Too hard to crack?
eggs with drug residues

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report four in **the use and misuse of antiobiotics in UK agriculture** series

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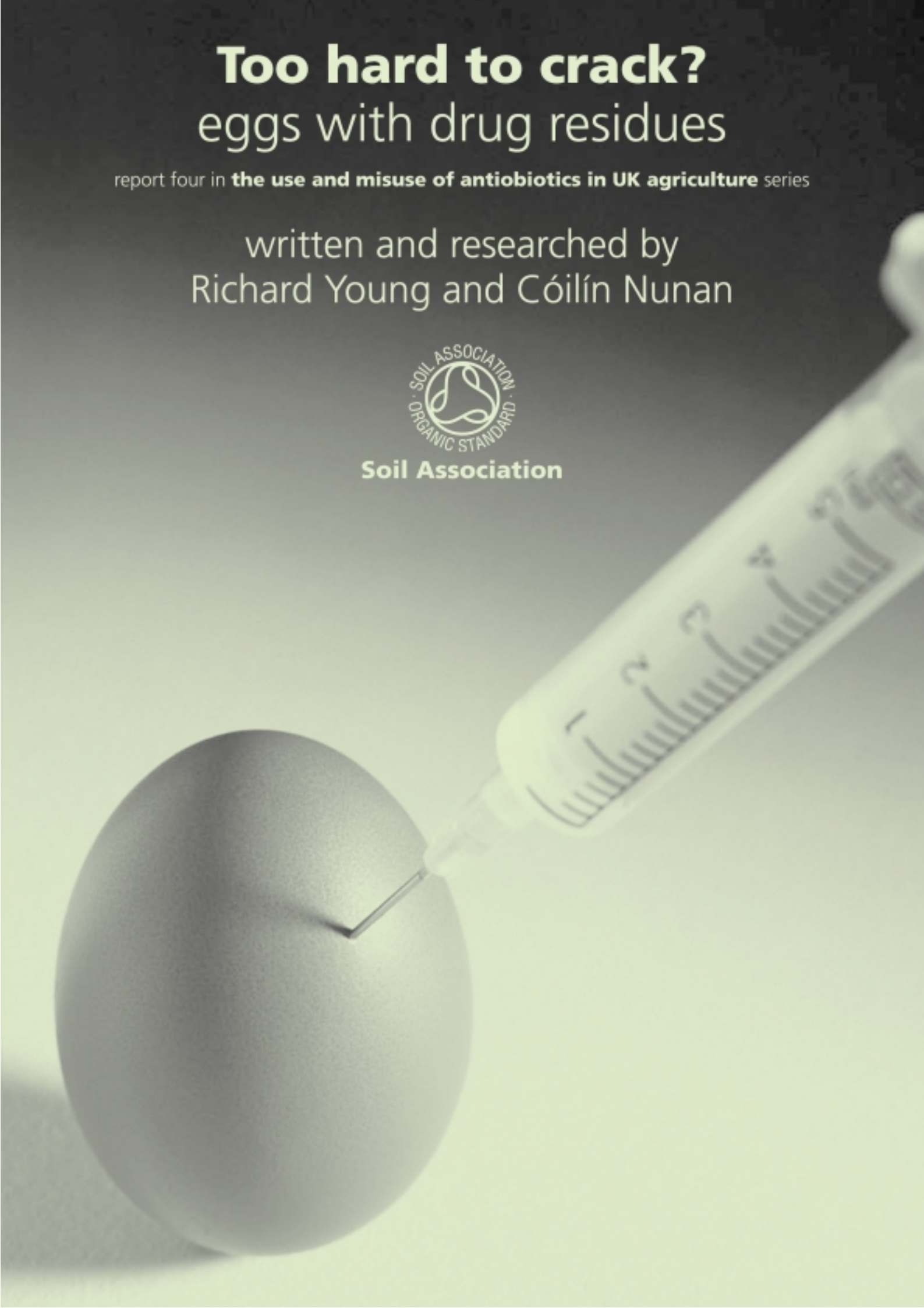

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Foreword

Peter Melchett - ***Policy Director, Soil Association***

For more than half a century the production of farm animals has been dominated by the intensive approach, not just here in Britain, but throughout the developed world. The welfare implications of taking animals out of fields and rearing them indoors in close confinement have been raised many times before. Ruth Harrison's book 'Animal Machines' brought the horrors of keeping sentient beings in this way to a wider public and organisations like Compassion in World Farming and Chickens' Lib were set up specifically to oppose this approach.

Industrialisation of livestock production has had even wider implications. It underpinned the post-war move away from mixed farming. For fifty years, the development of non-organic farming has been driven by the twin negative forces of continuous arable cropping and factory farming of animals. We can trace the decline of Britain's native song birds not just to the use of chemical sprays, but right back to the locking up of animals in sheds. We should not even call battery hens and broiler chickens farm animals, when their lives are so completely divorced from the land.

To maintain unnatural production systems it has been necessary to develop unnatural technologies, most notably in livestock production a range of drugs and feed additives to suppress the most obvious signs of disease.

Increasingly we have come to realise that the routine use of antibiotics to prop up the cruel, intensive approach has consequences for our own health. Antibiotic-resistant bacteria developing on farms can cause treatment failures for human patients suffering from serious food poisoning and have even contributed to the growing problem of hospital superbugs.

This report looks at another consequence of routine drug use - the presence of dangerous drug residues in food. It concentrates on just one drug and it shows how little is actually known about its impact on us, and how little regulators have attempted to find out. This raises a more general question – would a close examination of other drugs used in intensive animal production reveal similar concerns?

The GM juggernaut has been halted here in Britain for the time being. Increasingly we are realising that our countryside, the wildlife we all cherish and the health of farms animals depends largely on the way in which we farm the land. And our own health depends on our eating a healthy diet, with healthy food, and certainly not food contaminated with dangerous drug residues.

We hope this report will stimulate further debate about the future of food production, both organic and non-organic. This is a time of enormous change in agriculture. Large sums of public money are now being redirected, away from buying increased production to buying public goods – a beautiful countryside with more wildlife, less pollution, producing high quality food that people want to buy. We believe that the routine use of dangerous drugs that could affect human health should have no place in this new agriculture.

Executive summary

This report contains important food-safety information for British consumers which we feel should have been issued by the Food Standards Agency (FSA) last year. In 2003, over 12% of eggs tested by government scientists contained residues of lasalocid, a toxic antibiotic. Some of these eggs were contaminated at significantly higher levels than ever previously recorded in Britain. Even one sample of organic eggs was found to be positive. This is part of an alarming trend: official figures demonstrate the increasing incidence of lasalocid residues in eggs over the last six years.

Lasalocid is sold worldwide as Avatec® 15% by the pharmaceutical company Alpharma. It has been routinely added to some poultry feeds for nearly 30 years to control a parasitic infection, which is a problem in intensive systems. Although it is illegal to feed lasalocid to laying hens, eggs are extensively contaminated.

This report shows that last year many people will have ingested quantities of lasalocid which exceeded, sometimes many times over, the Acceptable Daily Intake - a key safety level that toxicologists rely on in safety assessments. This suggests potential health effects for some consumers. Certain subgroups of the population are particularly at risk. These include babies, young children, people with heart conditions or high blood pressure and those on diets, such as the Atkins diet, which recommend above average egg consumption.

This report also suggests there is a potential link between Sudden Adult Death Syndrome and the consumption of lasalocid residues in food.

Key findings

Increasing drug use

- Though data for lasalocid sales is considered commercially sensitive in the UK, it is known that total sales of lasalocid and three other drugs in the same class increased by 27% between 2000 and 2002, from 153 to 195 tonnes of active ingredient (about 1,200 tonnes of product), enough to medicate 2.5 million tonnes of chicken feed.

Residues

Residue levels

- The percentage of egg samples contaminated above 50 parts per billion (ppb) has increased from 0.5% in 1998 to 1% in 1999, 3.3% in 2000, 2.3% in 2001, 6.7% and 2002, and 12.4% in 2003.
- Sampling is 'targeted' to areas where inspectors believe problems are most likely. No information is available on what proportion of the industry is covered by this. However, if the 2003 results were representative of the whole industry, more than three million eggs eaten every day by British consumers would have been contaminated with lasalocid above 50 ppb.
- Last year some UK eggs contained lasalocid residues at 3,450 ppb. This report presents data showing that residues may be occurring at up to 18,000 ppb.

