• American Public Health Association • Center for Science in the Public Interest •
• Consumer Federation of America • Consumers Union •
• Environmental Defense • Food Animal Concerns Trust •
• Global Resource Action Center for the Environment •
• Institute for Agriculture and Trade Policy •
• Natural Resources Defense Council • Physicians for Social Responsibility •
• Science and Environmental Health Network • Sierra Club •
• Union of Concerned Scientists •

August 3, 2000

Office of Health Communication
National Center for Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road, Atlanta, GA 30333
VIA FAX: 404-639-5489
cc: VIA EMAIL aractionplan@cdc.gov

Dear Sir or Madam:

We appreciate the opportunity to comment on the Interaction Task Force's "Public Health Action Plan to Combat Antimicrobial Resistance." Although the Plan's comprehensive provisions on medical overuse of antibiotics are laudable, and though it contains some useful items related to agricultural antibiotic use, **we are extremely disappointed by the Plan's conspicuous failure to advocate a straightforward initiative that could *immediately* be launched to substantially reduce unnecessary use of medically important antibiotics – namely, banning the subtherapeutic use of those antibiotics in animal agriculture.** ("Medically important antibiotics" – those that are used human medicine or are closely related to such antibiotics – that are also used subtherapeutically in animals include penicillin, tetracyclines, erythromycin, and bacitracin, as well as tylosin and lincomycin (both are related to erythromycin) and virginiamycin (related to Synercid).

In contrast to the complexities of convincing millions of doctors and patients to change their behavior to limit medical overuse of antibiotics (which is clearly a vital objective), existing legal authorities allow direct restriction of the roughly 40% of antibiotics that are used in agriculture each year. However, the Plan merely provides for the "refine[ment] and implement[ation] of the proposed FDA framework for approving new antimicrobial drugs and, *when appropriate*, for re-evaluating currently approved veterinary antimicrobial drugs" (Action Item #61). Even then, the Plan fails to specify a date by which the Framework will be implemented and protective actions taken – instead, the timeline is described as "initiated." Moreover, the Framework itself is quite weak, as previously noted by many of the signatories to this letter.

The Plan suffers from other notable weaknesses as well. Although it states that agencies will "develop and implement procedures for monitoring antimicrobial drug use" in agriculture (Action Item #5), it fails to specify that antibiotic producers will be required to submit these data. Nor does it suggest that these data will be made available to the public in any form, much less provide any timeline for actually doing so. It is outrageous that such data are not now available to both policymakers and the public, given their relevance in setting policy in this critical area.

In addition, the Plan fails to provide for meaningful steps addressing antibiotics in animal wastes from confined animal feeding operations (CAFOs), also known as factory farms. Rather, it merely calls for pilot studies – which would not even be *initiated* for three to five years – on the extent of environmental contamination from antibiotic residues in animal wastes (Action Item #21).

In short, the steps described in the Plan's agricultural provisions simply are not commensurate with the severity of this emerging public health crisis.

We urge the Task Force to strengthen the Plan's provisions on animal agriculture by including the following commitments and timeframes for action:

1. **Ban subtherapeutic use of medically important antibiotics:** By August 2001, FDA will propose a rule barring subtherapeutic uses of medically important antibiotics, and will take final action on that proposal by October 2002. The rulemaking should also specify that no future approvals will be granted for subtherapeutic use of medically important antibiotics.
2. **Rescind approval of fluoroquinolones for therapeutic use in poultry:** By December 2000, FDA will propose to rescind the approval of fluoroquinolones for therapeutic use in poultry, and will take final action on that proposal by February 2002. Fluoroquinolones are the drug of last resort for treating multi-drug resistant Salmonella.
3. **Require submission of key data on antibiotic use**: By April 2001, FDA will propose a rule requiring submission of data on antibiotics used in animal agriculture (e.g., production volume, drug form, and animal species), and will take final action on that proposal by June 2002. FDA should also commit to promptly making those data available to the public (in aggregated form where needed to protect legitimate trade secrets). These data should be made available in a format consistent with the epidemiological disease surveillance databases currently used by the Centers for Disease Control.
4. **Limit antibiotics in "factory farm" wastewaters**: By December 2000, EPA will propose effluent guidelines under the Clean Water Act that include limitations on antibiotics in effluents from confined animal feeding operations (CAFOs), and will take final action under that proposal by [insert Consent Decree date]. (Additional information on this issue is provided in a letter sent to EPA today (copy attached))

