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The National Residue Program for Meat, Poultry, and Egg Products

An evaluation

The Pew Charitable Trusts

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Any opinions and conclusions expressed herein are those of The Pew Charitable Trusts and do not necessarily represent the views of the above individuals.

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Overview

Contamination of the nation's food chain—specifically meat and poultry products—can occur through exposure to the residues of drugs and pesticides used in agricultural production and also via industrial chemicals and other environmental contaminants. In order to protect consumers from hazardous levels of these compounds, the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA) administers the National Residue Program (NRP), a science-based system designed to assess drug and chemical exposure in various food-producing species.

The FSIS is responsible for the safety of domestic and imported meat and poultry products, ensuring that they are free of adulterants and a wide range of biological and chemical contaminants. Through the NRP, FSIS inspectors conduct thousands of tests each year and, where possible, compare the results with tolerance levels (i.e., the maximum levels allowed by law). These limits are established by the Food and Drug Administration (FDA) or the Environmental Protection Agency (EPA) during the drug approval or pesticide registration process. The selection of compounds included in the NRP's sampling plans is decided by the Surveillance Advisory Team (SAT), consisting of representatives from the FSIS, FDA, EPA, Centers for Disease Control and Prevention (CDC), and the USDA's Agricultural Marketing Service and Agricultural Research Service. Chemical compounds tested in this program include approved and unapproved veterinary drugs, pesticides, and environmental contaminants.

The FSIS has the authority to take enforcement action (e.g., fines, facility closures) against businesses that market products containing potentially hazardous levels of harmful chemicals. In addition, violations are reported to the EPA and FDA; the latter agency has on-farm jurisdiction and investigates producers linked to residue violations with cooperation from state agencies. Repeat violators are included in the Residue Repeat Violator List maintained by the FSIS, which is a resource for potential buyers of livestock.

The Pew Charitable Trusts undertook a study to assess the process by which the NRP tests for veterinary drugs and other chemical compounds as part of a larger effort to determine risks in the U.S. meat and poultry supply. This study explored the following questions: (1) Is the NRP monitoring the compounds most important to public health? (2) If not, what changes should be made to ensure that monitoring prioritizes these compounds? (3) How does the system incorporate new scientific evidence and address emerging hazards?

The report found major deficiencies in data transparency and the quality of reporting on the decision-making processes underlying compound selection, the documentation of the sampling plans, and the reporting of sampling results. The study also highlights concerns about the NRP's ability to effectively monitor or respond to emerging risks.

Pew's analysis raised questions about whether the NRP consistently prioritizes the selection of compounds based on their public health risk to consumers. Some compounds that experts agree pose a significant public health hazard, such as dioxins and certain heavy metals, are not tested for routinely, while others posing little risk are regularly included in sampling plans. Other considerations may warrant the inclusion of a compound with relatively low public health risk, but the NRP's sampling plans and other public documents do not provide such information, making it impossible to understand whether a compound was included based on such considerations. Likewise, in many cases, the program offers no justification for decisions to exclude drugs such as dexamethasone and dipyrone, which scored higher in the NRP's published risk assessment than several monitored compounds. Finally, decisions to include some compounds, such as avermectins, are based at least in part on studies that are outdated or were not peer-reviewed.

A Note on the Methodology

Sources of data for this evaluation included a close examination of: (1) the past six editions of the USDA FSIS Residue Sampling Plan, known as the Blue Book; (2) the past five editions of the Residue Sample Results, known as the Red Book; (3) FSIS Directive 10,800.1 on residue sampling, testing, and other NRP verification procedures for meat and poultry products; (4) FSIS guideline CLG-MRM1.04 for the screening for and confirmation of animal drug residues; (5) FSIS guideline CLG-PST5.06 for the screening for pesticides; (6) the FSIS' report on the most recently available dioxin survey (for fiscal year 2013); and (7) the results of the FSIS' livestock slaughter establishment residue questionnaire. The literature cited by these documents was analyzed, as were any original data sources related to the methods and metrics used to determine acceptance or rejection of specific chemical levels. Federal Register notices, and other publicly available FSIS publications relevant to the NRP, were also considered. Results of the 2012 European Union targeted sampling for bovines, pigs, poultry, and eggs* were also reviewed, as were expert opinions published by relevant national or international standard-setting authorities, such as the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee of Food Additives, the European Medicines Authority, and the European Food Safety Authority, and peer-reviewed journals. Relevant assessments of the National Residue Program that were performed by the National Academy of Sciences, the USDA's Office of the Inspector General, and the U.S. Government Accountability Office were also considered. A draft of this evaluation was shared with the FSIS, FDA, and EPA in early November 2015, and the agencies provided comments and materials that informed the final report. Of note, the FSIS published the 2013 and 2014 Red Books in the last week of December 2015, as this report was being prepared for publication. Some of the data transparency deficiencies identified in the 2012 Red Book have been corrected in these latest publications. To ensure maximum transparency, these instances are clearly highlighted in the final published report.

The following text will summarize and highlight selected aspects of the study, while a comprehensive and systematic analysis of all considered compounds is provided in Appendices A through D. Documents supplied by the agencies to support their responses to Pew's draft are available in supplemental Appendices E through H, which can be downloaded from the report Web page.

* European Commission, "Residues of Veterinary Medicinal Products—Control and Monitoring," Council Directive 96/23/EC (2012), http://ec.europa.eu/food/food/chemicalsafety/residues/control_en.htm.

In order to address the program's limitations, this report makes nine recommendations for strengthening the NRP:

1. Provide transparent documentation and reporting of sampling plans and results.
2. Consistently apply the NRP's public health-based risk criteria to all compounds considered for monitoring, and base decisions first and foremost on the direct risk to consumers through food consumption. If clear reasons prevent this from being achieved for all compounds, be transparent and explicit about this limitation. Regularly revisit decisions to monitor compounds of comparably lower public health risk.
3. Clearly acknowledge and explain when a compound is included in the NRP for reasons other than direct public health risks, such as enforcing legal requirements for pesticide use.
4. Monitor compounds that pose an important public health risk even if such action presents regulatory or technological challenges (e.g., the lack of an identified tolerance level, difficulty detecting the presence of a heavily metabolized drug).
5. For compounds of important public health risk but without established tolerance levels from the FDA or EPA, consider using applicable guidelines, such as the Codex Alimentarius' maximum residue limits.
6. Adopt standards for strength of scientific evidence and minimum data quality.
7. Develop a system to routinely incorporate new scientific evidence and evaluations of relevant technological advancements.
8. Provide specific justifications, based on dietary exposure risk, for the inclusion or exclusion of all considered compounds.
9. Include compounds that the NRP determines pose an emerging and important public health threat using tools such as rapid risk assessments or expert panels, and clearly document the assessment of new and emerging risks. Base decisions on the most rigorous scientific analysis available and re-evaluate them as more data become available.

Pew's assessment builds on previous examinations of the NRP published since 2010 by USDA's Office of the Inspector General, a National Academy of Sciences committee, and the Government Accountability Office. The report also benefited from the insights and expertise of four external peer reviewers who are trained in toxicology or other relevant disciplines. The FSIS, EPA, and FDA officials who oversee the NRP were given an opportunity to review the report before publication.

Findings: Assessment of the NRP

Residues of drugs, pesticides, and environmental contaminants in meat and poultry products can cause acute and chronic health problems. For nearly 50 years, the NRP has monitored chemicals in these products. This report assesses the program's effectiveness in monitoring residues of compounds in meat and poultry products that pose an important risk to public health. The report focused on a few specific areas and methodologies that are representative of the types of justifications and data being used in the NRP's selection process (they are listed below). These highlighted areas were selected based on a comprehensive evaluation of the NRP (see the appendices) and emphasize factors that could have significant effects on whether residues were detected and, more importantly, on how the detection of a residue could affect public health.

Based on this analysis, Pew found deficiencies in data transparency and the quality of reporting in: (1) the decision-making processes that determine which compounds should be included in the NRP, (2) the documentation of sampling plans, and (3) the reporting of sampling results.

The report found that the NRP does not consistently prioritize the selection of compounds based on their health risk to consumers. As a result, some compounds that experts agree pose an important hazard to public health are not tested for routinely, yet others posing little, if any, public health risk are regularly included. While considerations other than public health risk, such as the enforcement of legal requirements on pesticide use, may in some cases merit the inclusion of compounds in the NRP, such justifications are not specified in the program's residue sampling plan, and no evidence exists that these considerations motivated the inclusion of compounds with comparably low public health risk.

This report identified the following limitations in the NRP:

- Some substances that experts agree are of importance to public health are not included, particularly those without established tolerances or action levels in the U.S., even if the dose at which adverse health effects are expected is known. This occurs even with some compounds widely accepted as a public health threat, for which comparable regulatory limits have been set by other competent national or international standard-setting authorities.[1]
- The NRP has not set strict standards regarding data quality and documentation (including the need to incorporate relevant new scientific data), and there are no clearly established, coherent, transparent, and consistently used criteria on which to base decisions about which compounds should be included.
- In some cases, decisions by the NRP about which compounds to include are based on criteria other than actual risk to the consumer at the exposed level (e.g., basing decisions only on status under the Animal Medicinal Drug Use Clarification Act [AMDUCA] instead of using the risk-based criteria established by the SAT).
- Compounds that experts agree may pose a serious but emerging threat to public health are not included or considered (e.g., brominated flame retardants, byproducts of biofuel production, nanomaterials).

Background on the NRP

Established in 1967, the NRP monitors domestic and imported food animal products for the presence of chemicals, including veterinary drugs, pesticides, and environmental contaminants.[2] Two interagency groups, the SAT and the Interagency Residue Control Group (IRCG), have been established as a way for the USDA, EPA, and FDA to communicate about and coordinate residue monitoring. The IRCG meets monthly to address ongoing issues concerning the NRP.[3] The SAT meets annually with the primary function of establishing the scheduled sampling plan for the NRP for the next year. The selection of compounds included in the NRP's sampling plan is decided by the SAT, consisting of representatives from the FSIS, FDA, EPA, CDC, and the USDA's Agricultural Marketing and Agricultural Research Services. Chemical compounds tested in this program include approved and unapproved veterinary drugs, pesticides, and environmental contaminants. (See Appendix A.)

The goals and methods pertaining to how compounds are selected for the NRP are described in the yearly USDA FSIS Residue Sampling Plan, also known as the Blue Book. The results of these analyses are published quarterly and summarized annually in the Residue Sample Results, or the Red Book.

Many compounds included in the NRP have established tolerances or "action levels" that place limitations on the amount of a compound in a food product. Some compounds have a tolerance of zero because the compounds pose such a big health risk that no amount of residue is permitted in food, and other compounds have not been reviewed by regulatory agencies and therefore no tolerances have been set. Action levels may be determined in the absence of an established tolerance and signify concentrations below which no regulatory enforcement action will be taken.[4] The NRP records violations of tolerances as well as positive findings at lower, nonviolative levels.[5]

The EPA sets the tolerances for pesticides, and FDA sets them for veterinary drugs. Typically, tolerances are determined as part of a drug approval or pesticide registration process and may be revised as new information becomes available. Tolerances are listed in the U.S. Code of Federal Regulations (Title 40 for pesticides and Title 21 for veterinary drugs). Some substances are prohibited from human food entirely and so have a tolerance of zero. These include, for example, chlorhexidine in veal, carbomycin in chicken, and hygromycin B in swine and poultry.[6]

Before a pesticide can be applied to any food crop, the EPA must review its toxicity and exposure data and, if appropriate, establish a tolerance for the product's residues. The agency will set a tolerance only if it finds a pesticide as used poses a "reasonable certainty of no harm" to human health. If the public health risk is deemed unacceptable, a tolerance will not be set and the pesticide may not be used for the proposed purpose. When a pesticide is used according to label instructions, residues in food at the time of consumption are unlikely to exceed the tolerance. The EPA considers the following factors when setting tolerances: the toxicity of both the product and the byproducts created as it breaks down; frequency of application and amount used; residue levels on crops at the time of sale or consumption; and all possible exposure routes for the pesticide (i.e., consumption of all crops on which the pesticide is used, exposure from drinking water, and exposure in homes).[7] Conversely, if a review convinces the agency of a product's strong safety profile, the EPA may exempt the pesticide from the tolerance-setting requirement.