Inadequate testing

- Even though the problem is getting worse, roughly half as many tests are undertaken now as ten years ago. In 2003 UK regulators tested just 250 samples – yet we ate almost 10 billion eggs that year.
- Tests are carried out on a mixture of 12 eggs. The Food Standards Agency has confirmed that the results are average figures, which may not fully reflect contamination levels in individual eggs.
- No egg-based baby food has been tested since 1999, chicken liver is no longer tested using the most sensitive methods, and infant formula feed containing egg-yolk lecithin has never been tested.
- No eggs have so far been sampled in 2004 (up to the end of March).
- The UK does at least test for lasalocid in eggs, whereas many countries do not.

Which eggs are affected?

- Residues occur in free-range, battery and barn systems. Until recently no residues had been found in organic eggs, however one sample taken during 2003 contained 60 ppb.
- Contaminated eggs are not distributed evenly. When one egg in a box is contaminated, every egg in the box is likely to be contaminated.

Source of contamination

- Lasalocid is permitted in the feed of broilers, quail, turkeys. pheasants and of birds destined to become layers. Cross-contamination at the feed mill is the biggest single source of the problem, but use in young birds near laying age, failure to clean lorries between loads, the wrong feed being delivered and the wrong feed being fed on the farm are all implicated. A major feed additives website, sponsored by Alpharma, the manufacturers of Avatec, gives potentially dangerous information. In stating it is safe for the birds to include lasalocid in the feed of both laying hens and laying pullets, it could mislead some producers to believe this is also safe for consumers.

Organic farming

- Organic standards should be adequate to ensure that no residues of lasalocid occur in organic eggs, however, the use of conventional feed

mills to prepare organic rations and the use of conventionally reared layer replacements in organic egg production are clear weaknesses.

Regulatory muddle

No maximum residue limits in the UK

- The legislation governing the use of feed additives like lasalocid is effectively meaningless in the UK. This is because legally enforceable maximum residue limits (MRLs) for lasalocid in eggs and other foods have never been set. As a result no one gets prosecuted, regardless of how high the residues, or how often they occur. Neither Europe nor the United States have set an MRL either.
- However, an MRL of 50 ppb for lasalocid in eggs has been set in Australia. If Britain were to adopt the same safety limit, all the eggs reported in the UK as positive samples in 2003 would have contained illegal amounts of the drug. The highest level of contamination recorded was 69 times above this safety limit.

Safe levels of lasalocid consumption inappropriately assessed

- The acceptable daily intake (ADI) for any drug in humans is supposed to be based on experiments on the most sensitive animal species. The EU ADI for lasalocid, however, was established from studies on rats - one of the species least sensitive to lasalocid. Larger mammals are significantly more sensitive to lasalocid's toxicity. Even if rabbits had been the test species it is likely that the ADI would have been set well below its present level. In the UK/EU the ADI is 5 micrograms per kilo of human bodyweight (5 µg/kg). In Australia it has been set at 1 µg/kg.

No withdrawal period for young layers

- No withdrawal period has ever been suggested between lasalocid's use in layer-replacement birds and the sale of eggs from them. This despite the known fact that in some situations birds will begin to lay as early as the 16th week, when they can still legally receive lasalocid in feed and it is not known how long it takes for residues of lasalocid in laying birds to decline until they are no longer present in eggs.

No safety assessment for most commonly fed species

- Lasalocid is widely used in rearing layer replacements, pheasants and quail, yet its use in these species and any potential effects for human health resulting from this have never been reviewed by an EU scientific committee as they have been in broiler chickens and turkeys.

Breaches of safety limits

- In the absence of MRLs, British regulators issue reassurances about the safety of residue levels based on crude calculations of the extent to which these do or do not lead to breaches of the ADI. However, safety assessments using an ADI are less stringent than those using an MRL as they fail to take into account metabolites and undetectable residues, something which is done when an MRL is used. Regulators also significantly underestimate the average daily consumption of egg by young children and make no allowance for peaks in consumption

by individuals of all ages on any one day, a point acknowledged by the FSA.

- Calculations presented in this report show that breaches of the ADI are likely to have occurred in all age groups in 2003. Egg consumption data from the UK National Diet and Nutrition Survey confirms this.
- The largest breaches of the ADI probably occurred in babies. Lasalocid accumulates in egg yolk which is often recommended as a weaning food for babies as young as six months old because they contain high levels of essential fatty acids. Eating as many as four egg yolks a week has been recommended, yet eating only one egg yolk contaminated at recorded levels would result in the infant consuming 5 times more lasalocid than the ADI.
- ADIs do not apply to babies below 12 weeks of age. Despite this, no studies have been undertaken to establish how much lasalocid might be excreted in human milk. Comparing the way in which other antibiotics pass into milk, we suggest that babies may have consumed enough lasalocid through breast milk to breach the (lower) Australian ADI.
- Egg-yolk lecithin is included in some infant-formula milks, particularly those formulated for premature babies. There are scientific reasons for believing that lecithin will be a potent vehicle for lasalocid residues, but because infant formula with added egg yolk or egg-yolk lecithin has never been tested for lasalocid residues by British regulators it is not possible to estimate what breaches of the ADI may have occurred in this way.
- A 20 kg child consuming 2 eggs in one day contaminated at the highest level recorded in 2003 would have breached the ADI by more than three times.
- An adult eating four eggs in one day, which were contaminated at the highest level recorded in 2003, would have breached the ADI by more than twice.
- Since some eggs may have been contaminated at up to 18,000 ppb, far greater breaches of ADI may have occurred: babies may have consumed up to 25 times more lasalocid than the ADI and adults may have consumed up to 12 times more.

Lasalocid and human health

Effects on humans largely unknown

- We have been unable to find a single scientific review of the potential toxic effects for humans of consuming lasalocid residues in food. However, a review of monensin, a member of the 'ionophore' class of antibiotics to which lasalocid belongs, warned that ingestion of even small amounts in food would pose a danger to victims of coronary heart disease. Animal studies have shown that lasalocid has a similar toxic effect on the heart to monensin and that in some animal species it also has a potent toxic effects on the nervous system.

Sudden-death syndrome

- Cardiomyopathy, especially hypertrophic cardiomyopathy, is the most common cause of sudden death in people in the UK. Slight accidental overdosing with lasalocid can cause cardiomyopathy in animals.

Calcium ionophores, the subgroup of ionophores to which lasalocid belongs, induce hypertrophic cardiomyopathy in rats. Ventricular fibrillation is also linked to sudden death syndrome and calcium ionophores have been shown to render initially resistant laboratory dogs susceptible to ventricular fibrillation.

Cardiac arrhythmia

- Tony Blair suffers from supraventricular tachycardia, a type of arrhythmia involving rapid heartbeats. Half a million Britons suffer from similar conditions. Ionophore antibiotics like lasalocid may affect the electrical impulses to the human heart: in animals, they have been shown to increase heart rate and the force of contractions, even at very low doses. One sufferer who contacted the Soil Association experienced a dramatic improvement after giving up eggs.

Other serious diseases

- Lasalocid's toxicity is linked to its ability to carry ions (electrically charged atoms) across biological membranes. This can have profound effects on the health of individual cells and ultimately on the organism as a whole. Abnormalities in the movement of ions across cell membranes have been linked with a variety of human diseases such as myocarditis, Alzheimer's disease, syndrome X, Tarui's disease and possibly chronic-fatigue syndrome and prion disease.

Recommendations

Our main recommendation is that the marketing authorisation for Avatec® 15% CC and Avatec® 15% CC Game should be suspended as a matter of urgency. Its widespread use is even threatening the purity of organic eggs. We recommend a range of measures to increase public safety and overall understanding of this drug until action is taken:

Recommendations on consumer safety

Babies and children

- Parents should avoid feeding conventionally produced eggs or products containing them to babies under a year old.
- Children over 12 months of age should, if possible, eat only organically produced eggs/egg-based foods, because these are still the safest option.
- Breast-feeding mothers should eat organic eggs where possible or avoid eating more than two eggs (including all sources) on any day.

Adults

- Adults with heart problems should eat only organically produced eggs or, where this is not possible, should limit their egg consumption, including food containing eggs, to a maximum of two in a single day.
- Adults should avoid diets which involve high daily consumption of conventionally produced eggs.

