Antibiotics in Dust Originating from a Pig-Fattening Farm: A New Source of Health Hazard for Farmers?

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Pig-house dust originates from feed, bedding, feces, and the animals themselves. If the animals receive drugs such as antibiotics, residues of these substances may occur in manure, in the air, or on surfaces of the respective animal house. In a retrospective study, we investigated dust samples collected during two decades from the same piggery for the occurrence of various antibiotics. In 90% of these samples, we detected up to five different antibiotics, including tylosin, various tetracyclines, sulfamethazine, and chloramphenicol, in total amounts up to 12.5 mg/kg dust. High dust exposure in animal confinement buildings is believed to be a respiratory health hazard because of the high content of microorganisms, endotoxins, and allergens. Further risks may arise from the inhalation of dust contaminated with a cocktail of antibiotics. Apart from that, our data provide first evidence for a new route of entry for veterinary drugs in the environment. *Key words:* **antibiotics, dust, farmer, liquid chromatography, mass spectrometry, pig fattening, veterinary drugs.** *Environ Health Perspect* **111:1590–1594 (2003). doi:10.1289/ehp.6288 available via** *http://dx.doi.org/* **[Online 18 June 2003]**

In recent years, there has been growing interest in the occurrence, fate, and possible effects of human and veterinary drug residues in the environment (Daughton and Ternes 1999; Halling-Sørensen et al. 1998; Kümmerer 2001; Witte 1998). Studies with a special focus on drugs used in human medicine have established that these compounds mainly reach surface waters via the release of effluent from sewage treatment plants. Today, up to 80 compounds have been identified and quantified in the low range of nanograms to micrograms per liter (Heberer 2002). Studies performed in the United Kingdom, Denmark, Germany, and the United States reveal that these agents represent a new class of organic environmental contaminants worldwide (Kümmerer 2001). There is concern about effects resulting from the entry of these compounds into the environment, including the possibility of the spread of antibiotic resistance (Witte 1998) and/or effects on the endocrine system because of the ability of some of these compounds to behave as hormones (Daughton and Ternes 1999).

At present there are very few established routes for the entry of veterinary drugs into the environment. Recently, sophisticated analytical liquid chromatography combined with tandem mass spectrometry (LC-MS-MS) has led to the detection of tetracyclines on farmed land at concentrations of up to 300 μg/kg soil, which demonstrated that this group of antibiotics is persistent and can accumulate in soil after repeated fertilization with liquid manure from intensive pig farming. Furthermore, these field studies gave no proof of leaching of these compounds into deeper soil segments or into groundwater because of the strong sorption of the drugs in topsoil (Hamscher et al. 2000, 2002). Presently, there is only limited information available on the direct effects of these drugs on soil biota. Investigations in this field are difficult to perform because the soil microorganism community is a very complex system with at least 90% of the bacteria living in this compartment unidentified (Nwosu 2001).

Large-scale use of tetracyclines and several other veterinary drugs (e.g., various sulfonamides, tylosin) in pig production is common not only within the European Union (Anonymous 2001) but also in the United States (Kolpin et al. 2002) and, to our best knowledge, in China, Southeast Asia, and Russia. These drugs are in use or have been in use for many years as feed additives and for prophylactic, metaphylactic, and therapeutic purposes.

Large-scale pig production represents a considerable source of dust (Hartung 1997, 1998; Pedersen et al. 2000). This results both in high dust exposure for farmers and farm workers in animal confinement buildings, causing respiratory health hazards (Iversen et al. 2000; Nowak 1998; Platz et al. 1995; Radon et al. 2002), and in emissions of dust particles into the environment by way of the exhaust ventilation air (Hartung 1995; Seedorf and Hartung 2002). About 85% of the dust from animal confinement buildings consists of organic material, including protein (from pig skin), animal feed, endotoxins, fungi, and bacteria (concentrations of up to 50 million colony-forming units per gram of dust) (Hartung 1997). Today, there is no doubt regarding the health hazards of dust in animal confinement buildings, but there is still little knowledge concerning the possible risk of specific substances in dust (Nowak 1998). To determine whether antibiotics may also be contaminants in dust from animal confinement buildings, we undertook a retrospective study to analyze dust samples collected from a pig-fattening farm during the years 1981 to 2000 for the occurrence of various antibiotics, including tetracyclines, sulfonamides, tylosin, and chloramphenicol.