> Typically, tolerances are determined as part of a drug approval or pesticide registration process and may be revised as new information becomes available.

FDA sets tolerances for veterinary drugs destined for use in food-producing animals as part of the drug's approval process. The agency considers the following, among other factors, when setting tolerances: the toxicity of the compound; safety data related to possible microbial resistance; data on the presence, distribution, breakdown, and excretion of residues in food-producing species; and development of a verified analytical method for detecting a residue. FDA uses these data to calculate a "safe concentration": the maximum amount of a residue in any edible tissue that can be consumed every day without exposing the consumer to amounts in excess of the acceptable daily intake. The agency determines a tolerance and an appropriate interval between the last administration of a drug and slaughter so that residues in edible tissues are most likely below safe concentrations if the drug is used according to label instructions.[8]

When a food animal's tissue sample contains residues in concentrations that exceed a tolerance, the FSIS makes a decision about whether to condemn and dispose of the source product; if the product has already entered the marketplace, the FSIS conducts an assessment of public health risk and may request a recall. All tolerance violations indicate that the amount of residue present exceeds maximum legal limits allowed in food. However, some violations pose a greater risk to public health than others (e.g., because of the type of adverse effects they cause or the compound's potency), and their detection should be prioritized if sampling resources are limited.[9] The presence of a residue at levels below a tolerance does not violate the law but can provide valuable information about, for example, the actual use of a veterinary drug on farms or feedlots.

More on Tolerances

In December 2015, as this report was being prepared for publication, the FSIS issued a Federal Register notice seeking public comments on the agency's proposed process for responding to sampling results that reveal the presence of compounds for which there are no regulatory tolerances, such as environmental contaminants, heavy metals, industrial chemicals, and mycotoxins. In short, the FSIS will calculate *de minimis* levels (i.e., concentrations below which any risk to public health is negligible) based on health-based guidance values (e.g., reference doses, acceptable daily intakes) that are likely without appreciable deleterious health impacts. Agencies such as the EPA, the U.S. Agency for Toxic Substance and Disease Registry, and the Joint FAO/WHO Expert Committee on Food Additives are publishing such guidance values for chemical compounds.

Through a risk assessment approach that considers, among other factors, dietary exposure, the FSIS indicates that it will calculate the maximum concentration of these substances that can be present in the tested food without the total dietary exposure exceeding the health-based guidance values. NRP test results will then be compared to *de minimis* levels, and the decision to include or exclude substances in subsequent sampling years will be based, at least in part, on these findings. In addition, if test results are above *de minimis* levels, the agency may notify state and federal partners to initiate traceback and mitigation options. (See supplemental Appendix E for supporting documentation on the process for setting the *de minimis* levels provided by the FSIS.)

In addition to guidance values, the notice also clarified that the FSIS may identify potential compounds of concern through scientific literature reviews, expert elicitations, and collaboration with federal, state, and international partners as well as other approaches, such as communications with stakeholders and trade partners.* While this approach shows promise, time will tell if it is an effective strategy for addressing compounds without established tolerances.

* For more on the FSIS' notice, see Food Safety and Inspection Service, "National Residue Program: Monitoring Chemical Hazards," Docket No. FSIS-2015-0002, 80 Fed. Reg. 249 (Dec. 29, 2015), http://www.fsis.usda.gov/wps/wcm/connect/0387871c-201a-45a5-854e-4e717788baed/2015-0002.pdf?MOD=AJPERES.

How the NRP works

According to the 2014[10] Blue Book,[11] approximately 33 million cattle, 112 million swine, and nearly 9 billion poultry are slaughtered in the U.S. each year, yielding close to 110 billion pounds of meat (i.e., "dressed meat," after partial butchering and removal of internal organs and undesirable or inedible portions). In addition, approximately 3 billion pounds of meat are imported into the country each year.[12] The FSIS collects samples of meat and poultry from slaughter plants and at ports of entry throughout the United States and analyzes them against the established tolerances. Violations are referred to FDA for investigation and enforcement action at the farm and producer level.

The NRP operates a three-tiered sampling system:

- Tier 1. Sampling follows an established sampling plan created by the FSIS. In fiscal year 2015, for example, the FSIS aimed to collect up to approximately 800 random samples in each of nine animal production classes—beef cows, bob veal (very young calves), dairy cows, steers (castrated male cattle), heifers (young female cattle before the first calving), market hogs, sows, young chickens, and young turkeys—with multiple compounds analyzed in each sample. For tests using the multiresidue method (described on page 9), the target sample size is 400 for steers and heifers and 800 for the remaining production classes; for most tests to detect other compounds, smaller sample sizes are chosen.[13]

  The FSIS recently increased the targeted number of samples collected in the scheduled sampling. According to the 2014 and 2015 Blue Books, the new targeted number of samples was selected based on test sensitivity, so that a violation present, and randomly distributed, in a population at a rate of 1 percent would be detected (i.e., yield at least one positive sample) with 99 percent probability (violations present at a lower rate would be detected with lower than 99 percent probability). Appendix D provides more details about this calculation and highlights potential data reporting concerns with the FSIS' justification for the sample size as provided in the Blue Books. In 2013, the targeted number of samples was 600, and in 2012 it was fewer than 500, with varying numbers of samples for different production classes and compounds.[14]
- Tier 2. Sampling at the production level, which includes samples taken by plant inspectors and exploratory sampling at processing plants. For 2014, these included between 150 and 300 samples collected from sheep and goats and tested for different antimicrobial drugs,[15] and in 2015 they included an additional 100 samples of old breeder turkeys analyzed for certain veterinary drugs and metals.[16] Tier 2 sampling is meant to provide data for specific compound classes, follow-up investigations in response to the potential misuse of drugs and/or exposure to environmental chemicals, and information for future sampling plans.
- Tier 3. Targeted sampling at the herd or flock level, with goals similar to those of the tier 2 exploratory program but focused on a farm or geographical region. Tier 3 sampling is a new component of the NRP and was not yet in place for the 2014 NRP, the most recent year for which sampling results are available.

> The FSIS recently increased the targeted number of samples collected in the scheduled sampling.

The Role of the FSIS Inspector

This report focuses on the activities conducted by FSIS headquarters staff, such as designing the NRP sampling plan and reporting its results.

FSIS inspectors who work in slaughter and processing facilities play an important role in the NRP, particularly in implementing the tier 2 sampling program. They initially identify animals they deem more likely to contain residues in excess of established tolerances and then sample and test them. The selection of animals for residue testing is based, for example, on findings during antemortem or postmortem inspections (e.g., signs of recent illness or injury) or on a producer's history of residue violations.

To assess factors that may affect the performance of in-plant screening tests, the FSIS sent a questionnaire in 2014 to the public health veterinarians in its inspection force, which identified several obstacles to effective residue testing, including the need for more specific instructions, staffing shortages, and the challenge of balancing residue testing with other inspection responsibilities.*

* For more on the questionnaire, see Food Safety and Inspection Service, "FSIS Livestock Slaughter Establishment Residue Questionnaire Results," http://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-and-reports/chemistry/residue-questionnaire-results.

During federal fiscal year 2014—which began Oct. 1, 2013, and ended Sept. 30, 2014—the NRP's domestic tier 1 program collected 6,066 residue samples and found 12 violations in 10 samples (0.2 percent). The 10 positive carcasses were bob veal (8), beef cows (1), and mature sheep (1). Of the 12 residue violations, all but two were due to veterinary drug residues, primarily antibiotics and antiparasitic drugs. The inspector-generated (tier 2) program performed 210,705 screening tests—210,516 Kidney Inhibition Swab (KIS) tests and 189 tests under Collector-Generated (COLLGEN), Show Animals (SHOW), and State or Government Agency Testing (STATE)—and detected a total of 1,408 lab-confirmed residue violations (0.7 percent), again primarily due to veterinary antibiotics.[17]

These numbers are challenging to compare with results for fiscal year 2013, because the program switched from a calendar to fiscal year structure at the end of 2012, and issued a 2013 report covering a nine-month time frame. From Jan. 1 to Sept. 30, 2013, the FSIS collected 4,583 residue samples under the domestic tier 1 program and detected 19 violations (0.4 percent) in 15 samples—10 in bob veal and one each in dairy cows, heifers, steers, market hogs, and sows. The 19 individual violations were due to pesticides and animal drugs, primarily antibiotics. Under the tier 2 program, the FSIS analyzed 170,692 samples—KIS: 170,535 samples; Fast Antimicrobial Screen Test (FAST): 25 samples; COLLGEN: 64 samples; SHOW: 40 samples; and STATE: 28 samples—and detected 1,265 violations (0.7 percent), mostly due to animal antibiotics.[18]

By comparison, in 2012, the NRP's tier 1 domestic sampling program collected 5,838 residue samples and found 17 violations (0.3 percent). (See Appendix D for data quality concerns with the reporting of 2012 sampling results, including the number of samples collected and analyzed. Some of these concerns have been addressed in the

most recent Red Books, which were published after this report had been shared with the regulatory agencies overseeing the NRP.) The inspector-generated tier 2 program collected 214,864 samples—214,654 under KIS or FAST and 210 under COLLGEN, SHOW, or STATE—and found 1,182 violations[19] (0.6 percent).[20] Antimicrobial drugs constituted the majority of violations in scheduled sampling[21] isolated from the kidney and liver tissue where these chemicals are typically present in highest concentrations. The majority of violations in the tier 1 program were found in bob veal, with additional violations in market hogs and beef steers. And in the inspector-generated program (tier 2), the dairy cows and bob veal production classes had the most violations.

In addition to the domestic program, there is a port-of-entry Import Reinspection Sampling Plan, divided into three components: random sampling from a lot, increased sampling as determined by agency management, and intensified sampling when an initial sample fails to meet U.S. requirements. In fiscal year 2014, the import reinspection program analyzed 1,967 samples and detected eight residue violations (0.4 percent). Seven of the violations were due to the antiparasitic drug ivermectin.[22] During the nine months reported for fiscal year 2013, the FSIS collected 817 samples as part of the import reinspection program and detected four violations (0.5 percent). All four residue violations were due to antiparasitic drugs in the class avermectins.[23] In calendar year 2012, 1,299 samples were analyzed as part of the import reinspection program, with no positive samples detected.[24]

Veal and Bob Veal

"Bob veal" is meat from very young calves, up to 3 weeks of age or less than 150 pounds.* In the domestic scheduled sampling, the NRP only tests bob veal, even though meat from older calves (referred to as "veal" and defined as a separate class) is tested in the import scheduled sampling, and even though meat from older calves was included in the inspector-generated sampling.† The type of veal sampled therefore depends, in part, on the type of NRP program. This should be kept in mind when interpreting the data.

* Food Safety and Inspection Service, "Veal From Farm to Table" (2011), http://www.fsis.usda.gov/wps/portal/fsis/topics/food-safety-education/get-answers/food-safety-fact-sheets/meat-preparation/veal-from-farm-to-table/CT_Index.

† Food Safety and Inspection Service, "United States National Residue Program (NRP) for Meat, Poultry, and Egg Products: 2012 Residue Sample Results" (traditionally known as the Red Book) (2014).