Regulation

- The ADI for lasalocid should be reduced from its current level of 5 micrograms of lasalocid per kilo of bodyweight (µg/kg) two 1 µg/kg as in Australia, on a provisional basis and pending further review by scientists.

- Until such time as EU scientists are able to agree maximum residue limits (MRLs) for lasalocid in a range of foods, a provisional MRL of 50 ppb of lasalocid in eggs should be adopted, as in Australia.
- A provisional withdrawal period of 21 days between the use of lasalocid in layer replacements and the use of pullet eggs for human consumption should be introduced.
- Chicken feed containing lasalocid on sale to the public should contain a clear warning that, if fed to laying birds, eggs will be unsafe to eat.

Tighter testing regime

- Testing for lasalocid in eggs, broiler-chicken liver, quail eggs and quail muscle should take place every month of the year, not just from April to December as at present.
- Testing for lasalocid residues in egg-based baby food (last undertaken in 1999) should be introduced into the surveillance programme this year, using the most sensitive analytical methods available.
- Testing for lasalocid residues in infant formula and in supplementary feeds for premature babies containing egg-yolk lecithin should be introduced.

Studies on potential effect in humans

- The new advisory body set up by Public Health Minister Melanie Johnson to focus on adult sudden deaths and heart arrhythmias such as atrial fibrillation, should examine what part lasalocid residues in food might be playing in the incidence of these diseases.
- The Royal College of Pathologists should consider whether it would be practical to tests the livers of those who die unexpectedly from heart-related conditions for the presence of lasalocid.
- Scientific research should be commissioned into the behaviour of lasalocid in hens' eggs, quail eggs and meat, and egg-yolk lecithin.

Organic farming

- Organic egg producers should move as quickly as possible to end the practice of allowing conventionally reared layer replacements in organic egg production. Organic certification bodies should ensure that organically reared replacements are used wherever they are available, as required under the EU regulation. Until this is achieved it is imperative that the minimum six weeks conversion period between the buying-in of conventional replacements and the marketing of organic eggs is strictly adhered to.
- Advisory Committee on Organic Standards (ACOS), DEFRA and certification bodies should review the procedures of licensed organic poultry feed manufacturers with respect to lasalocid contamination, and consider whether further safeguards can be introduced.

1 – Introduction

Eggs are nutritious, versatile and easy to prepare. Each day we in Britain eat 26 million of them.

Shockingly, many of these eggs are contaminated with a dangerous drug, included as an additive in some poultry feed. You cannot see, smell or taste it, yet there is no official advice for consumers on which eggs are affected and which not. In Britain and other EU countries we do at least test for this drug and therefore know the scale of the problem. In many countries round the world, where it is just as likely that contamination is occurring, testing does not even take place.

The drug is lasalocid sodium, often referred to simply as lasalocid. It belongs to a group of antibiotics called ionophores, widely used as additives in livestock feed. In the United States and some other countries it is licensed as a 'growth promoter' in cattle. In Australia and New Zealand it is allowed in the feed and water of dairy cows to increase milk yield. However, in Britain and the rest of Europe it is permitted only in poultry production for the control of internal parasites.

Despite its known growth-promoting effects, lasalocid has so far escaped the bans imposed on other growth-promoting antibiotics. This is because ionophores are considered too toxic to be used in human medicine, and are therefore unlikely to cause antibiotic resistance problems.

Lasalocid's toxicity, however, presents a real and very different problem. Small quantities, which turn up as residues in eggs and some other poultry products, have the potential to cause or accentuate a number of serious health problems suffered by large numbers of people. Although this was known as far back as the 1970s, government policy (pre-BSE) was to maximize food production at all costs, and regulatory committees were even more heavily influenced by industry than today. As a result, lasalocid and several related drugs were licensed without adequate safety trials or the level of scrutiny that would now be applied.

At the heart of the lasalocid problem is an enigma. The drug is permitted for broiler chickens but not in egg production, yet contamination of chicken meat is low and that of eggs high. In 2003 one sample of eggs contained the

highest level of lasalocid residue ever recorded in the UK. Even so, no effort was made to trace the batch and take it off the market.

Because the ionophores are toxic, a system of regulation has been put in place to stop residues entering the food chain. In addition to the ban in laying-hen feed, producers of table poultry are supposed to withdraw lasalocid-medicated feed from birds at least five days before slaughter to allow residues in meat to fall below detectable limits.

To check that these precautions are taken, samples of poultry meat and eggs are tested from time to time. Any producer found to be supplying contaminated products gets a visit from the State Veterinary Service. This is supposed to deter cheating, but since contamination arises for a variety of different reasons, the system is not working. Testing for lasalocid is expensive, time-consuming and may be unrepresentative. We eat 10 billion eggs and 800 million chickens each year; we test only 250 samples of eggs and 300 samples of poultry meat.

Statements from both the government and the Food Standards Agency tell consumers that lasalocid residues in food pose 'no risk to health'. This report shows there is no evidence to support such an assurance. At the same time, there is no direct evidence that lasalocid residues in food are causing illness or death in people, but then no one has ever checked, even when symptoms are those that might be predicted from animal trials of the drug. What theoretical evidence there is however, points strongly towards a risk for several large vulnerable groups in society.

Because ionophores are used only in animal production, most doctors know little about them or their physiological effects. Despite the fact that we have been undertaking a global 'experiment', feeding lasalocid to humans via residues in food for over a quarter of a century, no one has even attempted to monitor the results.

Although the research for this report has been impeded because key scientific studies carried out by the drug's manufacturers have never been published, it has nonetheless been helped by the 'open government' policies introduced in recent years. The new Veterinary Residues Committee, which advises government on drug residues, has taken the problem of lasalocid residues seriously and regularly publishes detailed minutes of its meetings. The Veterinary Medicines Directorate and the Food Standards Agency have answered many of our questions.

It is not the aim of this report to stop consumers eating intensively produced eggs. Eggs are an important food and the organic poultry sector is still too underdeveloped to supply more than a tiny fraction of the market. Instead we offer tentative advice on how consumers can reduce the risks they face while the drug continues in use. We do, however, hope to convince regulators to face up to their responsibility to protect consumers and ensure that lasalocid is taken off the market as soon as possible.

This report has been timed to coincide with a two-day meeting of scientists in Brussels who are expected to make a recommendation soon about the safety of continuing to use lasalocid in poultry feed. A copy of this report has been sent to them.

The full chemical name of lasalocid:

[6–[7(R)–[5(S)–Ethyl–5–(5(R)–ethyl–tetrahydro–5–hydroxy–6(S)–methyl–2H pyran–2(R)–yl) tetrahydro –3(S)–methyl–2(S)–furyl]–4(S)–hydroxy–3(R),5(S)–dimethyl–6–oxononyl]–2,3–cresotic acid sodium salt]

Formula
$C_{34}H_{53}O_8Na$

Molecular weight
612.78

2 – The use of lasalocid

Lasalocid is an antibiotic, but for commercial and regulatory purposes it comes under the heading 'coccidiostat'. This is because its principal use is to control small intestinal parasites called coccidia, which can affect all poultry as well as other farm species. Unless specific management methods are adopted, coccidiosis can be a problem in poultry, especially at about at three to four weeks of age, though under the right conditions birds quickly develop natural immunity.

Because lasalocid and other related coccidiostats are cheap and freely available, it has been traditional for many years to add them to most types of feed for young birds as an insurance policy in case the condition arises.

Anyone can walk into an agricultural merchant's and buy a bag of chicken feed. Unless they know exactly what to ask for, they could come away with feed medicated with lasalocid since this is commonly added to starter crumbs, growers pellets and growers mash. Somewhere, in small print, a label will say that it should not be fed to birds over 16 weeks of age, but nowhere will there be a warning of the risk to human health should it inadvertently be given to laying hens.

The widespread presence of lasalocid in chicken feed is little understood by small-scale poultry keepers, and perhaps by commercial poultry producers too. According to one vet, who asked not to be identified, most chicken producers and even their own vets have no control over which coccidiostats are added to feed. 'Those decisions', we were told, 'are taken somewhere between the feed compounders and the big companies' to whom individual producers are contracted.

Consequently, lasalocid and other ionophores have been among the key drugs underpinning the intensive approach to poultry production for almost 30 years.