Materials and Methods

Collection of dust samples. We studied sedimentation dust collected from 1981 to 2000 in a 350–420-head pig finishing unit (60–110 kg live weight) over periods of 14–30 days using a standardized metal frame with an effective sampling surface area of 3,002 cm^2 (38 × 79 cm) covered with fresh aluminum foil. The sampling frame stood approximately in the middle of the pig house, where there was no exposure to high air currents, 1.5 m above the floor, which is the typical breathing height of humans. After the collecting period (each year 10–15 samples were collected in the piggery, one of which was then randomly selected for analysis in this study), technicians carefully sampled the dust from the aluminum foil using a clean, new brush and placed it into glass vials sealed with tight stoppers. Before sampling, we removed any remaining dead insects, spiders, and coarse particulate matter originating from ceiling materials. After the collection process, technicians covered the metal frame with fresh aluminum foil for the next collecting period and removed the glass containers to the laboratory, where they were allowed to cool down gradually for storage at 4°C.

Sample preparation and measurement. We removed 0.1 g samples from each of the glass

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We thank M. Mock and J. McAlister-Hermann for critical review and for careful proofreading of the manuscript.

S.S. was supported by a grant from the Wilhelm-Schaumann-Stiftung, Germany. We are grateful to the Volkswagenstiftung, Germany, for financial support to equip the laboratory for residue analysis in the Department of Food Toxicology.

The authors declare they have no conflict of interest.

Received 18 February 2003; accepted 17 June 2003.

containers and mixed them with 1.0 mL citrate buffer (pH 4.7), twice-extracted with 6 mL ethyl acetate as previously described for soil and liquid manure (Hamscher et al. 2002). We evaporated ethyl acetate to dryness and reconstituted samples with 1 mL 90% acetonitrile/10% 100 mM ammonium acetate.

We conducted high-performance liquid chromatography (HPLC) separation on a Puresil C18 Column (Waters Corp., Milford, MA, USA) with a gradient solvent system consisting of 0.5% formic acid (Riedel-de Haen, Seelze, Germany) in water containing 1 mM ammonium acetate (Merck, Darmstadt, Germany) (solvent A, pH 2.5) and acetonitrile (Baker, Griesheim, Germany) (solvent B), using an injection volume of 8 µL. We measured all compounds under investigation using two HPLC runs. First, we used the conditions recently described for the separation of tetracyclines, tylosin, and chloramphenicol (Hamscher et al. 2002). We baseline separated and analyzed seven sulfonamides with a modified gradient system for the second run (i.e., 100% solvent A for 1 min, linear gradient to 25% solvent B for 9 min, linear gradient to 50% solvent B for 1 min, and finally 50% solvent B for 3 min). After elution of the antibiotics, we rinsed the column for 3 min with 99% solvent B and reequilibrated it with 100% solvent A for 8 min.

We performed tandem mass spectrometry (MS-MS) for detection using an LCQ ion trap with an electrospray ionization source (Finnigan Mat, San Jose, CA, USA), with the source polarity set negative for chloramphenicol and positive for all other compounds investigated. The spray needle voltage was –5 kV for chloramphenicol and +5 kV for all other compounds. In the case of chloramphenicol, we turned the source fragmentation on with a collision energy set at 10 V. Drying gas was nitrogen generated from pressurized air in an Ecoinert 2 ESP nitrogen generator (DWT-GmbH, Gelsenkirchen, Germany). We set the sheath gas flow at 100 units and turned off the auxiliary gas; the capillary temperature was 150°C (described in detail by Hamscher et al. 2002). Table 1 contains the optimized LC-MS-MS conditions.