Given the growing crisis of antibiotic resistance, these actions – particularly the first – must be pursued vigorously. At the same time, we recognize that some other elements of the Action Plan will help smooth the transition away from use of medically important antibiotics, notably provisions for additional research on alternative husbandry and use of probiotics. We support these elements as well, along with efforts to curtail inappropriate medical use in humans. In addition, we support requiring prescriptions for all veterinary uses of all antibiotics as an essential aspect of assuring appropriate use of antibiotics.

Sincerely,

American Public Health Association
Center for Science in the Public Interest
Consumer Federation of America
Consumers Union
Environmental Defense
Food Animal Concerns Trust
Global Resource Action Center for the Environment
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Natural Resources Defense Council
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Science and Environmental Health Network
Sierra Club
Union of Concerned Scientists

(For further information, please contact Karen Florini, Senior Attorney, Environmental Defense, 1875 Connecticut Ave., Suite 1016, Washington, DC 20008, 202/387-3500.)

ATTACHMENT

- **American Public Health Association • Center for Science in the Public Interest •**
- **Environmental Defense • Global Resource Action Center for the Environment •**
- **Institute for Agriculture and Trade Policy • Natural Resources Defense Council •**
- **Science and Environmental Health Network • Sierra Club •**
- **Union of Concerned Scientists •**

August 3, 2000

The Honorable Charles Fox
Assistant Administrator for Water
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Mr. Fox:

The undersigned health, environmental, and agricultural groups are writing to urge that the Agency include a limitation on the discharge of pathogens and antibiotics in the upcoming effluent guidelines for Confined Animal Feedlot Operations (CAFOs), which are due to be proposed in December 2000. It is our understanding that the Agency has begun to examine issues related to setting a limit for pathogens in CAFO effluents, which we strongly support. However, it appears that **no** consideration has been given thus far to setting a limit for antibiotics themselves in CAFO effluents. It is critical that this issue be addressed in light of the possible contribution of antibiotics in CAFO effluents to the worsening crisis of antibiotic resistance - a crisis that poses a particular threat to children, the elderly, and others that may be more susceptible to bacterial diseases.

Background - The Emerging Crisis of Antibiotic Resistance

Antibiotic resistance looms as an emerging public health crisis for the 21st century. The advent of antibiotics following World War II has led to widespread use of these drugs in both human medicine and agriculture. But many antibiotics are losing their effectiveness as the target bacteria evolve resistance to them. The loss of antibiotics due to resistance reduces the number of drugs effective against infectious disease. The fewer the available drugs, the greater the likelihood that infectious diseases will ravage our society, as they did prior to the discovery of antibiotics before World War II.

Even loss of some treatment options can make once-treatable infections life threatening. Severely ill patients may die while physicians sequentially prescribe one antibiotic after another until they find one that is effective. Moreover, many people are allergic to certain antibiotics. If only one antibiotic remains to treat a disease and a person is allergic to it, the disease may be untreatable for that person.

Overuse of antibiotics in agriculture has led to serious antibiotic resistance problems in foods. Strains of *Salmonella* and other disease-causing organisms found in raw and undercooked meat are increasingly resistant to several antibiotics. One strain of *Salmonella* that is resistant to five different antibiotics increased from 0.6% of specimens tested in 1980 to 34% in 1997.

Moreover, bacteria can transfer resistance genes to unrelated species of bacteria, potentially contributing to resistance problems in a wide variety of pathogens. Already, drug-resistant diseases from tuberculosis to septicemia are realities in clinics and hospitals. The instances of reduced treatment options, clinical failures, and virtually untreatable diseases continue to rise.