Lasalocid is the active ingredient of the feed additive 'Avatec 15% CC Premix' and 'Avatec 15% CC (Game Birds)'. In the UK, it is licensed for use in:

- broiler chickens
- other 'chickens fattened for the table'

- layer-replacement chickens up to 16 weeks of age
- turkeys up to 12 weeks of age
- pheasants and partridge up to 12 weeks of age (NOAH 2002 pp.22–5)

The side column, taken from a feed additives website sponsored by Alpharma, shows that in some countries lasalocid is also either legally permitted or recommended for other species including sheep, duck, quail and rabbit feed, and is sold as Bovatec for use in dairy and beef production.

Throughout the EU, Avatec is not permitted in the feed of laying hens because its known tendency to cause very high residue levels in eggs. Yet, any producer consulting this official website could be misled into believing that it was acceptable to use feed containing lasalocid for both laying hens and laying pullets, since these are both marked with a smiling face symbol.

Current trends in usage

According to industry insiders, the use of lasalocid in broiler chicken production has declined in recent years. They maintain the drug has fallen out of favour because it makes chickens thirsty; they then drink more water and produce loose faeces. The result is 'wet litter syndrome', where high moisture levels in bedding increase bacterial contamination and cause a number of health problems, such as ulcerated feet and hock burn.

This, though, may not be the complete picture. Another source told us that broiler producers continue to use lasalocid in rotation with other coccidiostats, but stressed that they are now much more careful to observe withdrawal periods than in the past. Those who make decisions about the inclusion of coccidiostats in feed know that no samples are taken for residue analysis during January, February and March each year, and it has to be wondered whether they may now be using this testing 'holiday period' for lasalocid's turn in this process. The type of testing involved plays a role too. In 2003, the Veterinary Medicines Directive (VMD), a semi-autonomous agency of the Department for Environment, Food and Rural Affairs (DEFRA), planned to target producers where lasalocid-positive livers had been found the previous year (Crutcher 2003). Yet, it actually undertook no sensitive lasalocid testing of broiler livers at all during the year, as it had done in previous years, with the result that any samples contaminated at concentrations below 50 micrograms of lasalocid per kilo (µg/kg) would not have shown up. Although the current trend in broiler production is unclear, we assume that lasalocid use is:

- prevalent in turkey production, because other ionophores are more toxic to turkeys
- likely to have increased in game production, due to the banning of Emtryl (dimetridazole), a widely used additive in pheasant feed
- widespread in the rearing of layer replacements
- widely available for any young chickens
- regularly included in quail feed on veterinary prescription

Sales of lasalocid

Information on how much lasalocid is used in the UK is not publicly available. The VMD holds data on the annual sales of veterinary drugs,

Feed additives area

Sponsored by:

ALPHARMA
Animal Health Division

SPECIES	AVATEC lasalocid
Broiler	75 - 125*
Laying pullet	75 - 125
Breeder pullet	☺
(👎 in case of dwarf gene)	
Laying hen	☺
Breeder hen	👎
Turkey	90 - 125
Turkey breeder	☺
Guinea fowl	☺
Duck	☺
Quail	☺
Rabbit	☺
Goose	☺
Pheasant	☺
Partridge	☺
Horse	👎
Cattle	☺
Sheep	☺
Swine	☺

Numbers in table indicate authorised doses in ppm in the feed

☺	: No problems with the approved dose given to the authorised species
👎	: Adverse effects with the common dose to the authorised species
💣	: Severe adverse effects, mortality

(Feed Additives Forum 2004)

but is not able to release drug-specific information without the manufacturer's permission – which is never forthcoming. The law does not require pharmaceutical companies in the UK to reveal the quantities of veterinary drugs they sell each year. British consumers can log on to the internet and read exactly how much lasalocid is sold to Danish or Swedish poultry producers each year, but they cannot find out how much is used in the UK.

Since 1998 however, the drug companies have agreed to provide information on their veterinary drug sales to the VMD on the strict understanding that it is not disclosed to anyone else. Such information has not even been made available to the government's advisory committees, the Veterinary Residues Committee, Veterinary Products Committee and the Scientific Advisory Committee on Antimicrobial Resistance, which are governed by strict rules of confidentiality (Fitzgerald 2004a).

The VMD does publish summary totals for classes of drug, but these hide both the quantities and the species-use for individual drugs. One overall figure is published for all 17 licensed coccidiostats. We asked the VMD if we could be given an indication at least of whether sales of lasaslocid were rising or falling, but were politely told that 'we cannot provide this as only one product is involved and we would be divulging commercially confidential sales information' (Fitzgerald 2004b).

The VMD did agree, however, to supply one total figure for ionophores, the sub-class of coccidiostats to which lasalocid belongs (see Table 2.1).

Table 2.1 Trends in the sales of coccidiostats 2000-2002

	Tonnes active ingredient sold		
	2000	**2001**	**2002**
Ionophore coccidiostats	153	190	195
Other coccidiostats	63	52	55
Total coccidiostats	216	242	250

Source: VMD 2004

As can be seen, the use of ionophores has increased significantly, while that of other coccidiostats has fallen. These figures, however, fail to give a realistic impression of the scale of ionophores use in the UK. This is because they relate only to tonnes of active ingredient of the antibiotic part of the compound, but exclude the base (sodium in the case of lasalocid). Avatec for example contains 15% lasalocid sodium, Elancoban contains 20% Monensin. There is no published information on the precise calculations undertaken by the VMD to convert the sales data they receive from the drug companies into published data. However, the total quantity of ionophores products sold in the UK is likely to be in the region of 1,200 to 1,500 tonnes each year.

Swings and roundabouts

It is interesting to contrast the 26% rise in the sales of ionophores with the fall in sales of the now-banned growth-promoting antibiotics (see Table 2.2).

Table 2.2 Sales of antimicrobial growth-promoting products (tonnes active ingredient) in the UK, 1998–2002

	1998	1999*	2000*	2001	2002
	Tonnes active ingredient				
Growth–promoting products	46	23*	24*	43	27

* missing data (the VMD was unable to obtain complete figures)

Source: VMD website: www.vmd.gov.uk

This suggests that producers may simply be switching from banned drugs to others with known growth-promoting effects. While ionophores have not officially been classified as 'antibiotic growth promoters' in UK poultry production, they do increase growth rates and feed-conversion efficiency in a similar way (Johnston 2000a).

The licensing of lasalocid

While lasalocid is an antibiotic, is has always been officially classed as a coccidiostat, for controlling parasites rather than bacteria. Coccidiostats routinely added to feed, were classed as 'feed additives', rather than veterinary medicines. As a result lasalocid fell outside veterinary medicines legislation.

This anomaly has its roots in history, but its consequences have a major impact today. When Britain joined the Common Market in 1973, American scientists were just beginning to develop an antibiotic called X-537A as a poultry-feed additive, yet the legislation which would eventually permit the use of lasalocid (as it came to be known) was already in place. Back in the 1970s analytical techniques were relatively crude and it was initially believed that neither the coccidiostats nor the growth-promoting antibiotics gave rise to residues (Young and Craig 2001 p46). As such, they were not subjected to the same scrutiny as other drugs. In relation to the coccidiostats the feed-additives directive states:

Certain purely medicinal substances such as the coccidiostats should during a first stage, be regarded as additives, since most member states have been using them for collective prophylaxis, principally in poultry farming...whereas, however, they will be examined further if a directive on medicinal feeding stuffs is drawn up
(EEC 1970 p1).

Essentially, these drugs were classed under feed legislation because they were being used in feed, whereas they should have been licensed under medicines legislation because of their medicinal properties. Unfortunately, the process never got past the 'first stage' referred to in the directive and once they were ready for the market, new coccidiostats, such as the ionophores, came to be licensed under the comparatively lax feed-additives directive. Arguably this laid the foundations for the super-intensification of livestock production we have witnessed over the last 30 years. Lack of licensing clarity and lack of rigour in assessment, both features of feed additives legislation, have been to the advantage of drug companies looking to get, or keep, suspect feed additives on the market.