Calibration curves constructed for the three tetracyclines, tylosin, and the seven sulfonamides ranged from 0.1 to 10 ng per injection and were linear with $r^2 > 0.99$ for the MS-MS procedure. We obtained quantification by comparing the peak areas of the sample with that of the external calibration curves and corrected all data for recovery.

Because of matrix effects (signal enhancement) during LC-MS-MS analysis, we based calculations for chloramphenicol on the method of standard addition. Therefore, we spiked the sample from 1989 with chloramphenicol standard additions of 1, 2.5, and 5 mg/kg and the samples from 1991 and 1992 with chloramphenicol standard additions of 1, 2.5, 5, and 10 mg/kg. Then we constructed a linear regression curve. Finally, we calculated the concentration in the sample from the intercept of this regression curve with the *x*-axis.

Recovery studies. We conducted recovery studies with residue-free dust samples at concentrations of 0.2, 0.5, and 1.0 mg/kg. We calculated the recovery rates as an average of three individual experiments. The limit of quantification based on these studies was 0.1 mg/kg for the tetracyclines and tylosin and 0.05 mg/kg for the sulfonamides. The limit of detection was approximately 2-fold lower.

Results

Table 2 shows the summary of all results for this retrospective study, and Figure 1 presents the molecular structures of all detected antibiotics. We detected up to five different antibiotics at total concentrations ranging from 0.2 to 12.5 mg/kg dust in 18 of 20 samples; chromatograms and mass spectra of a sample containing five antibiotics are shown in Figure 2. Tylosin was present in 16 of 20 samples, three of which had concentrations of > 5 mg/kg. In 13 samples, sulfamethazine was present at concentrations of up to 2.9 mg/kg, and several tetracyclines were present in 12 samples (0.2–5.2 mg/kg). In another three samples, we detected chloramphenicol—which

Table 1. Characteristics of HPLC and MS-MS methods: retention times (RT), optimized MS-MS parameters, and product ions for the determination and quantification of various antibiotics in dust.

Method/compound	RT (min)	Precursor mass (*m/z*)	Collision energy (%)	Product ions, *m/z* (relative abundance, %)
HPLC method 1				
Oxytetracycline	7.21	461	20	426 (7), 443* (100), 444 (9)
4-epi-Tetracycline	7.17	445	20	410 (6), 427* (100), 428 (13)
Tetracycline	7.52	445	20	410 (4), 427* (100), 428 (7)
4-epi-Chlortetracycline	8.07	479	27	444* (68), 461* (51), 462* (100)
Chlortetracycline	8.48	479	27	444* (51), 461* (54), 462* (100)
Tylosin	9.60	917	28	754 (3), 772* (100)
Chloramphenicol	10.34	321	24	176 (9), 194* (100), 237* (8), 249* (13), 257 (10)
HPLC method 2				
Sulfadiazine	8.66	251	30	92 (7), 94 (10), 108 (10), 156* (68), 174* (100)
Sulfathiazole	9.38	256	27	108 (5), 156* (100), 174 (2)
Sulfamerazine	9.81	265	30	92 (5), 108 (5), 156* (19), 174* (56), 190* (100)
Sulfamethazine	10.66	279	30	124 (6), 156 (3), 174 (4), 204* (100)
Sulfamethoxypyridazine	11.42	281	30	108* (9), 126* (28), 156* (100), 188 (11), 215* (21)
Sulfamethoxazole	13.20	254	34	108 (9), 147* (45), 156* (72), 188* (100), 190* (42), 194* (13)
Sulfadimethoxine	13.73	311	33	108 (9), 156* (100), 218* (29), 245* (97)

*Ion used for quantification.

Table 2. Antibiotic residues in pig-house dust.