The NRP's sampling plan changed significantly in 2012 with the FSIS' adoption of an improved and more sensitive multiresidue analytical method for detecting chemical and drug residues.[25] The new method allows a sample to be simultaneously analyzed for residues of many different drugs in various drug classes, and it is more sensitive than the previous test method.[26] Specific detection limits for the new method differ by compound and tissue type but are generally in the range of between 5 and 500 parts per billion for veterinary drugs, as per CLG-MRM1.03,[27] and between 5 and 50 ppb for pesticides, as per CLG-PST5.06.[28]

The new analytical method has made it feasible for additional chemicals to be included in the NRP. The number of pesticides included in the program nearly doubled between 2014 and 2015. (See Appendix C.) Because the NRP provides no justification for this expansion of testing or the inclusion of the additional compounds, it is

impossible to evaluate whether in some cases pesticides were primarily included because analytical methods can now detect them, rather than because of their risk to public health.

After reviewing a draft of this report, the agencies provided Pew with documents including a prioritized list of pesticides monitored by the NRP. (See supplemental Appendix F.) These materials indicate that other considerations are taken into account in determining whether to include a compound in the scheduled program. These include the previous detection of a compound in meat or poultry muscle or fat samples, and the propensity of the compound to accumulate in fat or muscle (based on its high affinity to fat). Unfortunately, this current prioritization scheme is not explained in the Blue or Red Books or otherwise available to the public. It also differs considerably from the prioritization scheme described in the 2012 Blue Book, the most recent Blue Book to contain a comprehensive description of a prioritization scheme.

The FSIS also reviewed a draft of Pew's report and in response stated that the agency is working with FDA and EPA to develop a new prioritization model. FSIS staff noted that they have participated in discussions about improving the NRP at a National Academy of Sciences meeting, at a meeting of FDA's Food Advisory Committee, and with the National Advisory Committee on Meat and Poultry Inspection.[29] While the agency shared slide presentations that outline potential prioritization models under discussion (see supplemental Appendix G), neither these models nor the FSIS' activities related to updating the NRP are described in the Blue Book or otherwise publicly available.

Sampling Program for Imports

The FSIS expressly states in the Red and Blue Books that when laboratory resources are limited, resource allocation should focus on domestic products because imported ones have been previously inspected in their country of origin. This more relaxed monitoring may be appropriate for countries with strong regulatory systems. However, the list of compounds monitored in a particular country may not align perfectly with those selected by the FSIS. For example, some countries may regularly use chemicals, including adulterants, not normally used in U.S. food production. In fact, most residue violations detected in the import reinspection program since the methodology changed in 2012 were due to avermectins, a class of antiparasitic drugs.*

The FSIS' scarce resources could perhaps be much better marshalled for active, real-time intelligence gathering to determine which chemicals are being used in countries with less-than-active surveillance programs. The USDA and EPA recently received access to a database that lists tolerances by country worldwide, which could aid such information gathering because the existence of a tolerance is indicative of use. In addition, countries determined by the FSIS to have "equivalent" meat and poultry safety standards cannot use substances in exported products that are prohibited by the agency.

* Food Safety and Inspection Service, "United States National Residue Program (NRP) for Meat, Poultry, and Egg Products: 2013 Residue Sample Results" (traditionally known as the Red Book) (2015); Food Safety and Inspection Service, "United States National Residue Program (NRP) for Meat, Poultry, and Egg Products: FY2014 Residue Sample Results" (traditionally known as the Red Book) (2015).

Analysis of the NRP

General concerns about data transparency and reporting

This report found major deficiencies in data transparency and the quality of reporting in both the sampling plan description and the reporting of results, even though some concerns with the reporting of sampling results have been addressed in the most recent Red Books, released by the FSIS after a draft of this report was shared with the responsible regulatory agencies. The NRP does not provide a transparent explanation of how an initial list of drugs, pesticides, and environmental contaminants is created for consideration, exactly how the compounds ultimately included were selected, and why others were not included. Although Pew acknowledges the logistical challenges of documenting discussions and decision-making that occur in nonpublic venues, transparency should be a foundational characteristic of the NRP, and a variety of approaches may be employed to overcome the logistical challenges, such as holding public meetings or creating public documents that summarize the SAT decision-making process in sufficient detail to provide adequate transparency. The important negative consequences of the lack of transparency are discussed at length in the next section of this report, which examines specific limitations of the NRP. However, transparency issues were not limited to the selection process; they also include the description of the sampling plan and the reporting of sampling results. (See Appendix D.) These issues complicated the evaluation of sampling plans and the interpretation of sampling results, and they raise fundamental concerns.

Adequacy of the compound selection

By definition, a residue violation indicates that the maximum level allowed by law has been exceeded.[30] However, some violations pose a greater public health threat than others.

One of the NRP's stated goals is to identify and test for residues of compounds that pose a particularly important public health risk. Specifically, "FSIS selects compound classes for sampling from the list of prioritized veterinary drugs based on the relative public health concern."[31] Notably, other considerations such as the enforcement of legal requirements on pesticide use may also provide a rationale for inclusion of compounds into the NRP. While this rationale may be justified, transparency dictates that it must be clearly stated if and when it applies, in order to differentiate this case from the inclusion of compounds based on direct public health concern.

Most compounds included in the program meet the public health risk standard. For example, the program tests for residues of drugs such as penicillin and other beta-lactam antibiotics, which can prompt serious allergic reactions. (See Appendix A.) The NRP also tests for a variety of other chemical compounds that may cause serious adverse reactions in humans. (See Appendix B.) These include, for instance, beta-agonists, such as clenbuterol, that can lead to an increase in blood pressure and heart rate as well as the exacerbation of asthma. Clenbuterol residues in meat have repeatedly caused food poisoning,[32] underscoring the potential human health impact of these residues.

Also rightfully included in the NRP is chloramphenicol, an antimicrobial drug that can lead to potentially fatal aplastic anemia, a very serious blood disorder caused by the body's sudden inability to produce red and white blood cells as well as platelets. It leads to a number of very severe symptoms including heightened susceptibility to infection and propensity for bleeding in susceptible individuals, even at extremely low exposure levels.[33] Similarly included are a variety of drugs, pesticides, and environmental contaminants that are known or suspected carcinogens, such as nitrofurans, carbadox, and chlorinated hydrocarbons; these may conceivably pose a human health risk at the concentrations encountered in food. (See Appendix B.)

Not all sampling decisions are based on direct human health effects, however. For example, the NRP regularly samples for antimicrobial residues, as clearly stated in the rationale provided in the Blue Books, because of their potential to induce antimicrobial resistance in bacteria present in or on the exposed animals, which can potentially be passed to humans.[34] (See Appendix B.) Public health concerns about antimicrobial resistance development are distinct from the toxicity concerns associated with the other compounds in the NRP. In the latter case, the ingestion of residues in food can directly cause adverse effects such as organ damage or tumor development. In the former case, the presence of drug residues can select for resistant bacteria in the food, on the farm where the animals were reared, or in the environment. This can ultimately make infections of humans with foodborne or other pathogens more severe and difficult to treat. Public health risks posed by the development of antimicrobial resistance are different from the toxicity concerns associated with the other compounds included in the NRP. These differences have to be acknowledged in the sampling plan description and considered in any risk-based ranking of compounds for inclusion.

A number of additional compounds, such as dioxins and certain heavy metals, which are included in the European Union monitoring program because of their risk to public health, are not routinely incorporated into the NRP, according to the Blue Books. As indicated in these resources, some of these compounds were considered, but ultimately not included; a clear rationale for this decision is, in many cases, not provided. Other compounds, such as copper or mercury, were not even considered for inclusion in the NRP, based on information in the Blue Books.[35] Notably, the 2013 and 2014 Red Books list 17 metals detectable by a "metals method," including copper, cadmium and lead but not mercury. Unfortunately, this information is not reflected in the 2013, 2014, or 2015 Blue Books.

In the Blue Books, no rationale is provided for how veterinary drugs were selected for consideration in the NRP's scheduled sampling, nor is the list of pesticides and environmental contaminants considered for inclusion provided.[36] In additional cases, no rationale is provided for the appropriate inclusion of compounds such as certain hormones and pesticides such as carbamates and neonicotinoids. (See Appendix A.) Although the inclusion of many of these compounds in the NRP is justified by their public health risks,[37] the lack of an explicit justification for inclusion in the NRP raises transparency concerns and limits the ability to evaluate the SAT's decisions about which compounds to include.

> Public health risks posed by the development of antimicrobial resistance are different from the toxicity concerns associated with the other compounds included in the NRP.

Specific concerns about the NRP

The NRP does not consistently prioritize sampling based on public health risk to consumers; therefore, some compounds that experts agree pose an important risk to public health are not tested for routinely, yet other compounds that pose little, if any, public health risk are routinely included. While factors other than direct risk to the consumer may be valid considerations in the selection of compounds for monitoring in the NRP, a transparent program has to specify these considerations and clearly distinguish these rationales from decisions based on direct public health risks. There is no indication in the Blue or Red Books that any of the compounds in the NRP with comparably low public health risk were included for other considerations, such as enforcement of pesticide application requirements. While antimicrobial resistance development is clearly stated as a rationale for the inclusion of certain drugs (see Appendix B), the different nature of the associated public health concerns is not acknowledged or addressed.

This report identified a number of concerns and their underlying determinants that contributed to this systematic failure in the NRP.

1. The exclusion of a substance posing an important risk to public health because:

- The compound does not have an established tolerance or action level, even if the compound is widely accepted as a public health risk, the concentration at which adverse health effects are expected is known, and comparable regulatory limits, such as maximum residue limits (MRLs), have already been set by other competent national or international standard-setting authorities.

  e.g., dioxins

- Limitations in scientific knowledge and diagnostic assays complicate testing, primarily for emerging concerns and/or compounds that are extensively metabolized (i.e., broken down in the body). To protect public health in the face of uncertainty, an approach that errs on the side of caution may, at least in some cases, be justified.[38] This may be the case even though compounds without a clearly established and quantified public health risk at a given exposure dose pose a particular challenge, and despite the fact that in some cases, other monitoring programs (e.g., for animal feed) may be in place to test for these substances, which may help detect livestock exposures.

  e.g., pentachlorophenol and some other halogenated hydrocarbons

  This exclusion is particularly problematic because the reasons for not including substances posing an important public health risk are documented in the Blue or Red Books only rarely. Therefore, a determination of whether the compounds posing an important public health risk are indeed included in the NRP cannot be reached by a review of the Blue and Red Books alone.

2. The lack of strict standards regarding data quality and documentation, and the absence of clearly established, transparent, consistent, and documented criteria for all decision-making about which compounds to include. The lack of standards includes:

- No minimum data quality requirements (e.g., peer-reviewed studies, consensus expert panel), even for crucial information on which compound selection decisions are based. There is also no established routine mechanism for periodically updating information to reflect current scientific knowledge. Even if high-quality peer-reviewed studies may not be immediately available for some emerging compounds, consistent minimum data quality standards should be established (e.g., minimum technical requirements for expert elicitations) to ascertain internal consistency in the decision-making process.

  e.g., nonsteroidal anti-inflammatory drugs (NSAIDs)

- No transparent, consistent, scientifically based, and rigorously documented criteria for all decisions about compound selection for the NRP (discussed on the following pages).

  e.g., pesticides

3. Certain compound selections are explicitly based on criteria other than actual risk to the consumer at the exposed level, such as concerns about antimicrobial resistance development, but differences in the underlying rationale are not acknowledged or addressed.

   e.g., AMDUCA-prohibited drugs (discussed on the following pages)

4. The lack of a structured program intended to monitor emerging risks.

   e.g., brominated flame retardants, byproducts of biofuel production, nanomaterials whose hazards are not yet clearly defined, and environmental risks such as contaminants from gas fracking spills

Deficiencies in National Residue Program Oversight

The U.S. Department of Agriculture's National Residue Program (NRP) monitors veterinary drugs and other chemical compounds in the U.S. meat and poultry supply, but needs greater scientific rigor and transparency to effectively address public health risks. Following are four deficiencies in the program that could threaten Americans' health and must be addressed.

