rank for ceftiofur and oxytetracyline (the pairs of drugs switch positions in the ranked list). While assigning uniform criterion weights in multicriteria-based ranking models is a default commonly explored, in the future, a better characterization of uncertainty associated with these weights would be obtained by comparing results using second independently determined sets of expert weights.

We also explored the impact data set selection on the drug ranking. In particular, we explored the scenario in which only the USDA and Sundlof *et al*. data were used to determine the LODA score based on surveys, A1, *i.e.,* the expert opinion data was not included. When excluding expert opinion in A1, the overall scores and rank of five drugs were impacted (see Figure A6.24). More specifically, the overall scores for amikacin, doramectin, kanamycin, spectinomycin, and tetracycline were reduced and consequently, the rank of each of these drugs, among the 54 drugs evaluated by the model, was lower. The experts indicated that the likelihood of use of amikacin, doramectin, kanamycin, spectinomycin, and tetracycline was larger than estimated from the earlier published studies. The scores for all other drugs were identical to the

values obtained with the full model. This scenario identified the information added by inclusion of the expert opinion but also demonstrated that for most of the drugs, data from the earlier studies were in agreement with expert opinion, at least in terms of the scoring scheme used in this multicriteria-based ranking model.

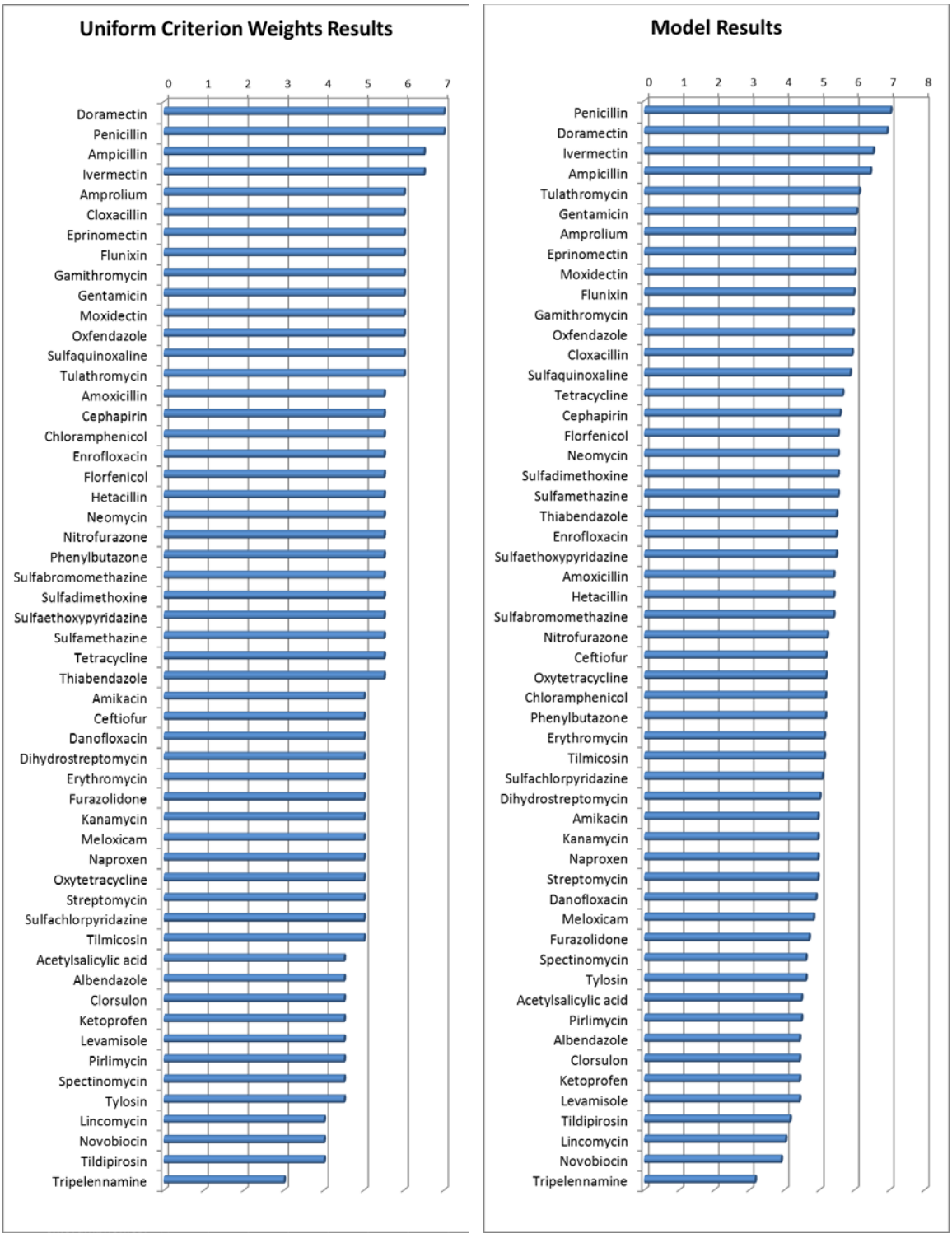


Figure A6.22 Model structure uncertainty: Comparing scores and ranking of the 54 drugs evaluated by the multicriteria-based ranking model when using uniform criterion weights or expert-determined criterion weights (labeled "Model Results").

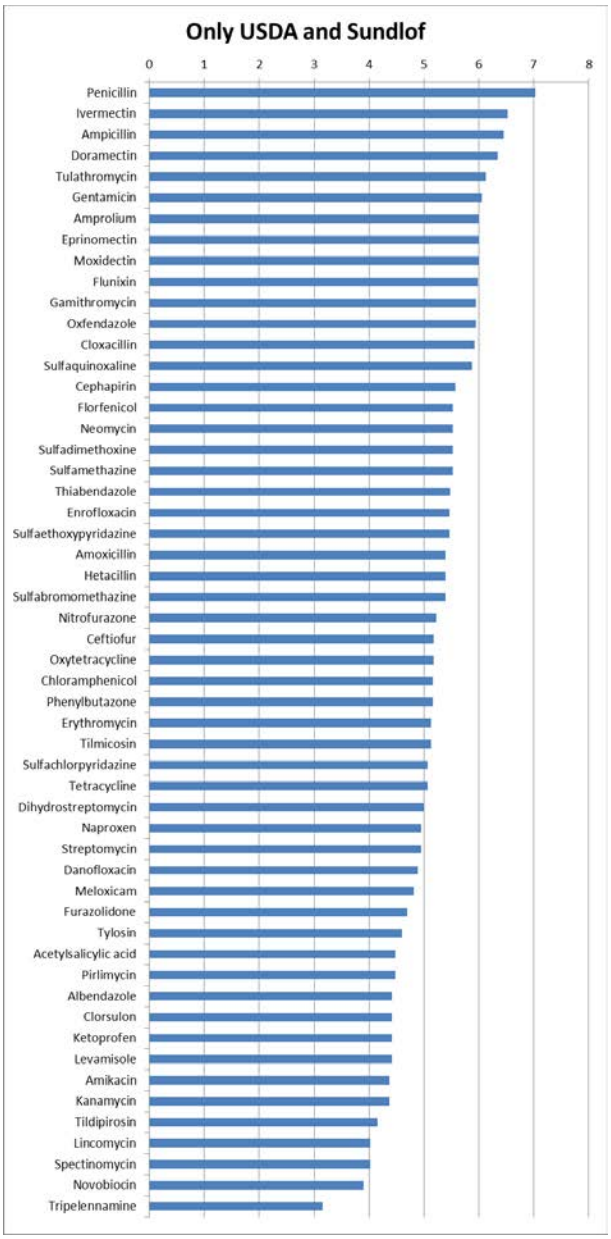


Figure A6.23 Model structure uncertainty: Scores and ranking of the 54 drugs evaluated by the multicriteria-based ranking model when only USDA and Sundlof et al. data were used to determine the LODA score based on surveys, A1 (that is, excluding expert opinion data).