Sampling year	OTC (mg/kg)	TC[a] (mg/kg)	CTC[a] (mg/kg)	TYL (mg/kg)	CAP (mg/kg)	SMZ (mg/kg)	Sum (mg/kg)
1981	1.10	—	—	0.42	—	1.85	3.37
1982	0.18	—	—	0.09	—	0.06	0.33
1983	—	0.19	2.12	5.65	—	2.90	10.86
1984	—	—	—	—	—	—	—
1985	—	—	—	—	—	—	—
1986	—	—	—	12.18	—	0.32	12.50
1987	—	—	—	8.72	—	0.39	9.11
1988	—	—	—	0.72	—	0.43	1.15
1989	—	—	—	0.45	1.96	0.34	2.75
1990	—	—	—	0.14	—	0.09	0.23
1991	0.43	—	0.32	0.26	9.07	0.41	10.49
1992	—	—	—	0.35	5.49	0.05	5.89
1993	—	0.19	—	0.10	—	0.12	0.41
1994	—	0.23	—	0.37	—	0.12	0.72
1995	—	0.37	0.52	0.29	—	—	1.18
1996	0.29	5.18	—	0.55	—	0.16	6.18
1997	—	0.47	—	0.16	—	—	0.63
1998	—	0.50	—	0.20	—	—	0.70
1999	—	0.61	—	—	—	—	0.61
2000	—	0.19	—	—	—	—	0.19

Abbreviations: —, not detectable; CAP, chloramphenicol; CTC, chlortetracycline; OTC, oxytetracycline; SMZ, sulfamethazine; TC, tetracycline; TYL, tylosin. The values (mg/kg dust) represent the means of two replicates per sample, which have been corrected for mean recovery investigated in the concentration range of 0.2–1.0 mg/kg: 103 ± 21% for OTC, 89 ± 21% for TC, 94 ± 18% for CTC, 27 ± 8% for TYL, and 49 ± 16% for SMZ. Calculations for CAP were based on the method of standard addition as described in "Materials and Methods." SMZ was the only sulfonamide that could be detected.
[a]Including their 4-epimers.

has been prohibited for use in animal husbandry in the European Union since 1994—at levels between 2.0 and 9.1 mg/kg.

Discussion

The use of high amounts of veterinary drugs has led to the occurrence of tetracycline and sulfonamide residues in liquid manure and soil, as well as in surface water and, in the case of sulfonamides, also in groundwater (Berger et al. 1986; Hamscher et al. 2000, 2002; Langhammer et al. 1988; Lindsey et al. 2001; Winckler and Grafe 2001). The highest concentrations occurred in liquid manure (milligram per kilogram range) and in soil (microgram per kilogram range), with trace amounts in surface water and groundwater samples (lower microgram per liter range). In comparison, the present investigation showed that dust originating from a pig-fattening farm represents a new route of entry into the environment for drugs applied in animal houses. The lower milligram per kilogram concentration range and the number and frequency of compounds detected in dust may indicate a possible health risk for humans via this environmental source. The antibiotics in dust may originate mainly from animal feed mixed with veterinary drugs, for example, for therapeutic use. This feed is usually in powder or pellet form, which can release distinct amounts of dust during handling. Another source of antibiotics may be dried liquid manure particles, which are regular constituents of dust in animal confinement buildings (Donham 1993). Because sulfonamides and tetracyclines are poorly metabolized in pigs, high amounts of the parent drugs are therefore excreted, and these substances build residues in liquid manure (Berger et al. 1986; Donham 1993; Hamscher et al. 2002; Winckler and Grafe 2001). We recently demonstrated the stability and accumulation of tetracyclines in dried liquid manure particles in environmental samples (Hamscher et al. 2002).