During the 1990s total responsibility for this area passed from Britain to Europe, but perhaps because of the confusion which has reigned for so long,

The history of lasalocid

Following the commercial success of penicillin, after the Second World War soil bacteria were systematically tested for the presence of further antibiotics. Lasalocid was discovered in 1950, its chemical structure established in 1970 and the bacteria which produce it, *Streptomyces lasaliensis*, finally identified in 1974. Commercial manufacture commenced in 1977 with the drug company Hoffman-La Roche marketing it as a poultry-feed additive. Hoffman-La Roche (later Roche Products Limited) ceased marketing antibiotic feed additives during the 1990s. Today lasalocid is manufactured for the world market by Alpharma Animal Health Ltd, a division of the giant US/Norwegian pharmaceutical company Alpharma (Berger et al 1951, Westley et al 1974, NOAH, 2001a, Alpharma website).

there has never even been a UK regulation to implement the feed-additives directive in UK law.

Veterinary medicines licensed for use in the UK have been through a rigorous process in order to gain approval by the Veterinary Products Committee (VPC). In future, drugs licensed under similar procedures in the EU (either by other member states or centrally) can also be available to UK producers. Under new legislation just agreed by the European Council, all such drugs will also only be available throughout the EU under veterinary prescription (Vet Rec 2004). Lasalocid, however, will remain outside these new rules too.

Writing frankly to the Marsh Committee on the dispensing of veterinary medicines, Jeremy Johnson, from Schering-Plough Animal Health, argued in 2000 that the coccidiostats should be reclassified as veterinary medicines and become available only under veterinary prescription, rather than over the counter as at present. He wrote:

You may not have detailed knowledge of the products but some of them are known to be toxic or ecotoxic. Some of the products also interact with other medicines producing toxic effects, and withdrawal periods are considered necessary in order to protect the consumer…There is no mention why the coccidiostats have been ignored, despite the fact that some of them will kill horses, turkeys or other in-contact animals as they are selectively toxic to some species (Johnson, 2000a)

In a recent UK report, the VPC concluded that 'coccidiostats are used solely for the treatment or prevention of disease in animals and should therefore be authorised as veterinary medicines under EU Legislation 2001/82/EEC' (VPC n.d.a). This is an important development since such a move would require both the setting of maximum residue limits (see Chapter 3) and the establishment of legally binding withdrawal periods in all classes of stock to which lasalocid is given. While the UK government 'accepted' this recommendation, it has nevertheless gone along with an EU timetable which means this reclassification is unlikely to take place before 2012 (VPC n.d.b)

Omissions in the current licensing laws for lasalocid

For more than 20 years the approval of new feed additives, and the reviewing of some existing ones, was the task of two EU committees. The Scientific Committee on Animal Nutrition (SCAN) was a committee of scientists which reviewed the safety data provided by drug companies to support licensing applications. The Standing Committee on Animal Nutrition (confusingly also known as SCAN) evaluated the opinions expressed by the scientists.

Lasalocid was reviewed on three separate occasions and considered safe for use in broiler and other table chickens, turkeys and beef cattle (SCAN 1982a, 1990, 1991a). It was, however, not licensed for beef cattle in Europe as it was in, for example, the US. The reason for this is not known, but it could relate to the strong public opposition at the time to the use of hormones in beef production and the milk-boosting hormone BST in dairy cows. Possibly Hoffman-La Roche feared that any negative publicity could have seen lasalocid banned in poultry production as well.

Significantly, however, SCAN never passed an opinion on the safety of using lasalocid in layer-replacement hens, pheasants or quail, three of the areas where its use today is most substantial in the UK.

Current EU review of lasalocid and other coccidiostats

A review of lasalocid and other related drugs is finally taking place at a European level. Additives that were listed in Annex 1 of Feed Additives Directive 70/524/EEC before 1988 are all being 're-evaluated'. Work originally begun by the now disbanded Scientific Committee on Animal Nutrition has been taken up by a new committee, set up by the European Food Safety Authority (EFSA). It is known as the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). The British members on the committee are Dr Paul Brantom, a biochemist and toxicologist who works for BIRA International Ltd, and Dr Andrew Chesson, a biochemist and microbiologist with the Rowett Research Institute in Aberdeen (EFSA website).

In total seven coccidiostats have been under review. Companies had to supply a dossier of safety and other data before 1 October 2000 and the process should have been completed before 1 October 2003. There have, however, been delays and while FEEDAP has now formally 'adopted an opinion' on four of the drugs, nicarbazin, monensin, halofuginone and decoquinate it has not yet completed the process of re-evaluating lasalocid.

Lasalocid and organic farming

It is not clear how organic certification bodies would respond if they received a request from an organic producer to use lasalocid. Avatec is only licensed for continuous prophylactic use and is not effective as a treatment once coccidiosis develops. Under normal circumstances routine medication is not permitted in organic farming throughout the EU. There are a limited number of exceptions to this rule, mostly relating to the use of vaccines, sheep dips and fly strike, but there is no evidence that this has ever been extended to include the use of lasalocid, at least, on Soil-Association-certified farms. In contrast there is a coccidiosis vaccine which can be used in certain circumstances and at least one effective veterinary medicine, which could be used on veterinary prescription for a short period to treat a serious coccidiosis problem should this occur. Nevertheless, organic farming standards have a number of weaknesses in relation to lasalocid.

Conventionally reared layer replacements

For some years, organic standards like those of the Soil Association have permitted layer replacements[1] for organic production to be conventionally reared, where organic replacements are not available. The birds can be bought in up to 18 weeks of age and after 6 weeks on organic feed their eggs can be sold as organic.

The practice is already being phased out as part of wider moves to reduce the number of derogations originally permitted when organic poultry production was still in its infancy. Technically the use of conventional layer replacements is supposed to cease by the end of 2004. However, it seems unlikely that all organic farms will be ready to make the change by then. While the practice continues there would appear to be no danger of residues of lasalocid occurring in organic eggs as a result of this derogation, providing the six-week conversion period is strictly adhered to.

1 Layer replacements are young birds destined to become laying hens.

Lasalocid in feed

However, contamination of laying-hen feed at feed mills, due to the use of lasalocid in rations for other classes of livestock, such as layer replacements, is a major part of the overall problem. This is the suspected cause of lasalocid residues in one sample of organic eggs during 2003, though an investigation is still proceeding.

Organic feed can be prepared in conventional mills producing lasalocid-medicated feed. It is recognised that this is not an ideal situation. Scientists in Northern Ireland found that even two batches after lasalocid-medicated feed had been prepared, it could still contain enough of the drug to produce detectable residues in eggs. In the same study very low, but detectable, residues of lasalocid in feed were still found in a fourth batch. It appears that in these trials no cleaning was undertaken between each batch of feed (Kennedy et al 1996, Kennedy et al 1998) and it should be possible to produce lasalocid-free feed if thorough cleaning is undertaken as required by organic certification bodies.

Ideally organic feed would not be prepared in conventional mills. The Soil Association would like to see all organic feed produced by organic mills. Unfortunately, the UK organic feed market is too small to make dedicated equipment economically viable for most firms producing organic feed, at the present time. Instead the Soil Association requires that feed compounders follow detailed procedures, which involve meticulous segregation of ingredients, the thorough cleaning of equipment and a sufficient quantity of feed being flushed though the system to remove all traces of drugs or prohibited conventional ingredients, before feed is produced for organic livestock.

The fact that lasalocid residues have now been found in organic eggs suggests that the system is not working adequately. This report, therefore, recommends that organic standards and certification committees throughout the organic sector review their procedures with respect to the issue of potential lasalocid contamination, and consider whether further safeguards should be introduced.

Lasalocid in manure

Lasalocid could also enter organic systems through bought-in manure for use on organic land. Organic farmers are permitted in some circumstances to buy in manure from free-range and other high-welfare conventional poultry systems. The use of lasalocid is permitted in some of these, and since up to 90% of ingested lasalocid is excreted in manure (2–6 mg/kg), significant quantities could be present in fresh poultry manure brought on to organic farms. Studies have shown, however, that in aerobic conditions, at 32°C and 85% humidity, lasalocid levels in manure decline by 50% in 48 hours and 75% within 15 days, though under anaerobic conditions levels of lasalocid declined slowly (SCAN 1982a). Soil Association organic standards require bought-in manure to be stacked for 12 months or composted under aerobic conditions for at least six months before being spread. While there is no published information on the precise process of lasalocid breakdown in manure, it seems probable that any lasalocid entering organic farms in this way will have been rendered harmless. In conventional farming, on the other hand, there are no legal requirements for composting, so there remains the possibility of substantial release of ionophores into the environment.