Deficiencies

The exclusion of some substances that experts agree pose a significant public health threat

A lack of strict standards for data quality, documentation, and transparency

Examples

Dioxins

Dioxins are potent pollutants that research has shown can cause cancer as well as developmental and neurological disorders in humans. They are not routinely monitored by the NRP, however, because maximum safe concentrations for these toxins in meat, poultry, and egg products have not been set in the United States.

Dexamethasone

Dexamethasone is a steroid hormone that can cause spikes in blood glucose levels in diabetics. It has been considered by the NRP for regular testing and was scored a higher risk in the program's assessment than several monitored compounds. The program does not provide a justification or data to support its exclusion of dexamethasone.

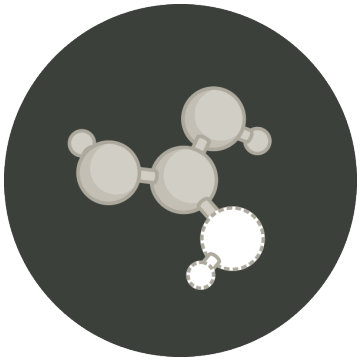
Continued on the next page

Deficiencies in National Residue Program Oversight

Deficiencies

Inconsistent processes for determining which drugs and other chemical compounds to monitor

Lack of a systematic process to address emerging risks



Examples

Fluoroquinolones

The NRP has devoted significant time and resources to creating criteria for identifying hazardous compounds to monitor but does not follow them consistently. The use of certain drugs in livestock is restricted by law (i.e., the Animal Medicinal Drug Use Clarification Act of 1994). One example are fluoroquinolones, broad-spectrum antimicrobial drugs used in humans and animals. The NRP has chosen to include fluoroquinolones in its sampling program simply because of the legal restriction on its use, not because of the program's own risk analysis.

Brominated flame retardants

The NRP lacks a procedure for periodically updating its sampling program based on advances in scientific knowledge or the latest uses of chemicals in food production and elsewhere in the environment. For example, brominated flame retardants are chemicals added to consumer products to reduce flammability, and their use is increasingly common. Understanding of the health risks they pose is limited, and they are not included in the NRP.

Finding 1: The NRP excludes substances of important public health risk, especially if they do not have an established tolerance or actions level.

It can be challenging to decide on the appropriate criteria for determining whether a compound poses an important public health concern. For instance, acute and chronic toxicity may have to be weighted, and risks for different population subgroups may have to be balanced. These considerations have been aptly discussed elsewhere.[39] Even if the magnitude of the public health risk may be debatable for some compounds, other compounds excluded from the NRP's scheduled sampling clearly do pose an important public health risk and should therefore be considered for inclusion in the residue program. These include, for instance, dioxins and dioxinlike substances, as well as certain heavy metals such as cadmium, lead, and mercury.[40] There are regulatory and/or technological challenges to monitoring many of these substances, such as a lack of established tolerances—despite an understanding of dose-response relationships—or extensive metabolism (i.e., breakdown in the body) with wide cross-species variation in metabolites (i.e., breakdown products) associated with varying chemical and toxicological properties. New technological and/or regulatory approaches may be needed to overcome some of these challenges. For example, regulatory or statutory changes may be needed to allow the FSIS to collaborate with other agencies to adopt temporary maximum limits for compounds of important public health concern but without established tolerances, or the FSIS may work with the agencies to expedite the development of tolerances for these compounds. This may require additional human and capital resources, and at least a theoretical potential exists for scientific disagreements among the agencies in their assessments of maximum safe levels for these compounds.

Other features that some of the excluded compounds with great public health concern share include the propensity to reach high concentrations in edible tissues of a food animal and cause chronic toxicity with even low-level exposure. Exposure to many of these compounds, such as many heavy metals and numerous pesticides, can occur from accidental spills or cross-contamination. Therefore, there may be a need for continuous monitoring, rather than occasional targeted sampling, to assess whether environmental contaminants have migrated into the food chain. In addition, it may be important to monitor even low-level exposure to some of these compounds to safeguard against potential chronic toxicity effects, such as cancer development.

Only a few of the particularly hazardous drugs, pesticides, and environmental contaminants are discussed extensively in the Blue and Red Books. One example discussed (though not included in the NRP's scheduled sampling) is dioxin and dioxinlike compounds (DLCs), recognized as being among the most potent chemical toxicants, per the European Food Safety Authority (EFSA).[41] They belong to a class of over 200 persistent organic pollutants that also includes polychlorinated biphenyls and dibenzofurans. Only some congeners (i.e., closely related chemical substances) cause the toxicological effects typical of dioxins and are considered DLCs.[42] Individual DLCs differ in potency but cause adverse effects through a common molecular mechanism of action.[43] They can contaminate meat and poultry, especially products with large amounts of fat, where they tend to accumulate.

The adverse effects of dioxin exposure have been documented extensively in humans as well as animals and appear to be highly consistent across species.[44] Animal studies have involved experiments on laboratory animals and epidemiological studies of wildlife and domestic species, including after accidental poisoning through contaminated feed or environmental spills.[45] Specific toxic effects of DLCs include endocrine disruption,

carcinogenicity, immunotoxicity, and neurotoxicity, as well as developmental, cardiovascular, and liver toxicity, among others.[46]

Because of their tendency for bioaccumulation and their toxicological effects, an expert panel convened by the EFSA grouped DLCs into the category of "high potential concern" (i.e., the highest of four categories) in rankings of residues and contaminants in bovine, swine, and poultry meats that present potential public health hazards.[47] DLCs ranked higher here than the other evaluated compounds, including various compounds that are regularly included in the NRP because of their risk to public health (e.g., chloramphenicol, beta-agonists, and nitrofurans).

In spite of their potential toxicity, DLCs are not routinely included in the NRP because their tolerances or action levels (the maximum concentrations of a drug, chemical, or marker residue[48] allowed in food products that, when exceeded, trigger a regulatory action) in meat, poultry, and egg products have so far not been established.[49] Notably, FDA has established a temporary tolerance for polychlorinated biphenyls for animal feed, including feed of animal origin, as well as for food packaging materials, and the European Union has set DLC MRLs for meat and meat products.[50]

A targeted sampling during the 2012-13 NRP survey of beef and poultry detected dioxins, albeit at a decreased level compared with targeted samplings performed in previous years.[51] Targeted surveys are conducted every five years to determine background exposure levels for some compounds such as dioxins. However, this system may not detect exposure incidents occurring over a very limited time frame. Inclusion of DLCs as a regular component of the domestic scheduled sampling appears scientifically and technologically feasible, and protective of public health.

In response to a review of a draft of this report, the FSIS pointed to information on the website of the World Health Organization, which highlights the high cost of quantitative chemical analysis of dioxins.[52] The FSIS also noted that sampling for dioxin is difficult and that a dioxin analysis cannot be incorporated into the FSIS multiresidue method. It has decided against including testing of dioxins in its routine testing programs not only in light of the cost but also because the data collected in its five-year surveys of dioxins showed a decreasing trend in the levels of this environmental contaminant. Notably, this is not the rationale for not including dioxins in the Blue Book. (See Appendix A.)

Contamination with heavy metals, such as cadmium and lead, as well as inorganic arsenic that may be found in the environment or in certain feed additives,* is also discussed in the Red and Blue Books.

In contrast to the dioxinlike compounds, which accumulate in fatty tissues, these metals tend to build up in liver and kidney tissues. A variety of toxicological effects have been documented, with some examples summarized below:

- Lead and cadmium compounds are carcinogenic, and accumulation can cause kidney damage, decreased bone strength, and possibly cardiovascular disease.[53]
- Low-level lead exposure can result in anemia, developmental and behavioral effects in children, and neurological deterioration in adults.[54]
- Chronic low-level exposure to the highly toxic inorganic arsenic, primarily a concern in seafood, has also been associated with cardiovascular disease, diabetes, lower IQ scores, nervous system effects, and reproductive dysfunction.[55]
- Mercury exposure, primarily a concern in seafood, can have toxic effects on the nervous, digestive, and immune systems as well as individual organs.[56]

* Food and Drug Administration, "Re: Docket No. FDA-2009-P-0594" (2009). Since 2013, arsenic-based feed additives have largely been withdrawn from the U.S. market.

Arsenic in poultry is the only metal with an established tolerance. Arsenicals (i.e., compounds containing arsenic) are therefore regularly included in the NRP, which conducts targeted survey sampling for certain heavy metals. MRLs have been established for cadmium and lead in the European Union,[57] and inclusion of cadmium and lead as a regular component of the NRP domestic scheduled program appears both scientifically feasible and protective of public health. In addition, the NRP should consider including mercury, another heavy metal environmental contaminant with major human health effects.[58] According to the 2013 and 2014 Red Books, the NRP's metals method detects 17 different metals; however, mercury is not on that list, and a clear rationale for including most of these 17 metals, such as vanadium, thallium, or boron, is not provided in either the Blue or Red Books.[59]

Other compounds that experts agree pose an important public health risk but are not routinely included in the NRP's scheduled sampling are not discussed in the Blue and Red Books, and a justification for the rationale behind not incorporating these substances is missing. This is the case for several compounds regularly included in comparable monitoring systems in the European Union, including the heavy metal mercury and a long list of other compounds.[60] While some exposure risks may differ by geographic region, others, such as mercury, may pose a comparable public health risk in the U.S. and Europe. The absence of a clear rationale for how compounds were selected for consideration in the NRP raises transparency concerns because for substances not included in the NRP, adequate reasons for their exclusion often are not clear. While it may not be feasible to document decisions for inclusion or exclusion for every compound that may lead to residues in meat and poultry, greater transparency is needed, in particular for compounds that were included in the NRP risk ranking but not included in the NRP's scheduled sampling.

Finding 2: The NRP lacks strict standards on data and documentation, and transparent, consistent criteria on which to base monitoring decisions.

The Blue Book[61] lists a number of criteria to be considered when deciding which compounds to include in the NRP's scheduled sampling. However, these criteria raise several concerns because (1) they do not consistently prioritize public health importance; (2) the scientific merit of studies used to score compounds is often questionable; (3) the NRP's criteria are not transparent; and (4) the use of the criteria does not appear to be internally consistent.

The NRP's criteria do not consistently prioritize compounds of public health importance

For example, in the 2012 Blue Book, one criterion—"acute or chronic toxicity concerns"—measures the toxicity of each compound and the severity of its associated toxic effects. Compounds in the highest category include carcinogens, substances that cause significant acute effects such as anaphylactic responses to allergens, and those that bring about other potentially life-threatening reactions.[62] Yet two compounds that, based on the Blue Book risk ranking, also fall into the highest toxicity category—thyreostats and dipyrone—are not included in the NRP, while compounds that score one or two categories lower on the four-category scale, such as sulfonamides, xenobiotic hormones, gamithromycin, and tulathromycin, are included. A clear rationale for excluding thyreostats and dipyrone is not provided, nor is there a clear justification for including xenobiotic hormones, gamithromycin, and tulathromycin (beyond a general justification for including antibiotics; see Appendices A and B), even if inclusion of xenobiotic hormones appears justified based on their effect on public health.

The scientific merit of the studies used to score compounds is often questionable

Basing decisions about whether to include a compound on questionable, outdated, or otherwise not scientifically rigorous studies may lead to decisions that do not reflect the best and most current scientific knowledge or that may not be scientifically justified.