High dust exposure in animal confinement buildings may be a respiratory health hazard mainly because of the high contents of bacteria and endotoxins (Iversen et al. 2000; Nowak 1998; Platz et al. 1995; Radon et al. 2002). Our investigation suggests that antibiotics may play a novel and additional role in the assessment of this health hazard. In the present study we found several widely used veterinary drugs at substantial concentrations in dust samples from the last 20 years. The fact that these samples had been in storage at 4°C for this period suggests the persistence of these drugs in dust. Therefore, these preliminary results demonstrate the farmers' exposure (at least for up to 20 years) to various antibiotics via the contamination of dust. Consequently, allergic risks may arise from the occurrence of these compounds in the air. In particular, tylosin and sulfamethazine, which occurred in 80% and 65% of the samples, respectively, are drugs with known allergic potential (Barbera and de la Cuadra 1989; Caraffini et al. 1994; Choquet-Kastylevsky et al. 2002; Danese et al. 1994; Hjorth and Roed-Petersen 1980). In addition, farmers have been exposed to chloramphenicol, an antibiotic with severe side effects (Holt et al. 1993). Because of the genotoxicity of chloramphenicol and three of its metabolites (nitroso-chloramphenicol, dehydro-chloramphenicol, dehydro-chloramphenicol-base) in several *in vitro* and *in vivo* test systems, it was not possible to confirm an acceptable daily intake [Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) 1994]. Therefore, the European Union completely prohibited its use in livestock farming within its territory in 1994.

The development of antibiotic resistance is another risk that may also arise from the inhalation of dust contaminated with a cocktail of antibiotics. A recent survey on dust in pig-fattening buildings in Europe revealed average concentrations of inhalable airborne dust of 2.2 mg/m^3 (Takai et al. 1998). Consequently, a farmer working 8 hr/day in a confined pig building inhales about 6.3 mg of dust contaminated with approximately 0.02 µg of various antibiotics, assuming an average tidal volume of 0.5 L, 12 breaths/minute under resting conditions, and a total concentration of 3.4 mg of antibiotics per kilogram of dust (mean value derived from Table 2). This example includes several variables and can only give an estimate of the amount of antibiotics entering the respiratory tract of humans. In practice, the concentration of the antibiotics in the dust can be three times higher than that used in the calculation (Table 2). Furthermore, the dust concentration in the air is usually higher in winter than in summer, and the breathing rate can also be distinctly higher during work (up to 45 L), resulting in distinctly higher inhaled amounts of inhaled dust and antibiotics.

Although the resulting local concentration of antibiotics in the lung is far too low for any bacteriocidal or bacteriostatic effect, permanent exposure to subtherapeutic concentrations of various antibiotics represents optimal conditions for the development of antibiotic resistance.

An additional conclusion drawn from our study concerns the issue of dust as a source that can provide enormous amounts of information about the former and present use of veterinary drugs in intense livestock production. In the early 1980s, there was heavy use of tylosin in pig production, which is reflected in the analytical data obtained for 1983 and 1986–1987. Following the growing knowledge of possible allergic health hazards related to this compound (Barbera and de la Cuadra 1989;