3 – The ‘safety’ of lasalocid

According to the Veterinary Medicines Directorate (VMD), lasalocid has ‘low acute toxicity’ (VMD 2001c). Alpharma, the drug’s manufacturer, promotes it as ‘non-toxic, producing no adverse effects when used as directed’ (Alpharma 2003). For 20 years the relative safety and low toxicity of lasalocid have repeatedly been stressed to the farming industry. In 1984, for example, it was introduced to turkey growers in the UK as ‘Avatec: the safe ionophore anticoccidial’ (Comben 1984a) and four years later it was promoted as the only ionophore that could safely be used in combination with the antibiotic tiamulin (Lodge et al 1988).

It has been claimed that of the six ionophore anticoccidial drugs licensed in the UK, lasalocid is the second-least toxic (Oehme and Pickrell 1999). In fact, the toxicity of each ionophore varies dramatically between species. In rats, cattle and horses, monensin is significantly more toxic than lasalocid, but in chickens lasalocid is three times more toxic than monensin. In rabbits, lasalocid is equally as toxic as monensin, but in dogs it is slightly more toxic than either monensin or narasin (CAFA 1997 p172, Oehme and Pickrell 1999, Galitzer et al 1986). Salinomycin, supposedly the least toxic ionophore, is far more toxic to turkeys than either monensin, maduramicin or lasalocid (CAFA 1997 p173, Lodge et al 1988, Stuart 1983, Horrox 1984, Comben 1984b). Whether lasalocid is more or less toxic to humans than other ionophores is therefore unclear. Thousands of animals have suffered and died in the quest to understand ionophore toxicity, yet we still have no idea which of these drugs poses the greatest risk to humans.

Toxic effects in farm animals

Despite lasalocid’s official ‘low toxicity’ there have been many documented cases of severe illness and death in farm animals given feed containing only slightly more than the doses recommended. In addition, numerous laboratory experiments show that lasalocid is highly toxic to some species, even at relatively low doses.

On several farms where broiler-breeders[1] were accidentally given feed containing levels of lasalocid approved for broiler chickens, egg production decreased and fertility and hatchability declined sharply. Many chicks had

1 Broiler breeders are hens laying fertile eggs to produce chicks for the broiler industry.

severe muscle weakness and were unable to break out of the egg (Perelman et al 1993). In another example, ten dogs were poisoned by lasalocid contamination of commercial dog food. They suffered depression, muscle weakness progressing to paralysis and quadriplegia, respiratory-muscle failure and lower motor-neuron malfunction (Safran et al 1993). Three hunting dogs developed acute neurological symptoms consistent with lasalocid poisoning after the consumption of several broiler chickens that had died on a farm where lasalocid was added to broiler feed (Espino 2003). Lasalocid and other ionophore poisonings are also frequent in turkeys (Pritchard et al 2001).

Under experimental conditions, cattle given 10 mg/kg bw (milligrams per kilogram of the animal's bodyweight) of lasalocid became anorexic and developed watery diarrhoea (Galitzer and Oehme 1984) and a cow fed 35 mg/kg bw died (FOI 1982 Additional Animal Safety Study 4). Symptoms at lethal doses included muscle tremors and increased heart and respiratory rates (Galitzer and Oehme 1984). Post-mortem examinations revealed that cattle dying from lasalocid poisoning had 'gross and microscopic lesions consistent with cardiomyopathy' (Galitzer et al 1986). Pigs fed 58 mg/kg bw of lasalocid also died (Hoffmann-La Roche 1982, quoted in Galitzer and Oehme 1984), and a much lower dose of just 15 mg/kg bw was sufficient to kill a horse (Hanson 1981). Doses as low as 1 and 2 mg/kg bw administered intravenously were sufficient to cause significant cardiac effects in open-chest anaesthetized cats (Prasad 1983).

Lethal and 'safe' doses

Since most toxicity studies are carried out on rats, it is possible to compare the toxicity of lasalocid relative to other substances for that species (see Table 3.1). The LD_{50} is the dose of a substance which kills 50% of the animals under study; it is measured in mg/kg bw. The LD_{50} for lasalocid has been established by the EU's Scientific Committee on Animal Nutrition at 100 mg/kg bw in adult rats (SCAN 1990), and elsewhere it has been put at 122 mg/kg bw (CAFA 1997 p172). So one-thirtieth of a gram of lasalocid is sufficient to kill an average adult rat weighing 330 g.

Table 3.1 shows that compared with the pesticide Aldicarb, where just 1 mg/kg bw will kill a rat, lasalocid does have (as the VMD and others stress) relatively low acute toxicity in rats. However, it is a far from harmless substance: the organophosphate pesticide malathion is eight times less toxic to a rat than lasalocid.

Table 3.1 - LD_{50} of various chemical in rats

Substance	LD_{50} in rats (mg/kg bw)
Aldicarb (Temik) - carbimate pesticide	1
Potassium cyanide - poison	10
Monensin - ionophore feed additive	35
Dieldrin - insecticide, now largely banned	40
Paraquat - herbicide	58
Lasalocid - ionophore feed additive	**100 or 122**
Malathion - organophosphate pesticide	885
Enrofloxacin/ciprofloxacin - antibiotic	5000
Tetracycline - antibiotic and feed additive	10,000

Sources: CAFA 1997 p172, SCAN 1990, Pesticide Management Education Centre 2001a, Pesticide Management Education Centre 2001b, Pesticide Management Education Centre 2001c, Material Safety Data Sheet 2003, Bayer 2002

Two other important safety thresholds are the 'no observed effect level' or NOEL, which is the highest dose at which a drug can be fed to animals without any observable effect, and the 'no observed adverse effect level' (NOAEL), the highest dose at which a drug can be fed without any adverse effects being observed. In some cases the NOEL and the NOAEL will refer to the same dose, while in others they will vary considerably.

Neither definition is completely objective, since whether or not an effect is observed will depend to a large extent on how hard the scientist looks, what is being looked for, how sensitive the equipment is, etc. In the case of the NOAEL, a further layer of subjectivity is introduced as it is up to the scientist to decide whether an observed effect is 'adverse' or not.

The lack of clarity in the definitions and the fact that scientists have not used the terms consistently probably explains the wide variety of published values, as Table 3.2 shows. This report uses the term 'NOEL' to cover both NOEL and NOAEL, even though, if precise criteria were agreed between researchers, these thresholds would be distinct.

It can also be seen from the table that lasalocid is considerably more toxic in larger mammals such as cattle, pigs, dogs, and horses than it is in rats and mice. This is potentially relevant to an estimation of its toxicity in large mammals such as humans.

The price animals pay for us to eat cheap chicken

Acute-toxicity studies[1] have been undertaken in a range of animal species. Such studies cause great suffering. In one experiment at the Roche Research Station for example, four out of eleven horses and one of an unknown number of donkeys died establishing the LD_{50} for lasalocid. A further three horses were poisoned to establish the LD_{50} for monensin.

One 'lucky' horse died quickly after a low dose of lasalocid, while three others required a second higher dose. One horse was given a third still higher dose from which it eventually recovered. All 14 horses suffered severe pain and distress over a period of days or weeks. The horses given two or three doses were allowed recovery periods between each dose, but went through the same suffering on each occasion. One horse remained in the trial for 330 days. Typical symptoms were profuse sweating (monensin only), groaning, nasal discharge, anorexia, inability to rise, circling and dragging the feet. As one author put it, 'in equine ionophore toxicity, recumbency is followed by frequent attempts to rise with thrashing of the limbs until death supervenes' (Novilla 1992).