The monitoring of avermectin and other compounds with well-researched toxicity profiles is based on studies with questionable scientific rigor, at least for the sources cited in the Blue Book supporting the inclusion in the residue program; whether additional sources were considered cannot be determined from the Blue and Red Books. In the case of avermectin, for instance, the 2015 Blue Book (Page 14, footnote 9) lists an online proceedings paper by the Asia Pacific Association of Medical Toxicology that has not been peer-reviewed.[63] In fact, after discussing potential toxicity, this article notes that mammals "are less susceptible to the toxic effects of avermectins because … avermectins do not readily cross the blood-brain barrier," and also that avermectins enjoy a "wide margin of safety."[64] Therefore, the questionable publication that the FSIS uses to justify including avermectins supports the view that avermectins are generally safe for humans, a conclusion in line with the general scientific literature.[65] Rigorous peer-reviewed articles, reflecting recent advancements in the understanding of avermectin toxicity in humans (or the lack thereof)[66] are not included in the Blue Book. As a result, the human health risks are not being accurately communicated to the general public.

The justification for many other compounds included in the program is based on tertiary review sources that are not peer-reviewed and often do not specifically relate to assessments of human toxicity. (See Appendix B.) Other studies that may be available and may meet more stringent data requirements are not used by the SAT, or are at least not listed in the Blue Book to support decisions on whether to include the substance. If such studies have indeed been considered by the SAT, they need to be listed to ensure the transparency of the NRP. As new and/or more rigorous scientific studies are published, monitoring decisions should be updated to ascertain that they reflect the best currently available science.

The NRP's criteria are not transparent

The NRP's criteria are only discussed at a generic level in the 2015 Blue Book, and individual compound risk scores are only provided in the 2012 Blue Book. It is not clear from the Blue Book whether the 2012 numbers were used in subsequent years or if they were updated. A number of major transparency concerns exist with the published prioritization scheme. For example, acute and chronic toxicity are combined into a single criterion without further supporting data.[67] Therefore, it is not clear whether a compound's score is based on acute or chronic toxicity. This makes it challenging to evaluate and re-create the SAT-generated scoring and may lead to an internally inconsistent ranking as acute and chronic effects tend to differ in long-term health consequences (e.g., acute neurological symptoms such as dizziness vs. chronic effects such as tumor development).

For several other criteria, it is not clear what scientific information was used in the ranking, or exactly how drugs were scored. The criterion "relative number of animals treated," for instance, is based on "economic data of doses sold as well as surveys of treatment practices in animal populations that are representative of national feedlot, dairy, poultry, and swine production."[68] Yet these surveys are not clearly explained, the algorithm used to combine different data sets is not provided, no additional information is given, and it is not possible to evaluate or re-create this analysis. It is also not clear how the SAT determined the risk categories for individual criteria or the relative weights for the individual criteria in the final score. For example, for withdrawal time, the category cutoffs were chosen as zero, seven, and 14 days, indicating that, everything else being equal, a compound with eight days' withdrawal time poses a considerably greater risk than one with seven days' withdrawal, but the same

is not true for compounds with six and seven days' withdrawal, respectively. Because these categorizations and weights can have an important impact on the final scores, transparent documentation of their determination is important.

> Even more concerning is the fact that the publicly available description of the prioritization scheme does not accurately reflect the scheme that is being used.

The justification for pesticide monitoring in the NRP is particularly unclear because a draft list of considered compounds is not provided, and the basis for selecting specific compounds is not discussed in sufficient detail. Safety factors employed to account for the uncertainty associated with extrapolation—such as using laboratory animal data to infer safe concentrations in humans—are not provided but may vary widely across compounds, and data sources and algorithms are not discussed in detail. A wide variety of pesticides are included in the NRP, representing a wide variety of chemical classes, functions (i.e., herbicide, fungicide, insecticide), labeled applications (e.g., on crops or seeds, indoor residential use, on golf courses, directly on pets and/or livestock), and adverse health effects. (See Appendix C.) Some pesticides have been banned for decades because of their toxicity. Although monitoring for them may be justified because they may have accumulated in the environment, their risks and rationales for inclusion clearly differ from pesticides intentionally used today on livestock or in their environments. Among intentionally used pesticides, some rationale for inclusion is provided for chlorinated hydrocarbons, organophosphates, and pyrethroids. However, a large and varied group of other pesticides is also included, whose numbers have increased considerably since the 2014 NRP, but a rationale for their inclusion or expansion in the 2015 Blue Book is not provided. Pesticides for which no rationale is provided are registered for various uses, including on livestock, their environments, pets, in residential homes, on ornamental crops, golf courses, ponds, or irrigation systems. Without a clear justification, it is very hard to determine why the pesticides were selected, what concerns motivated the EPA to include them in the NRP (e.g., environmental contamination, inappropriate use on animal feed or livestock animals), and what public health issues the residues (at concentrations expected in meat and poultry products) are likely to cause.

Even more concerning is the fact that the publicly available description of the prioritization scheme does not accurately reflect the scheme that is being used, according to EPA and FSIS officials who reviewed a draft of Pew's evaluation. EPA staff subsequently provided information on the scheme currently in use, which differs substantially from the description in the 2012 Blue Book and was not publicly available at the time this report was prepared.

In other cases, the rationale provided is not a convincing justification for inclusion in the NRP. For example, permethrin (see Appendix A), a member of a class of compounds called pyrethroids, is generally regarded as very safe for most species of mammals, is noncarcinogenic, is widely used in households and on pets, and is extensively metabolized in animals and humans.[69] In light of these findings, the EPA's rationale for including pyrethroids is questionable. Moreover, the FSIS does not explain which chemical moiety (i.e., a part or functional group) of the pesticide the program tests for, and what the risk of exposure is from residues in food relative to other routes of exposure (e.g., indoor pesticides, pet products), which may occur concurrently and at much higher concentrations. Even though intentional and accidental exposures may have to be considered separately for policy decisions, it is not clear whether limited resources are best used monitoring permethrin and other comparably safe compounds, rather than those of greater public health concern.

The NRP's criteria do not appear to be internally consistent

According to the 2012 Blue Book, compounds considered for inclusion in the NRP's scheduled sampling are scored based on a set of criteria that are combined to calculate the "relative public health score."[70] However, decisions about including compounds do not appear to be strictly based on this score. For example, according to the rankings in the 2012 Blue Book, beta-agonists earned a final score of 2.75 and were included, as was melengestrol acetate with a score of 3.[71] Dexamethasone—a steroid hormone that can cause spikes in blood glucose levels for diabetics—scored higher on the scale but is not monitored. A justification or data supporting the exclusion are not provided. Similarly, methyl prednisone, eprinomectin, clorsulon, thyreostats, lasalocid, and dipyrone all had higher scores and were excluded.

It is important that the rationale for all monitoring decisions be clearly stated and documented. Relatively safe compounds such as avermectins or most NSAIDs* should be separated from those with acknowledged toxicity concerns. Further, the rationale for all monitoring decisions should be fully explained, including whether the decision is motivated by acknowledged acute toxicology issues, such as hypersensitivity to certain antimicrobial drugs (e.g., penicillins) or acute toxicity from drugs in the beta-agonists class (e.g., clenbuterol), seen in humans after they have eaten meat contaminated with these drugs,[72] or whether it is based on chronic toxicity concerns. Clear documentation of the rationale used in making monitoring decisions is a central component of a transparent, consistent, internally and externally valid, and scientifically based system that can accommodate new scientific evidence and address existing as well as new hazards.

Finding 3: The NRP does, in some cases, explicitly base monitoring decisions on criteria other than actual risk to the consumer at the exposed level.

The Animal Medicinal Drug Use Clarification Act (AMDUCA) is a law whereby Congress has acknowledged that, in some cases, a veterinary drug such as an antibiotic may have to be used off-label (e.g., at a higher dose, for a longer time, for a disease not on the label, in a different species) to ensure effective therapy as determined by the prescribing veterinarian. Under the NRP, all veterinary drugs prohibited under AMDUCA are assigned a high sampling priority and are included in the program if "methodologies and resources are available."[73] In these cases, the SAT chooses explicitly not to use the criteria it developed for the sole purpose of deciding whether to include a compound in the NRP, but no compelling reason for this choice is provided.

However, in several cases, AMDUCA-prohibited drugs are actually approved for certain uses in livestock species. For example, fluoroquinolones—a class of antimicrobial drugs—have restrictions for some off-label uses, but they are approved for other uses. The *a priori* decision to include such compounds, absent any other considerations, appears questionable. Rather, the inclusion of AMDUCA-prohibited drugs should be based on the same considerations as all other drugs. If a drug is AMDUCA-prohibited because it poses a particular threat to public health, it clearly merits inclusion in the NRP. However, the simple fact that a drug may be AMDUCA-prohibited, without any other justification, should not merit inclusion in a transparent, consistent, and scientifically based

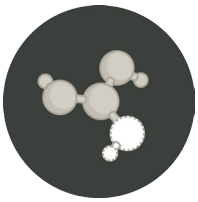
* Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and aspirin, are widely used in human and veterinary medicine to reduce pain, fever, and inflammation. Because they are very safe, most NSAIDs are available over the counter without the need for a doctor's prescription.

monitoring system, especially because a variety of different considerations may converge for a drug to be AMDUCA-prohibited.

More on AMDUCA and Prioritization

In response to a review of a draft of this report, the FSIS explained that because the expected number of animals treated with AMDUCA-prohibited drugs can be zero if no uses in food-producing animals are permitted, the agency would be unable to calculate a "score" in the risk ranking that prioritizes their public health impact. For this reason, the SAT recommended that these drugs always be ranked as of high public health concern.

This explanation, which is not provided in the Blue Book, demonstrates a major shortcoming of the prioritization model, which should apply to all drugs. At a minimum, the model's inability to rank all drugs should be clearly acknowledged in the Blue Book, rather than simply stating that the drugs were prioritized as ones of high importance because of their AMDUCA status.



Finding 4: The NRP does not monitor emerging compounds that may pose a serious threat to public health.

As chemicals and drugs are developed, or new uses are found for existing compounds, new residue threats emerge (referred to as "emerging compounds" in this report). If such threats are ignored because of a lack of established tolerances, diagnostic challenges, or shortages of resources, public health may not be optimally protected.

Data available for evaluating emerging compounds may be scarce initially, with assessments of potential public health risks relying on preliminary studies and a variety of assumptions that bridge data gaps. Scientific approaches such as rapid risk assessments or the convening of expert panels may help evaluate new emerging risks.[74] Targeted sampling studies of animal feeds or environmental sources may also provide information on the potential introduction of emerging compounds into the food chain.[75] Toxicological or epidemiological studies may inform upper "safe" exposure levels (i.e., levels not expected to negatively affect human health). A preliminary inclusion of emerging compounds into the NRP could occur after considering the potential or definitive risks posed by them (by exposure through the meat supply) and the economic and opportunity costs of including them. These preliminary assessments should be updated as more data become available, so that decisions about the inclusion of emerging compounds are based on the best available science.

Residues of a variety of new compounds have recently become of emerging concern with meat and poultry products. Potential new threats include compounds that can accumulate in the food chain, such as brominated flame retardants, byproducts of biofuel production, and nanomaterials.[76] In many cases, the foodborne hazards

associated with meat are not yet clearly defined, and new environmental hazards such as contaminants from gas fracking spills continue to emerge.[77]

Emerging risks can also include chemicals intentionally added to food or feed products, either to take the place of more valuable ingredients in order to increase profits (i.e., "economically motivated adulteration," such as the use of melamine in infant formula and pet food to suggest higher protein levels) or as feed additives or supplements. For example, copper, selenium, or zinc can be used to improve animal health and increase production parameters such as average daily gains.[78]

> Residues of a variety of new compounds have recently become of emerging concern with meat and poultry products.