The Role of CAFOs

About 40% of all antibiotics used in the United States are used in animal agriculture, with animal production increasingly concentrated in CAFOs. Given that total production of antibiotics in the U.S. now exceeds 50 million pounds annually, and given that a significant fraction of animals are produced in CAFOs, the usage of antibiotics in CAFOs is on the order of millions of pounds each year.

Although some antibiotics may be significantly metabolized, many are largely excreted intact and thus can be present in CAFO effluents. Indeed, as noted by the Ecological Exposure Research Division of EPA's National Exposure Research Laboratory, "[i]n some cases as much as 80% of antibiotics administered orally pass through the animal unchanged into bacteria rich waste lagoons and is then spread on croplands as fertilizer leaving the antibiotics available for entry into ground water and runoff into surface waters carrying both the drugs and resistant bacteria or genetic material (R-plasmids) to other bacteria in soils and waterways."

Similarly, at a March 2000 symposium of the American Chemical Society on Pharmaceuticals and Personal Care Products in the Environment, scientists from the U.S. Geological Service noted that "antibiotics are transported into surface and ground water in areas with animal feeding operations." Scientists from USDA observed that "land disposal of animal manure could also introduce pharmaceuticals in surface water and in groundwater." In addition, a Swiss study found high levels of veterinary antibiotics in two lakes in the region of Switzerland with the highest density of animals; the large amounts of sulfonamides – antibiotics used in animal feed – suggested the source might be runoff from land adjacent to the lakes. (Abstracts of cited studies from the Symposium are contained in the Appendix to this letter.)

Recently, scientists from the U.S. Centers for Disease Control and Prevention investigated levels of antibiotics in CAFO lagoon wastewater, as well as in agricultural drainage wells, monitoring wells near the lagoons, and tile line inlets and outlets. For example, tetracyclines were measured at levels ranging from 11 to 540 micrograms per liter (jt g/L), beta lactams at 2.1 to 3.5 jt g/L, and macrolides at 15 to 275 jt g/L.

Previously, other investigators had tested effluents from German sewage treatment works and groundwaters/surface waters for 18 antibiotics representing macrolides, sulfonamides, penicillins, and tetracyclines. The penicillins (which are susceptible to hydrolysis) and the tetracyclines (which can precipitate with calcium and similar cations) were not found, but the others were detected in the microgram per liter range. Since CAFO effluents do not enter sewage treatment works and thus may undergo less hydrolysis and precipitation, the penicillins and tetracyclines may also be present in CAFO effluents. Italian researchers have also reported the presence of tylosin and erthromycin in river water and sediments in Italy. In addition, oxytetracycline has been detected in sediments under fish farms.

Although the environmental persistence of antibiotics used in CAFOs varies, it is important to note that even those with short half-lives may be of concern. As noted by the Chief of the Environmental Chemistry Branch of EPA's own National Exposure Research Laboratory, "chemicals continually infused to the aquatic environment essentially become 'persistent' pollutants even if their half-lives are short — their supply is continually replenished." The ongoing release of antibiotic-containing CAFO wastes thus means that even readily degraded antibiotics essentially act as persistent contaminants in the environment.

Finally, spillage of feed containing antibiotics may also contribute antibiotics to CAFO effluents directly, without passing through animals. The extent of this potential pathway apparently has not been studied to date.

Once antibiotics have entered CAFO effluents, they can enter waterways and spread through the environment in relatively low concentrations – thus killing susceptible bacteria and leaving resistant survivors to multiply. Those resistant bacteria can subsequently come into contact with people who contact that water through recreational activities, or whose drinking water becomes contaminated. Indirect transmission may also occur (e.g., if pets enter water and then carry resistant bacteria into the home on their fur).

The Need for EPA Action

In light of the data described above, we believe EPA is obliged to gather the data needed to support inclusion of a limitation on antibiotics in CAFO effluents, and to propose such a limitation as part of its current CAFO effluent guideline development.