Post-mortem examinations revealed the horses had: bladder distension, dark purple congested lungs, kidney and heart damage, and small dark circular areas on the alimentary tract. (Hanson et al 1981)

1 Acute-toxicity tests establish an average lethal dose.

Table 3.2 Published toxicity thresholds (NOELs and LD_{50}s) for lasalocid and monensin in various species

	Lasalocid NOEL (mg/kg bw)	Lasalocid LD_{50} (mg/kg bw)	Monensin NOEL (mg/kg bw)	Monensinx LD_{50} (mg/kg bw)
Rats	0.5 or 1.8 or 2 or 2.4 or 4	100 or 122	1.25	35
Mice	2.4	146		61-110, or 125 or 135
Dogs	1		1.25 or 4	20
Poultry	2.5 or 4.2	71.5	<18	200
Pigs		>35 and <58		16-17, or 50
Rabbits		40	0.76	40
Cattle	1	35		50 to 80
Horses		21.5		2 or 3

Sources: CAFA 1997 p173, Department of Health and Aging 2003, Galitzer and Oehme 1984, Oehme and Pickrell 1999, SCAN 1981, SCAN 1990

Safety of lasalocid for humans

The acute toxicity of lasalocid clearly demonstrates its potential harmful effects, but as Derek Renshaw, a toxicologist with the Food Standards Agency (FSA), has explained, this is not directly an issue for consumers because even the highest amounts found in food are significantly lower than the doses which killed animals in experimental studies (Renshaw 2003). However, our concerns relate to what are known as 'sub-acute' toxic effects, such as changes to the blood, electrical impulses that control the heart and chemical reactions within the brain and nervous system.

Sub-acute effects do not, by definition, cause death within 48 hours, but the possibility still remains that residues in food could trigger a sequence of effects which might cause damage or even death over a longer period, especially in vulnerable individuals (see Chapter 6). This was recognised by scientists in the United States more than 20 years ago (Pressman and Fahim 1983) and restated more recently by British-government scientists in Northern Ireland:

Concern has previously been expressed that consumers may be exposed to pharmacologically active and potentially detrimental concentrations of ionophores such as lasalocid in food (Kennedy et a1 1996).

Setting limits in food

Throughout the EU, veterinary medicines are licensed under a directive which requires maximum residue limits (MRLs) to be established for drugs before they can be marketed (EEC 2001).

The setting of MRLs for drug residues in food is an important food-safety procedure. An MRL is 'the maximum concentration of residue resulting from the use of a veterinary medicine that is legally permitted…on or in food' (MAVIS 1998).

Food found to contain residues of a drug above the MRL can be removed from the market. One of the EU directives governing MRLs states:

Where there is evidence of residues of authorized substances or products of a level exceeding the maximum limit for residues…the competent authority shall take all necessary measures to safeguard public health which may include prohibiting… products from leaving the farm or establishment. (EU 1996)

Both the VMD and the FSA rely heavily on the concept of MRLs to assure the public that residues of drugs and pesticides in food pose no harm. As the VMD puts it: 'we can therefore be assured that consumer safety will not be compromised if veterinary medicine residues in food do not exceed the MRLs' (VMD 1999a p23).

Yet alarmingly, when it comes to the ionophores no MRLs have been set, despite the fact that they are recognised as some of the most toxic drugs used to control disease in farm animals.

Managing the problem

Withdrawal periods are another key mechanism for ensuring food is free of dangerous residues. These are defined as 'the period necessary between the last administration of the veterinary medicinal product to animals… and the production of foodstuffs from such animals to ensure that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits' (EC 2003 p64).

This begs the question of how it is possible to establish withdrawal periods that give consumers a high degree of assurance, when an MRL has not been set. Since 1999 the VMD has been attempting to paper over the cracks on this point by using arbitary residue concentrations instead, which it has termed the 'differential action levels' (DALs).
These were originally suggested by an earlier committee as a way of reducing the 'burden on resources' (VRC 2003d). However, the use of DALs has recently been dropped as part of moves by the Veterinary Residues Committee (VRC) to be more open about the problem. Judging by the committee minutes, Brian Vernon, a representative of the livestock-feed industry on the VRC, would like to see this action level reintroduced and believes it was set 'on a toxicological basis'. However Dr Paul Brantom, a toxicologist who sits on both the VRC and the EU committee reviewing the safety of the coccidiostats (see Chapter 2), was recently reported to have said that, if it is to be used again he 'would have to be convinced that it was on a sound basis' (VRC 2003c p13).

While there are published withdrawal periods for lasalocid in broiler chickens, turkeys and pheasants, their legal status in the absence of MRLs is unclear. But for layer replacements and for quail – two groups where the drug is most widely used, but has never been scientifically evaluated – there are no withdrawal periods at all in force.

Conscious of these issues, the European Commission is now attempting to tack the process of setting MRLs 'to avoid risks to humans' on to a long-overdue review of the coccidiostats (EU 2002). However, it remains an open question whether it will be possible to undertake such a complex task effectively in this way. Were the coccidiostats to be classified as veterinary medicines (as they should be, see Chapter 2), the pharmaceutical companies would be obliged to provide adequate data to enable the regulators to set MRLs, but while the manufacturers of the coccidioststs have been asked to provide additional information, it may not be sufficiently detailed to enable scientists to do this properly. As Liisa Vahteristo the Scientific Coordinator of

the FEEDAP panel undertaking this difficult task explains: 'the Panel tries to propose MRL[s] for coccidiostats but often the data available does not allow that' (Vahteristo 2004).

Four years ago a senior representative of a leading drug company wrote,

As for toxicity in man, there is a well-established European process to assess the risk to consumers of residues of veterinary medicines, which the coccidiostats have not been through…The coccidiostats are now being reviewed but we can as yet find no mention of whether European MRLs will be required for these compounds or when. (Johnson 2000a).

Four years on, MRLs have still not been established.

The problem is not just one for the European Union. Regulators in Australia, New Zealand, the United States and Canada have previously set MRLs for lasalocid, at least for some animal tissues, but are now seeking new information from the companies to review safety. Just how difficult this is can be seen from the current contradictory assessments of existing data in the following table:

Table 3.3 MRLs for lasalocid in various countries (in µg/kg)

	Australia[1]	Canada	New Zealand	United States
Cattle liver	Not set	650	No data	No data
Chicken liver	700[2]	Not set	5000	400
Chicken meat	50	Not set	200	No data
Chicken skin, fat	1200	350	200	1200[3]
Eggs	50	Not set	No data	No data

Sources: FSANZ 2004, VDD n.d., MAF n.d., FOI 2001

1 Temporary values while a full review is taking place.

2 In March 2004 the Australian chicken liver MRL was changed from 50 µg/kg to a temporary value of 700 µg/kg.

3 In 2001 the US increased its MRL for chicken skin and fat from 300 µg/kg to 1200 µg/kg.

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is undertaking a review and has recently admitted that 'the present MRLs, based on usage of lasalocid, are inadequate' (FSANZ 2004). However, the large increase in the chicken liver MRL and the recent setting of a very high MRL for chicken skin and fat raises the question of whether some changes are being made for political rather than scientific reasons. In 2003 Australia carried out its first ever lasalocid testing. One of 5 samples of chicken liver tested had residues above the then MRL of 50 µg/kg. In March of this year, a temporary twelve-fold increase of the MRL for chicken liver was announced (FSANZ 2004).

How much can we take?

In order to set an MRL for a particular chemical, it is first necessary for regulators to agree what constitutes an overall safe daily dose. The 'acceptable daily intake' (ADI), as this is called, is the quantity of the chemical that, it is believed, can be ingested daily over a lifetime without

appreciable health risk. To allow for the fact that individuals vary in size the amount is expressed per kilo of human body weight (kg bw). The ADI of veterinary drugs is usually impossible to estimate directly because there is no experimental data for human exposure to the substance – either at all, or regularly over periods of time. Instead, the method used for setting the ADI is based on animal experiments. Under normal circumstances the lowest NOEL in the most sensitive species determined by these experiments is then used for calculating the ADI according to the following formula:

$$\text{ADI} \quad \frac{\text{NOEL}}{\text{Uncertainty factor}} \quad (\text{mg/kg bw})$$

The 'uncertainty factor' in the equation is usually taken to be 100: a safety factor of 10 is to allow for possible differences in sensitivity between animals and humans and another safety factor of 10 is to take account of differences between individuals (i.e sensitive people could be 10 times more reactive than the average person). This gives an ADI set at 100 times below an animal-derived NOEL. This is the 'huge' safety margin which the industry often cites. It is then proposed that all humans could safely consume this amount of the drug in their food every day throughout their lifetime, without suffering harmful effects.

Lasalocid's ADI and its shortcomings

The fact that no MRLs have been set for lasalocid in the UK and rest of the European Union casts some doubt on the validity of the current ADI, because if this had been undertaken thoroughly it would have been based on studies which could also have been used to set the MRLs immediately.