How the NRP Addresses Emerging Risks

In response to a review of a draft of this report, the FSIS clarified that the agency is taking action to assess certain emerging risks. In general, the FSIS stated that the SAT looks to other agencies for guidance, as appropriate, when evaluating emerging risks; for instance, on the issue of nanomaterials, the FSIS tracked FDA's related activities. More specifically, the agency identified two examples to demonstrate how it responds to natural and man-made disasters, specifically possible crude oil contamination and its sampling efforts related to potential exposure of grazing cattle to perfluorooctanoic acid and perfluorooctanesulfonic acid.*

* For examples the FSIS provided to Pew, see Food Safety and Inspection Service, "Crude Oil Contamination," http://askfsis.custhelp.com/app/answers/detail/a_id/1397/~/crude-oil-contamination; and supplemental Appendix H.

The NRP does not seem to consistently consider compounds that pose emerging threats—or represent economically motivated adulteration—for inclusion into scheduled or targeted samplings (even though this determination is currently difficult to make for contaminants and pesticides because a list of compounds considered for inclusion is not provided). The absence of such emerging risks strongly suggests that no effective monitoring for new threats is being conducted. Although the 2015 Blue Book discusses a "next-generation selection and ranking process" that could theoretically allow for the inclusion of new and emerging compounds, it does not provide any specific criteria.

Takeaways From Other Analyses of the NRP

The National Academy of Sciences

The National Academy of Sciences' Committee on the Use of Public Health Data in FSIS Food Safety Programs* reviewed the NRP and discovered a number of issues. It noted that some pesticides and environmental contaminants were not being monitored because of a lack of established tolerances and expressed concerns about how the FSIS weighed human, animal, and environmental health in its decision-making process.

The committee also analyzed the "risk score" that informed the sampling algorithm used for the NRP. It had significant concerns regarding the validity of FSIS' methodology for determining this score, which is more accurately characterized as a sampling priority for regulatory enforcement.

The Government Accountability Office

In 2014, the Government Accountability Office published a report titled "FDA and USDA Should Strengthen Pesticide Residue Monitoring Programs and Further Disclose Monitoring Limitations."† It found data transparency issues (e.g., failure to disclose limitations in the NRP's data and failure of the NRP's annual reports to meet the Office of Management and Budget's standards for reporting) and concluded that users "may not have accurate information and may misinterpret the results of the program." In addition, the report noted a general decline in the number of product samples taken between 2000 and 2011 (though multiple tests may have been performed on the same product sample, leading to an increase in the total sample size) and a focus only on "major" production classes (whereas ducks, geese, ostriches, emus, squabs, and rabbits have not been tested since 2003). Differing priorities were also noted for residue testing between the EPA and the USDA, as well as challenges in using data across agencies.

The USDA's Office of the Inspector General

In 2010, the USDA's Office of the Inspector General generated an audit report of the FSIS' National Residue Program for Cattle.‡ The report included several specific recommendations for improving the NRP, such as steps to improve coordination among the USDA, FDA, and EPA through the development or updating of memorandums of understanding, charters, and processes to evaluate issues identified by the SAT.

* National Academy of Sciences' Committee on the Use of Public Health Data in FSIS Food Safety Programs, "Presentation of FDA Drug Residue Program by Dr. Neal Bataller" (Sept. 22–23, 2011).

† Government Accountability Office, "Food Safety: FDA and USDA Should Strengthen Pesticide Residue Monitoring Programs and Further Disclose Monitoring Limitations" (2014).

‡ U.S. Department of Agriculture, "FSIS National Residue Program for Cattle," ed. Office of Inspector General (2010).

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The report also suggested developing:

- Formal plans and milestones for the SAT to determine the availability of resources needed to test for all substances earmarked for inclusion.
- Policies and procedures to conduct risk-based periodic, structured reviews of the NRP's sampling procedures to ascertain appropriate sampling methodology.
- Strategies to work with FDA to expedite the development of new testing methods.
- Policies and procedures for substances with no tolerance (e.g., heavy metals, pesticides with canceled registration), to be developed in collaboration with FDA and the EPA.
- The exchange of data among agencies to enhance research and identify trends.
- Outreach to industry, private practitioners, and other nongovernmental experts to obtain relevant data on which to base their decisions.

Recommendations

To sum up, Pew makes the following recommendations for strengthening the NRP:

1. Provide transparent documentation and reporting of sampling plans and results.
2. Consistently apply the NRP's public health-based risk criteria to all compounds considered for monitoring, and base decisions first and foremost on the direct risk to consumers through food consumption. If clear reasons prevent this from being achieved for all compounds, be transparent and explicit about this limitation. Regularly revisit decisions to monitor compounds of comparably lower public health risk in light of the opportunity costs and the risks posed by other compounds.
3. Clearly acknowledge and explain when a compound is included in the NRP for reasons other than direct public health risks, such as enforcing legal requirements for pesticide use.
4. Monitor compounds that pose an important public health risk even if such action presents regulatory or technological challenges (e.g., the lack of an identified tolerance level, difficulty detecting the presence of a heavily metabolized drug).
5. For compounds of important public health risk but without established tolerance levels from the FDA or EPA, consider using applicable international guidelines. These include the Codex Alimentarius' maximum residue limits and the Threshold of Toxicological Concern approach.[79] If the FSIS' current authority is not sufficient to include compounds without established tolerances, the necessary operational, legislative, or regulatory changes—for example, close collaboration with the agencies responsible for setting tolerances, namely FDA and EPA—should be sought to make sure the compounds of important public health concern are routinely incorporated into the NRP. If other valid reasons merit inclusion into the NRP, these should be clearly identified.
6. Adopt standards for strength of scientific evidence and minimum data quality. Decisions about compound selection for the NRP should be based on the best available scientific evidence, such as findings in a body of

peer-reviewed publications or deliberations of independent expert advisory panels. For some emerging risks, rigorous scientific studies may not be immediately available, and other sources (e.g., expert opinion studies such as formal expert elicitations) may have to be used; however, to ensure consistency, minimum data quality standards should be developed for these circumstances (recognizing that standards for emerging risks may differ from the case of established risks with ample scientific data available).

7. Develop a system to routinely incorporate new scientific evidence and evaluations of relevant technological advancements. This should include periodic re-evaluations of available scientific evidence on which prioritization decisions are based and evaluations of new statistical methods relevant to the NRP.
8. Provide specific justifications for the inclusion or exclusion of all considered compounds based on dietary exposure risks associated with a single food of concern, and critically compare these exposures to other routine exposures to the compound, such as environmental exposures in the home or workplace. Also document why certain considered compounds, in particular those that scored higher than some of the included compounds in the SAT risk ranking, were ultimately not included in the NRP's scheduled sampling.
9. Include compounds that the NRP determines pose an emerging and important public health threat using tools such as rapid risk assessments or expert panels, and clearly document the assessment of new and emerging risks. Decisions to include these compounds may be based on scientific assessments that systematically evaluate the public health risks, for example, through risk assessment, and may be informed by other sampling projects, for instance, sampling of animal feeds for emerging compounds that may lead to tissue residues after consumption by livestock species. Inclusions into the NRP may initially take the form of targeted sampling projects (tier 2 or tier 3 sampling) to evaluate the presence and levels of emerging compounds in tissue. As soon as sufficient data are available, these compounds should be broadly addressed and undergo rigorous and up-to-date scientific analysis, and decisions should be re-evaluated as more information becomes available.

Conclusion

In order to best protect public health, it is essential for a regulatory agency such as the FSIS to base its decisions on sound science and actual risks to public health. This requires the agency to constantly update the processes and procedures used in its operations. Although the FSIS did revise the sampling and testing methods it uses to monitor chemical residues in meat and poultry products in 2012, more work needs to be done to ensure that its National Residue Program includes compounds that are actually an important risk to human health. Many chemicals that experts agree pose a significant public health risk—in particular, environmental contaminants—should be included, even if no established tolerances exist.

Decisions about whether to include compounds in the NRP should be made using consistent, scientifically based criteria that assess the public health risk posed by the specific dietary exposures. These decisions should be predicated on the best available scientific evidence, or at least on evidence that meets minimum quality standards. Decisions should be clearly documented and periodically reviewed to incorporate advances in science and technology. To ensure a consistent system based on public health risk, any decision to include compounds—both drugs and pesticides—posing little, if any, risk should be critically reviewed in light of the associated opportunity costs. If considerations other than public health risks merit their inclusion, then this fact should be clearly acknowledged and addressed. Emerging chemical compounds pose significant technical and regulatory challenges that the NRP should address transparently and methodically. The NRP's sampling plan and results should be reported in a way that meets standards of data quality and transparency and that allows key decisions to be recapitulated and critically evaluated.

Appendices

The appendices contain the systematic scientific analyses performed during the review of the NRP. They support and further explain the conclusions reached in the report and provide additional technical information for interested readers.

Appendix A contains a comprehensive overview of all veterinary drugs considered for inclusion in the 2014 scheduled sampling (based on data provided in the 2015 Blue Book), lists compounds (including veterinary drugs, pesticides, and environmental contaminants) ultimately included in the 2015 program, and provides the justifications listed in the 2015 Blue Book for inclusion (where available).

Appendix B contains an overview of the rationale provided for inclusion of different compounds in the 2015 NRP (based on the 2015 Blue Book) and an analysis of the type of references cited in the 2015 Blue Book for these rationales.

Appendix C provides a summary of the pesticides included in the 2015 NRP (based on the 2015 Blue Book), indicates whether these pesticides were included in the 2014 NRP, and gives further information about the pesticides including their registered uses.

Appendix D lists selected major concerns about transparency and quality of reporting for the Blue and Red Books.

Appendix A: Compounds considered by the SAT for inclusion in the NRP's 2014 scheduled sampling for domestic and imported products[80]

Drug class Compound*	Rationale for inclusion, as indicated in the 2015 Blue Book (AMDUCA-prohibited drugs[81] are identified as such)
1. Antimicrobial drugs	
Aminoglycosides spectinomycin, hygromycin, streptomycin, dihydrostreptomycin, amikacin, kanamycin, apramycin, gentamycin, neomycin	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma).
Beta-lactams amoxicillin, ampicillin, cloxacillin, nafcillin, cefazolin, desfuroylceftiofur (DCCD), dicloxacillin, penicillin G, oxacillin, desacetyl cephapirin	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma). Some beta-lactams are AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).†
Carbadox	Antimicrobial. Carbadox is genotoxic and carcinogenic in rodents; no established ADI.
Chloramphenicol and derivatives chloramphenicol, thiamphenicol, florfenicol	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma). AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern). Chloramphenicol causes bone marrow suppression or aplastic anemia in susceptible individuals. Florfenicol has been associated with testicular degeneration and atrophy in toxicity studies in dogs, rats, and mice.
Fluoroquinolones ciprofloxacin, norfloxacin, danofloxacin, enrofloxacin, sarafloxacin, difloxacin, desethylene ciprofloxacin, desmethyl danofloxacin, marbofloxacin, orbifloxacin	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma). AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).†
Glycopeptides avoparcin, vancomycin	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma). AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).†
Macrolides lincomycin, pirlimycin, clindamycin, tilmicosin, erythromycin, tulathromycin, tylosin, gamithromycin	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma).
Nitrofurans furazolidone, nitrofurazone	Antimicrobial. AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern). Nitrofurans are potential carcinogens "not generally recognized as safe under any conditions where animal product may become a component of food."
Sulfonamides sulfapyridine, sulfadiazine, sulfathiazole, sulfamerazine, sulfamethazine, sulfachloropyridazine, sulfadoxine, sulfamethoxypyridazine, sulfaquinoxaline, sulfadimethoxine, sulfisoxazole, sulfacetamide, sulfamethoxazole, sulfamethizole, sulfanilamide, sulfaguanidine, sulfabromomethazine, sulfasalazine, sulfaethoxypyridazine, sulfaphenazole, sulfatroxazole	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma). AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).†
Tetracyclines tetracycline, oxytetracycline, chlortetracycline	Antibiotic (i.e., development of antimicrobial resistance; allergies; childhood asthma).