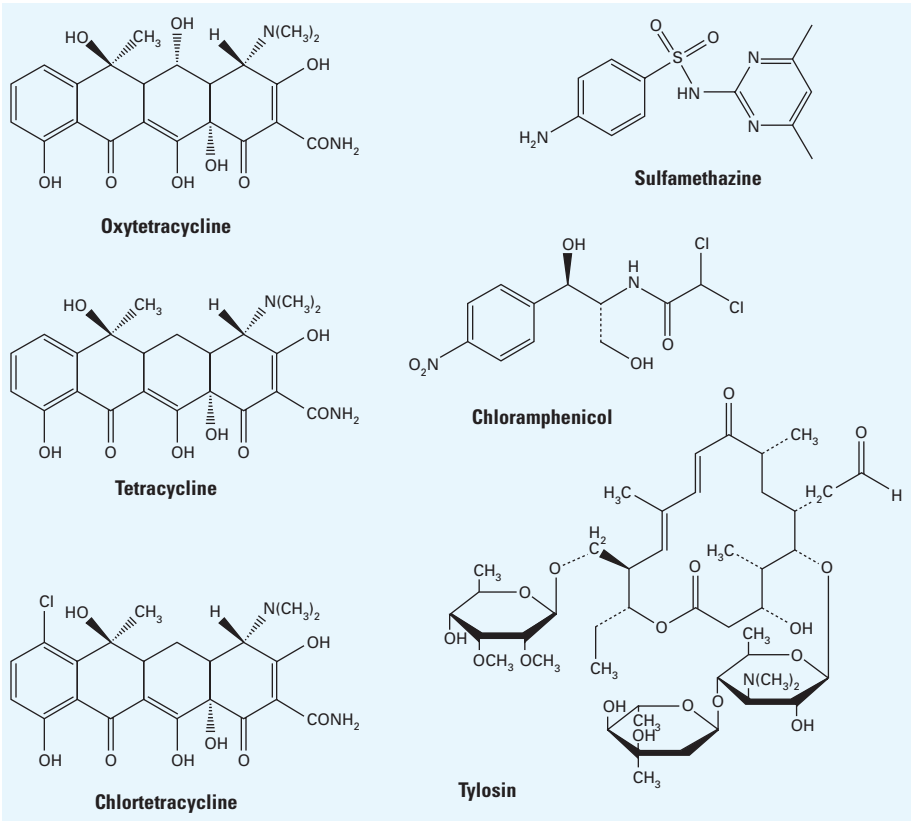

Figure 1. Molecular structures of the antibiotics frequently occurring in dust samples originating from a pig-fattening farm.