We request an opportunity to meet with you at your earliest convenience to discuss this issue. To arrange such a meeting, please contact Tim Searchinger or Karen Florini at Environmental Defense, 202/387-3500, 1875 Connecticut Ave., NW, Suite 1016, Washington, DC 20008.

Very truly yours,

American Public Health Association, Washington, D.C.
Center for Science in the Public Interest, Washington, D.C.
Environmental Defense, Washington, D.C.
Global Resource Action Center for the Environment, New York, NY
Institute for Agriculture and Trade Policy, Minneapolis, MN
Natural Resources Defense Council, Washington, D.C.
Science and Environmental Health Network, Boston, MA
Sierra Club, Washington, D.C.
Union of Concerned Scientists, Washington, D.C.

APPENDIX

ISSUES IN THE ANALYSIS OF ENVIRONMENTAL ENDOCRINE DISRUPTORS

Monday, March 27, 2000
American Chemical Society National Meeting
San Francisco, CA
Pharmaceuticals and Personal Care Products in the Environment – An Emerging Concern

Selected Abstracts (reproduced in full):

Occurrence of antibiotics in surface and ground water near confined animal feeding operations and waste water treatment plants using radioimmunoassay and liquid chromatography/electrospray mass spectrometry. M. Meyer, D.W. Kolpin, J.E. Bumgarner, J.L. Varns and J.V. Daughtridge. U.S. Geological Survey, 3916 Sunset Ridge Rd., Raleigh, NC 27607.

Approximately half of the 50 million pounds of antibiotics produced in the United States are used for agriculture and half for human health. Recent studies in Europe indicate that pharmaceutical compounds are common contaminants in surface water. Radioimmunoassay tests developed for clinical and regulatory use were adapted to screen for multiple classes of antibiotics in liquid waste and surface-water. A tandem reverse phase/mixed mode solid-phase extraction and liquid chromatography/mass spectrometry method was used to analyze for 21 analytes from four classes of antibiotics. Initial results indicate that antibiotics are transported into surface and ground water in areas with animal feeding operations and wastewater-treatment plants.

Concerns about pharmaceuticals in water reuse and animal waste. Herman Bouwer. U.S. Water Conservation Laboratory, USDA-ARS, 4331 E. Broadway Rd, Phoenix, AZ 85040.

Pharmaceuticals in sewage effluent could find their way into groundwater via seepage from contaminated streams and lakes, artificial recharge with sewage effluent, or drainage or deep-percolation from fields irrigated with sewage effluent. The latter is the most serious because contaminant concentrations in the deep-percolation water can be a multiple of those in the irrigation water. Land disposal of animal manure could also introduce pharmaceuticals in surface water and in groundwater.

Occurrence of macrolide and sulfonamide antibiotics in the aquatic environment of Switzerland.

Norriel S. Nipales, Christa S. McArdell, Eva Molnar and Walter Giger. Swiss Federal Institute for Environmental Science and Technology (EAWAG) and Swiss Federal Institute of Technology, (ETH), Ueberlandstrasse 133, PO Box 611, Dübendorf, CH-8600, Switzerland, fax: 41-1-823-5028, mcardell@eawag.ch.

Antibiotics are used in considerable amounts for the treatment of human infections and in veterinary medicine. Many of these substances end up in the aquatic environment, often unchanged, through natural excreta or improper disposal. The presence of antibiotics in the environment may contribute to increase resistance of microbes to some antibiotics. The aim of this study is to determine the amount of antibiotics that reaches the aquatic environment through different exposure routes, and to look at the environmental fate of these substances to provide a basis for risk assessment. Macrolide and sulfonamide antibiotics were used as model compounds. The developed method includes solid phase extraction followed by separation and quantification by LC-MS. Initial studies on waste water treatment plant effluents and lake water showed the presence of sulfamethoxazole, trimethoprim and some macrolide antibiotics up to concentrations of 60 ng/L.