* Drug classes and/or compounds not included in the NRP are indicated in gray type.

† Listed as AMDUCA-prohibited in 21 CFR § 556; however, this fact is not explicitly stated in the 2015 Blue Book.

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Drug class Compound	Rationale for inclusion, as indicated in the 2015 Blue Book (AMDUCA-prohibited drugs are identified as such)
2. Antiparasitics	
Avermectins* and milbemycins doramectin, ivermectin, moxidectin, eprinomectin	Effects on central nervous system (nausea, vomiting, dizziness, coma, death).
Benzimidazoles thiabendazole, albendazole, carbendazim, oxfendazole, mebendazole, cambendazole, fenbendazole	None provided.
Coccidiostats amprolium, halofuginone, lasalocid, nicarbazin, sulfanitran	None provided.
Nitroimidazoles ronidazole, dimetridazole, ipronidazole	None provided.
Other anthelmintic clorsulon, levamisole, morantel, pyrantel	None provided.
3. Nonsteroidal anti-inflammatory drugs (NSAIDs)	
Flunixin	GI ulceration, kidney damage, bleeding problems.
Phenylbutazone oxyphenylbutazone, phenylbutazone	AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).†‡
Other NSAIDs dipyrone, etodolac	None provided.
4. Hormones	
Diethylstilbestrol (DES) (synthetic hormone)	AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).‡
Xenobiotic hormones melengestrol acetate, trenbolone, zeranol	None provided.
Other hormones 17-beta estradiol, progesterone, testosterone	None provided.

* The Blue Book does not clearly describe which of the avermectin compounds are included in the NRP.

† The AMDUCA prohibition is only for dairy cows older than 20 months.

‡ Listed as AMDUCA-prohibited in 21 CFR § 556; however, this fact is not explicitly stated in the 2015 Blue Book.

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Drug class Compound	Rationale for inclusion, as indicated in the 2015 Blue Book (AMDUCA-prohibited drugs are identified as such)
5. Glucocorticoids	
prednisone, methyl prednisone, dexamethasone*	None provided.
6. Beta-agonists	
ractopamine, clenbuterol, cimaterol, zilpaterol, salbutamol	Increases in heart rate and blood pressure, anxiety, palpitation, skeletal muscle tremors; prolonged use can lead to severe exacerbation of asthma symptoms. AMDUCA-prohibited (i.e., veterinary drugs banned from extralabel use under AMDUCA are of high public health concern).
7. Metals	
Arsenicals	Gastrointestinal irritation, decreased red and white blood cell production, death, carcinogen (arsenic).
Heavy metals (cadmium, lead)	Stomach irritation, kidney damage, decreased bone strength, carcinogen (cadmium); central nervous system problems, anemia, brain and kidney damage, death (lead).
8. Pesticides, including veterinary insecticides (See Appendix C for a list of compounds included in the 2015 sampling program.)	
Chlorinated hydrocarbons e.g., aldrin, dieldrin, chlordane, DDT and congeners, endosulfan, heptachlor, mirex	Carcinogens and noncarcinogenic effects on immune, reproductive, nervous, and endocrine system.
Organophosphates e.g., chlorpyrifos, dichlorvos (DDVP), malathion, acephate, profenofos, coumpaphos	Neurological symptoms (e.g., headaches, dizziness, muscle twitches, weakness, tingling sensation, nausea).
Pyrethroids e.g., bifenthrin, permethrin, tefluthrin, L-cyhalothrin, cypermethrin, fluvalinate, resmethrin	Neurological symptoms (e.g., headaches, dizziness, muscle twitches, weakness, tingling sensation, nausea).
Compounds from various chemical classes e.g., triazoles, carbamates, imidazoles, urea derivatives, benzofurans, neonicotinoids, oxadiazine, benzyl urea derivative strobilurins.	None provided.

* Dexamethasone was considered until 2014 but is not included in the list of considered drugs in 2015.

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Drug class Compound	Rationale for inclusion, as indicated in the 2015 Blue Book (AMDUCA-prohibited drugs are identified as such)
9. Other classes	
Thyreostats 2-thiouracil, 6-methyl-2-thiouracil, 6-propyl-2-thiouracil, 2-mercapto-1-methylimidazole, 6-phenyl-2-thiouracil, 2-mercaptobenzimidazole	None provided.
Veterinary tranquilizers azaperone and azaperol, xylazine, haloperidol, acetopromazine, proprionylpromazine, chlorpromazine	None provided.
Dioxins and dioxinlike substances	Lack of established tolerance.

Appendix B: List of rationales provided for inclusion in the NRP*

Class	Justification provided in the NRP's Blue and/or Red Book	Reference source	Type of support provided in the NRP's Blue and/or Red Book
1. Veterinary drugs and pesticides			
AMDUCA-prohibited drugs	Veterinary drugs banned from extralabel use under AMDUCA are of high public health concern.	21 CFR § 556	None provided
Antibiotics	Development of antimicrobial resistance; allergies; childhood asthma.	CDC website; journal articles	Peer-reviewed journal article listed for statements on allergies and childhood asthma only
Avermectins and milbemycins	Effects on central nervous system (nausea, vomiting, dizziness, coma, death).	Conference paper	No peer-reviewed journal article
Beta-agonists	Increases in heart rate and blood pressure, anxiety, palpitation, skeletal muscle tremors; prolonged use can lead to severe exacerbation of asthma symptoms.	FDA website	No peer-reviewed journal article
Carbadox	Genotoxic and carcinogenic in rodents; no established ADI.	inchem.org Web pages	No peer-reviewed journal article
Chloramphenicol	Bone marrow suppression or aplastic anemia in susceptible individuals. AMDUCA-prohibited.	n/a	None provided
Chlorinated hydrocarbons	Carcinogens	EPA website	No peer-reviewed journal article
Florfenicol	Testicular degeneration and atrophy in animal toxicity studies (dog, rat, mice).	Pharmaceutical product information	Product leaflet
Flunixin	GI ulceration, kidney damage, bleeding problems.	Merck veterinary manual	Veterinary compendium
Nitrofurans	Potential carcinogen, "not generally recognized as safe under any conditions where animal product may become a component of food." AMDUCA-prohibited.	FDA import alert; Merck veterinary manual	No peer-reviewed journal article
Organophosphates, pyrethroids	Neurological symptoms (e.g., headaches, dizziness, muscle twitches, weakness, tingling sensation, nausea).	EPA fact sheet	No peer-reviewed journal article
2. Environmental contaminants			
Heavy metals and arsenic	Stomach irritation, kidney damage, decreased bone strength, carcinogen (cadmium); central nervous system problems that may lead to developmental and behavioral effects in children as well as decreased performance in adults, anemia, kidney and brain damage (lead); gastrointestinal irritation, decreased red and white blood cell production which can result in fatigue, abnormal heart rhythm, and nervous system effects, death, carcinogen (arsenic).	n/a	None provided

* The 2015 Blue Book does discuss dioxins and dioxinlike substances, but these are not included in the NRP's scheduled sampling.

Appendix C: Summary of pesticides included in the NRP's 2015 Blue Book

Compound	Chemical class	New in 2015	Missing from CLG-PST5.06	Function	Use	Source
Alachlor	Chloroacetanilide	-	-	Herbicide	Weed control	EPA[82]
Aldrin and/or dieldrin	Organochlorine	-	-	Insecticide	Canceled in 1987	EPA[83]
Bifenthrin	Pyrethroid	-	-	Insecticide, miticide	Broad spectrum, variety of uses indoors, outdoors, on pets, on livestock, and for agriculture	EPA[84]
Boscalid	Carboxamide	-	-	Fungicide	For use on various crops	EPA[85]
Buprofezin	Chitin synthesis inhibitor	Yes	-	Insecticide	Registered for use on a range of crops	FAO[86]
Carfentrazone ethyl	Triazolone	-	-	Herbicide	Weed control	EPA[87]
Chlordane and congeners	Organochlorine	-	-	Insecticide	Canceled in 1988	EPA[88]
Chloroneb trans	Organochlorine	Yes	-	Fungicide	Registered for variety of food crops	EPA[89]
Chlorpropham	Carbamate	Yes	-	Herbicide	Used on spinach, ginkgo trees, Easter lilies, and stored potatoes	EPA[90]
Chlorpyrifos and Chlorpyrifos methyl	Organophosphate	-	-	Insecticide, acaricide, miticide	Used to control insect and arachnid pests on various food and feed crops	EPA[91]
Cyhalothrin-L	Pyrethroid	-	Yes	Insecticide	Used to prevent various insect infestations on crops and against mosquitoes and cockroaches in nonagricultural settings	EPA[92]
Cypermethrin	Pyrethroid	-	Yes	Insecticide	Used on various crops as well as cattle and other livestock; pest control in various nonagricultural settings	EPA[93]
DDT and congeners	Organochlorine	Yes	-	Insecticide	DDT banned since 1972 (narrow emergency exception)	EPA[94]
Deltamethrin	Pyrethroid	-	Yes	Insecticide	Registered for use on various food and feed crops and food and feed establishments	EPA[95]
Dichlorvos (DDVP)	Organophosphate	-	-	Insecticide	Registered to control insects (e.g., flies, mosquitoes) in variety of sites and on pets	EPA[96]

Note: A rationale for inclusion is provided in the Blue Book only for chlorinated hydrocarbons (i.e., organochlorines), organophosphates, and pyrethroids.

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Compound	Chemical class	New in 2015	Missing from CLG-PST5.06	Function	Use	Source
Difenoconazole	Triazole	-	-	Fungicide	Broad-spectrum fungicide approved for various uses on seeds and crops	EPA[97]
Endosulfan and congeners	Organochlorine	-	-	Insecticide, acaricide	Broad-spectrum contact insecticide and acaricide for use on various crops and ornamental plants	EPA[98]
Fenoxaprop-ethyl	Aryloxyphenoxy proprionate	Yes	-	Herbicide	Weed control	EPA[99]
Fenpropathrin	Pyrethroid	Yes	-	Insecticide	Used to control various insects on crops	FAO[100] EPA[101]
Fenvalerate	Pyrethroid	Yes	Yes	Insecticide	Canceled in 2008	EPA[102]
Fipronil and congeners	Phenylpyrazole	-	-	Insecticide	Registered to control insect infestation (e.g., fleas, termites, ticks) in various indoor and outdoor settings and on pets	EPA[103]
Fluridone	unclassified	Yes	-	Herbicide	Weed control in ponds, reservoirs, irrigation canals, etc.	EPA[104]
Fluvalinate	Pyrethroid	Yes	-	Insecticide, miticide	Used to control insect and mite infestation on certain ornamentals, certain crops, buildings, and beehives	EPA[105]
Heptachlor	Organochlorine	-	-	Insecticide	Nearly all registered uses have been canceled	EPA[106]
Hexazinone	Triazine	Yes	-	Herbicide	Weed control	EPA[107]
Malathion	Organophosphate	Yes	-	Insecticide	Various food and feed crops, ornamental, pasture and rangeland, outdoor residential, building uses, etc.	EPA[108]
Metolachlor	Chloroacetanilide	Yes	-	Herbicide	Weed control	EPA[109]
Metribuzin	Triazine	Yes	-	Herbicide	Weed control	EPA[110]
Mirex	Organochlorine	-	Yes	Insecticide	All uses canceled in 1978	EPA[111]
Nonachlor and congeners*	Organochlorine	-	-	Insecticide	All commercial uses canceled in 1988	EPA[112]
Permethrin (cis, trans)	Pyrethroid	-	-	Insecticide	Used on numerous food and feed crops, on livestock and their housing, pets, clothing, residential indoor spaces, etc., to control mosquitoes and other insects	EPA[113]

* A major component of chlordane.