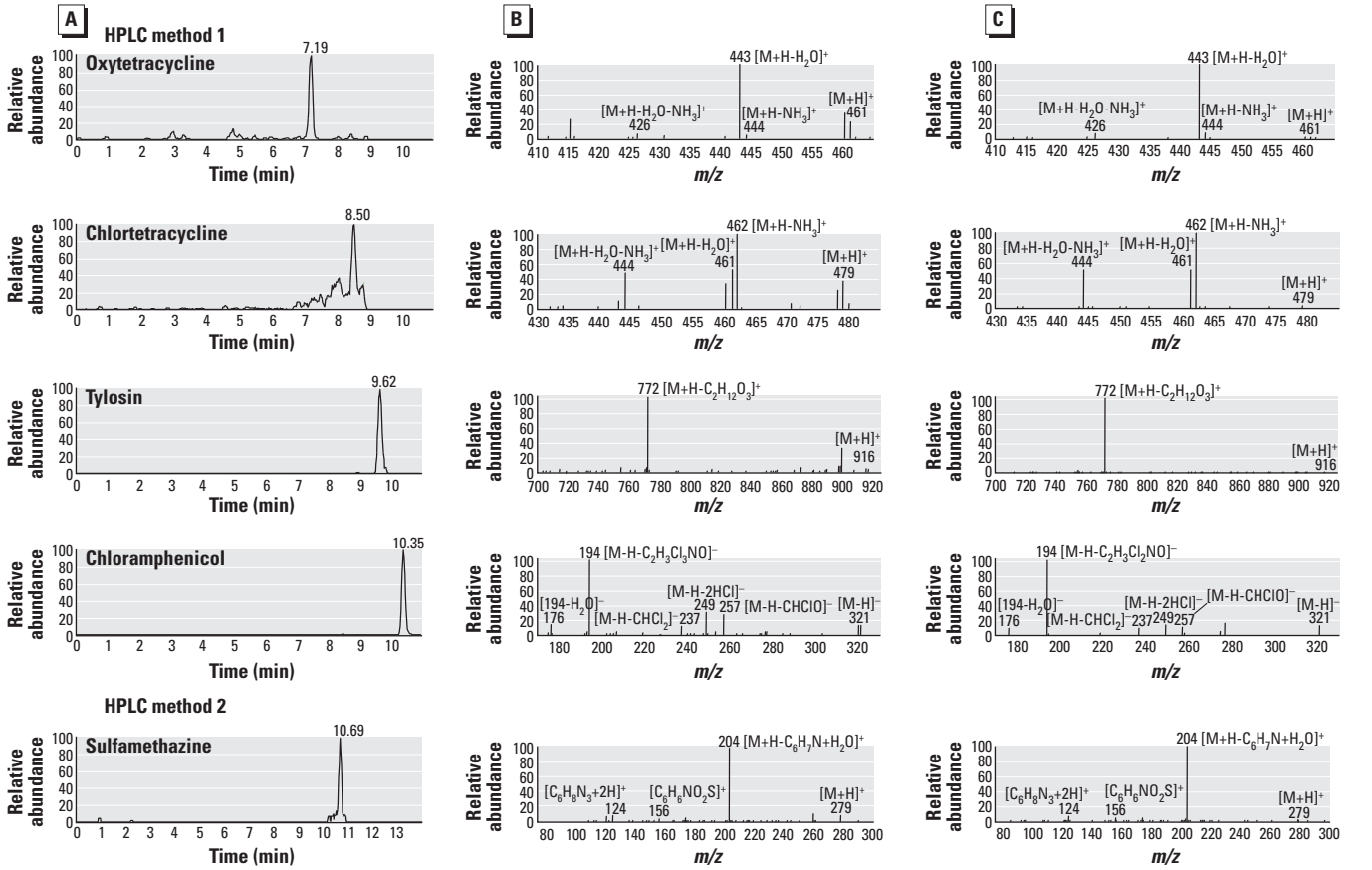

Figure 2. Chromatograms and mass spectra of compounds. (*A*) Reconstructed ion chromatograms of oxytetracycline (NL = 5.90 × 10^4; *m/z* = 443), chlortetracycline (NL = 7.34 × 10^4; *m/z* = 444 + 461 + 462), tylosin (NL = 6.43 × 10^4; *m/z* = 772), chloramphenicol (NL = 9.06 × 10^4; *m/z* = 194 + 237 + 249), and sulfamethazine (NL = 1.88 × 10^4; *m/z* = 204) in a dust sample analyzed with LC-MS-MS. (*B*) Corresponding tandem mass spectra of these compounds. (*C*) Tandem mass spectra obtained from a standard solution (representing 1 ng of each compound on column).

Caraffini et al. 1994; Danese et al. 1994; Hjorth and Roed-Petersen 1980) and its ultimate ban as a feed additive in the European Union in 1998, tylosin was no longer detectable in the dust samples collected in 1999 and 2000. We found chloramphenicol in only three samples before its ban in 1994 in intensive livestock farming in the European Union. Farm records reveal reconstruction of the confinement building in 1984; subsequently, no further use of antibiotics was necessary as a result of the animals' health status. Accordingly, the results show that the dust samples were free of any antibiotic compound for 1984 and 1985. Unfortunately, this antibiotic-free period was not permanent, and the data for 1986 show antibiotic use on an even greater scale than in previous years.

Conclusions

A new entrance route for veterinary drugs into the environment has been discovered. We detected substantial quantities of several antibiotics in dust from a pig finishing unit. Further efforts should be undertaken to confirm these preliminary findings, including the investigation of dust from larger pig production systems and from henhouses, and with a higher sampling frequency.

Because there may be adverse effects on animal and human health resulting from the exposure to dust contaminated with antibiotics, future research should take this type of exposure into consideration when assessing health risks to persons exposed to farm dust. This should include monitoring of human health, including the state of antibiotic resistance in farmers to antibiotics they are frequently exposed to.

In order to minimize the possible risks of antibiotics in dust, the use of antibiotics in livestock farming should be reduced whenever possible.

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