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Compound	Chemical class	New in 2015	Missing from CLG-PST5.06	Function	Use	Source
Piperonyl butoxide	Unclassified	-	-	Synergist (enhances insecticide)	Used to enhance the pesticidal properties of other pesticides (e.g., pyrethroids)	EPA[114]
Pronamide	Substituted benzamide	-	-	Herbicide	Weed control	EPA[115]
Propachlor	Chloroacetanilide	Yes	-	Herbicide	Weed control	EPA[116]
Propanil	Acetanilide	-	-	Herbicide	Weed control	EPA[117]
Propetamphos	Organophosphate	Yes	-	Insecticide	Used indoors to control cockroaches, fleas, termites, etc.	EPA[118]
Propiconazole	Triazole	-	-	Fungicide	Used on various food and feed crops and as material preservative	EPA[119]
Pyriproxyfen	Pyridine-based pesticide	Yes	-	Insect growth regulator	Used on various agricultural crops (e.g., fruits, vegetables, nuts), food storage and handling establishments, residential settings (indoor and outdoor), etc., to control mosquitoes and other insects and on pets	EPA[120]
Resmethrin (cis, trans)	Pyrethroid	Yes	-	Insecticide	Used on livestock and their housing, food handling establishments, food item transportation, and residentially to control mosquitoes	EPA[121]
Tefluthrin	Pyrethroid	-	-	Insecticide	Used on various food and feed crops	EFSA[122] EPA[123]
3-Hydroxycarbofuran	Carbamate (Carbofuran metabolite)	-	-	Insecticide, nematicide	Used to control insect pests on food and feed crops	EPA[124]
Acephate	Organophosphate	-	-	Insecticide	Used on various food and feed crops, in food handling establishments, greenhouses, outdoors, and around the home to control insect infestation	EPA[125]
Acetamiprid	Neonicotinoid	Yes	-	Insecticide	Control certain insects on various food and feed crops and ornamental plants	EPA[126]
Atrazine	Triazine	Yes	-	Herbicide	Weed control	EPA[127]

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Compound	Chemical class	New in 2015	Missing from CLG-PST5.06	Function	Use	Source
Azoxystrobin	Beta-methoxyacrylate	Yes	-	Fungicide	Used to control various pests on golf courses and turf farms	EPA[128]
Carbaryl	Carbamate	-	-	Insecticide	Used in various agricultural and residential settings and on pets (e.g., pet collars) and their environment, as well as on ornamentals, golf courses, etc., to control mosquitoes and other insects	EPA[129]
Carbofuran	Carbamate	-	-	Insecticide, nematicide	Used on food and food crops to control various insect pests, as well as ornamentals, tobacco, etc.	EPA[130]
Carboxin	Oxathiin	Yes	Yes	Fungicide	Used on various feed and food crops	EPA[131]
Clofentezine	Tetrazine	-	Yes	Miticide	Used to control mite infestation on various plants and food crops (e.g., apples, almonds, peaches)	EPA[132]
Clothianidin	Neonicotinoid	Yes	-	Insecticide	Seed treatment of corn and canola	EPA[133]
Coumaphos O, S	Organophosphate	Yes	-	Insecticide, acaricide	Control of insects, mites, and ticks on livestock and their environment	EPA[134]
De-ethyl atrazine	Triazine	Yes	-	Herbicide	Weed control	EPA[135]
Diflubenzuron	Benzamide	-	-	Insecticide, acaricide	Used to control insect infestation on various crops, pastures, ornamentals, and standing water, as well as on cattle	EPA[136]
Diuron	Urea derivative	-	-	Herbicide	Weed control and used to control mildew and algae in commercial fish production	EPA[137]
Ethofumesate	Benzofuran	-	-	Herbicide	Weed control	EPA[138]
Fluoxypyr-1-methylheptyl-ester	Pyridinoxy acid	Yes	-	Herbicide	Weed control	EPA[139]
Imazalil (eniloconazole)	Imidazole	-	-	Fungicide	Used on various crops post-harvest and in chicken hatcheries	EPA[140]
Imidacloprid	Neonicotinoid	-	-	Insecticide	Used on food, feed, seeds, pets, residential lawns, golf courses, etc., to control various insects	EPA[141]

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Compound	Chemical class	New in 2015	Missing from CLG-PST5.06	Function	Use	Source
Indoxacarb	Oxadiazine	-	-	Insecticide	Used to control pest infestation indoors and on various food and feed crops; flea control	EPA[142]
Linuron	Urea derivative	-	-	Herbicide	Weed control	EPA[143]
Metalaxyl	Phenylamide	-	-	Fungicide	Used on various food and feed crops, as well as ornamentals, residential outdoor uses, etc.	EPA[144]
Methomyl	Carbamate	-	-	Insecticide, molluscicide	Used on various food and feed crops, in various indoor and outdoor settings (e.g., animal kennels), and on certain animals (e.g., rabbits, horses) to control infestation with various insects	EPA[145]
Methoxyfenozide	Diacylhydrazine	-	-	Insecticide	Used on various food and feed crops	New York State Department of Environmental Conservation[146]
Myclobutanil	Triazole	-	-	Fungicide	Used on various food and feed crops, golf courses, ornamentals, etc.	EPA[147]
Norflurazon	Pyridazinone derivative	-	-	Herbicide	Weed control	EPA[148]
Profenofos	Organophosphate	Yes	-	Insecticide, acaricide	Used on cotton	EPA[149]
Pyraclostrobin	Strobilurin	Yes	-	Fungicide	Used on various food and feed crops	EPA[150]
Pyridaben	Pyridazinone derivative	-	-	Insecticide, miticide	Used on various food and feed crops, greenhouses, etc.	EPA[151]
Simazine	Triazine	-	-	Herbicide	Weed control	EPA[152]
Tebufenozide	Diacylhydrazine	-	-	Insecticide	Used on various food and feed crops, ornamentals, forestry, etc., to control narrow range of insects (lepidoperan species)	EPA[153]
Thiabendazole	Benzimidazole	-	-	Fungicide, anthelminthicide	Used on various food and feed crops, ornamentals, textiles, carpets, etc.	EPA[154]
Thiamethoxam	Neonicotinoid	-	-	Insecticide	Used on various food and feed crops	EPA[155]
Thiobencarb	Thiocarbamate	Yes	-	Herbicide	Weed control	EPA[156]
Trifloxystrobin	Strobilurin	Yes	-	Fungicide	Used on various food crops and ornamentals	EPA[157]

Appendix D: Specific data transparency concerns with the sampling plan description (2015 Blue Book) and reporting of the NRP's sampling results (2012 Red Book)*

The inadequate description of the sampling plan is reflected, for example, in the fact that the 2012 Red Book specifies the number of metals analyzed as seven (post-August sampling; see Table 15 on Page 34) but does not provide a comprehensive list of metals in either the 2012 Red Book or any of the 2012–15 Blue Books. As cadmium and lead are the only metals discussed in the 2012 Blue and Red Books, it is not clear what other metals may or may not be included in the 2012 NRP. The 2013 and 2014 Red Books contain tables that clearly specify which compounds are detected by each of the analytical methods.

Unfortunately, this information is not yet adequately captured in the 2015 Blue Book. For example, even though two drugs and/or drug classes, beta-agonists and carbadox, are listed as part of the "multiresidue" method (on Page 18 of the 2015 Blue Book), they are listed in the Blue Book separately from the multiresidue method in other sections of the same document (in Table 1 on Page 10), even though other drug classes are not, such as beta-lactam antibiotics, hormones, analgesic drugs, or sulfonamides. (See Appendix A for details.) This adds confusion about which compounds were actually included in the 2015 NRP and how many samples were analyzed for each compound, particularly because in some instances the listed target sample size is lower than for the multiresidue method.[158]

Other transparency concerns include the fact that certain pesticides listed in the 2014 and 2015 Blue Books (i.e., clofentezine, L-cyhalothrin, cypermethrin, deltamethrin, and mirex) are missing from the relevant analytical guideline that should specify their chemical analysis,[159] and also the lack of a transparent statistical justification for the selected sample size in the 2015 sampling plan. The calculations in the 2012 Red Book are not directly applicable to the 2014 sampling plan because before the 2013 Red Book was published, the only available detailed sample size calculation was provided in the 2012 Red Book, and these numbers were calculated for a probability of 90 or 95 percent detection even though that probability increased to 99 percent in the 2015 NRP. The appendix of the 2013 Red Book provides a detailed explanation of the sample size calculation, which will hopefully be incorporated into future versions of the Blue Book.

Inadequate reporting of the NRP's results is also demonstrated by the fact that the total number of samples analyzed as part of the scheduled sampling in the 2012 NRP is not consistently reported across the publication. According to the Executive Summary (Page 7), the total number of samples collected as part of the domestic scheduled sampling program was 5,838 (5,513 samples from U.S. federal plants and 325 samples from U.S. state plants).[160] A reader trying to recapitulate this number based on the various tables in the report (with no summary table provided) is left to calculate this number by adding the total number of pre-August samples reported in Table 4 and the total number of post-August samples reported in Table 16.[161] This calculation is not immediately obvious, especially because the tables are placed several pages apart in the report. Even more confusing is the fact that this calculation only yields 5,513 samples (3,282 pre-harvest samples and 2,231 post-harvest samples, respectively). This may indicate that the 325 samples from the U.S. state plants were omitted from the tables in which they should have been reported, and it raises concerns about the transparency and accuracy of the data reported. These concerns have been addressed in the 2013 and 2014 Red Books.

Similarly, the total number of samples analyzed for each compound in the inspector-generated sampling is not

* Some of the concerns identified in the 2012 Red Book have been addressed in the most recent Red Book releases, which occurred after a draft of this report was shared with FSIS as well as EPA and FDA. Instances where concerns have been addressed are highlighted above.

obvious from the 2012 Red Book, at least not without very complex and error-prone back-calculations between numerous tables and numbers cited in the text. For example, one analgesic drug, flunixin, was only analyzed in a subset of samples: those that were positive in screening tests conducted as part of the in-plant part of the inspector-generated testing; samples collected as part of other components of the inspector-generated sampling (i.e., COLLGEN, SHOW, STATE) were not tested for flunixin. Because the number of analyzed samples is crucially important for calculating positive rates and these numbers can easily be included in the relevant tables, it appears questionable why these numbers are not provided. These concerns were addressed in the 2013 and 2014 Red Books.

Endnotes

1 Competent authorities, in this context, are the authorities tasked with regulatory oversight over the drug approval process in a given jurisdiction.

2 Food Safety and Inspection Service, "United States National Residue Program (NRP) for Meat, Poultry, and Egg Products: Residue Sampling Plans" (traditionally known as the Blue Book) (2015).

3 See supplemental Appendix G.

4 "Unavoidable Contaminants in Animal Food and Food Packaging," 21 C.F.R. 109 and 509 (2015), https://www.gpo.gov/fdsys/granule/CFR-2012-title21-vol2/CFR-2012-title21-vol2-part109 and https://www.gpo.gov/fdsys/granule/CFR-2014-title21-vol6/CFR-2014-title21-vol6-part509.

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18 Food Safety and Inspection Service, "United States National Residue Program (NRP) for Meat, Poultry, and Egg Products: 2013 Residue Sample Results" (traditionally known as the Red Book) (2015).

19 This number is provided in Table 23, Page 44; the executive summary, Page 8, actually lists 1,166 residue tissue violations.

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