The EU ADI for lasalocid was set at 5 micrograms per kilo of body weight (5 µg/kg bw) in 1982, after EU scientists studied trials data, including the results of long-term feeding experiments in laboratory rats (Renshaw 2002, SCAN 1982a). The experiments produced a NOEL of 0.5 mg/kg bw (500 µg/kg bw). At doses higher than this, changes occurred in the composition of the blood, biochemistry and organ weights (ibid.). To this a simple uncertainty factor of 100 was then applied to obtain the ADI of 5 µg. While this is already more precautionary than the US and New Zealand ADIs of 10 µg/kg bw, it is nevertheless five times higher than the Australian ADI of 1 µg/kg bw. There is one key reason why the EU ADI may not have been set accurately.

We are not rats

The ADI is supposed to based on 'the most sensitive species, unless other data indicate otherwise' (Walker 1998). The limited information available shows that rats have the lowest published NOEL of 500 mg/kg. However, LD_{50} studies (cited in Table 3.2) show that rats are in fact one of the least sensitive species as far as lasalocid is concerned. Rabbits, for example, are two to three times more sensitive, yet no NOEL has been established in rabbits. According to Professor Vyvyan Howard, a specialist in foetal toxicology at Liverpool University, metabolic rate can be ten times higher in rats than in humans (Howard, 2004), so applying a ten-fold safety factor for differences between rats and humans recognizes only this basic physiological difference between species, but includes no safety margin whatsoever.

In the case of the ionophore salinomycin, the ADI was originally set at 50 µg/kg bw, based on experiments carried out on rats and mice (SCAN 1982b). However, a decade later the ADI had to be reduced to just 2.5 µg/kg bw when experiments showed rabbits were much more sensitive than rats or mice (SCAN 1992). The salinomycin NOELs in mice and rats, which had been put at 30 to 50 mg/kg bw in 1982, were estimated to be just 1.4 and 2.5 mg/kg bw respectively in 1992 (SCAN 1982b, SCAN 1992). Had the ADI for lasalocid been reviewed at the same time and also based on studies with rabbits, it seems likely that it would have been reduced to 2 µg/kg instead of 5 µg/kg and quite possibly even as low as the Australian ADI of 1µg/kg.

The real reason MRLs have not been set?

It is recognized that residue analysis in food is only practicable for what is termed the 'marker residue'. This is usually the drug in question (sometimes called the 'parent compound') but occasionally it is another chemical, which is released after the original drug begins to break down through the process of metabolism. Sometimes these metabolites can be more toxic than the drug itself.

Even when the metabolites are no more toxic than the parent compound, their presence can be significant if they make up a sizeable part of the total residues. Lasalocid begins to break down into a large number of metabolites very quickly. Its half-life in chicken liver is 36 hours (Kennedy et al 1995). Studies by the original manufacturers, Hoffman-La Roche, showed that residues of intact lasalocid in cattle liver represented just 15% of the total drug residues. No individual metabolite accounted for more than 3% and while five metabolites totalling 15% were identified, the company gave up on the task of trying to identify them all (Weiss 1990).

Talking about metabolites generally, Derek Renshaw from the Food Standards Agency explains the significance of this:

a lot of the metabolism of drugs is fairly minor changes, which just increase solubility and make it more easily excreted. Conjugation isn't going to change the toxicity [of a drug] apart from just making it more readily excreted. And some of the more minor changes like hydroxylation are probably going to do similar things. When you get to more major changes, involving splitting the molecule, you might well get completely new toxicity (Renshaw 2003).

Revised EU guidelines for assessing the safety of feed additives take the issue of metabolites much more seriously than in the past. They require that:

there is adequate data on the toxicity of the parent additive and any metabolites produced in the target species to which the consumer might be exposed. To this end a comparison of the metabolic fates of the additive in the target and laboratory animal species used for the toxicity testing is important (SCAN 1999).

Scientists are now also required to 'identify and quantify the appropriate marker residue(s) to be used for setting the MRL for the marker residue and the withdrawal periods for the final product' (ibid.). In the early 1980s when the ADI for lasalocid was set, no attempt was made to do this, because it was not a requirement at the time. Metabolites in chickens (the target species) were not compared with those in laboratory rats. And while total residues were established using radioactive carbon, these were not compared with the small fraction of unmetabolised lasalocid detectable in residue tests (SCAN 1982a). Taking metabolites into account would not alter the ADI,

since in the NOEL trials animals are given only the drug in feed, not a mixture of drug and metabolites, but it is essential for calculating MRLs and withdrawal periods.

Cold turkey

In 1991, the use of lasalocid throughout the EU was extended to include turkeys up to 16 weeks of age[2], based on the assumption that if its use in chickens posed no threat to human health, then its use in turkeys was unlikely to do so. At standard feed rates, measurable lasalocid residues ranging from 25 to 85 µg/kg in muscle, liver, kidney fat and skin were found for up to only two days, but when the total residues (including metabolites) were measured using radioactive carbon, after five days (the only period cited) they were up to 30 times higher (850 to 890 µg/kg) in liver than the normally detectable residues of unmetabolised lasalocid after three days. There is still confusion about the exact percentage of residues represented by lasalocid itself. The EU scientists put this at 3.8%, while US scientists more recently calculated it to be 6.3% (SCAN 1991b, FOI 2001).

On its own, this substantial difference between the detectable marker residue and the quantity of unidentified metabolites would have been enough to prevent lasalocid's approval in turkeys. However, it seems probable that there would have been significant pressure from the industry not to do this because it would then have called into question the validity of the previous approval in chickens. The record of the committee's deliberations states that:

in view of the analytical difficulties in identifying the precise nature of the hepatic residues the Committee took into account exceptionally [our emphasis] the bioavailability of these residues in addition (ibid.).

Bioavailibility of lacalocid metabolites

In crude experiments in the 1980s, Hoffman-La Roche showed that 30% of the lasalocid metabolites in cattle liver were 'bioavailable' (Weiss 1990). Essentially this means these were the potentially harmful residues. To this we can add the 15% of intact lasalocid to show that just under half (45%) of all lasalocid residues in cattle are bioactive. The same scientists stated that 'the results of our experiments with both cattle faeces and liver samples indicate that the metabolites produced by cattle are not significantly more ionotropic (see Chapter 6) than lasalocid (ibid. p841). They were not, however, able to show that these metabolites were either harmless or less dangerous than lasalocid itself.

Since lasalocid is not licensed for cattle production in the EU and there are indications that the process of metabolism in poultry and cattle is quite different, this study is of only limited value.

Yet, while there is some information on the bioavailable metabolites, there is none at all on the 55% of lasalocid residues deemed non-bioavailable. First, it has to be questioned whether the analytical methods available in the late 1970s and early 1980s, when basic studies were undertaken, were capable of providing the level of precise information required today. Second, as a result of a major EU-funded research project we now know that some residues not previously considered bioavailable can break down over time during digestion, and release their toxicity (O'Keeffe

2 This was subsequently reduced to 12 weeks, in order to reduce the risk of toxicity in turkeys.

et al 1999). To date there has been no published study of lasalocid residues in this respect. However, work by O'Keeffe and colleagues on another class of antibiotic feed additives, the nitrofurans, has raised major concerns and led to a ban on these drugs throughout the EU.

Dr Glenn Kennedy has taken a particular interest in the nitrofurans and poses the question, 'Does this mean that no residues = no problem?' – to which he answers: 'No. If an animal is treated with a nitrofuran, little or no parent drug can be detected. However, these drugs are extensively metabolised to form tissue-bound residues that cannot be detected by the methods used in control laboratories'. He then poses the further question: 'Is there any evidence that tissue-bound metabolites are harmful?' to which he answers, 'Yes. If meat containing tissue-bound residues of furazolidone (one of the banned nitrofurans) is treated with mild acid (as happens in the human stomach) a chemical called AOZ is released. It has been suggested that AOZ can be metabolised to a known cancer-causing chemical' (Foodbrand n.d.).

Like other government scientists Dr Kennedy has been unwilling to state his personal opinion on the safety of lasalocid, or to speculate on the outcome of the current EU review. In answer to a specific question about the bioavailability of lasalocid he did, however, say that a proportion of lasalocid residues would inevitably be tissue-bound, like those of the nitrofurans (Kennedy 2004).

Derek Renshaw of the FSA is one of the few UK scientists to have had access to the original manufacturer's trials data on lasalocid. Until last year he was on the committee undertaking a review of lasalocid and other coccidiostats. However, with the establishment of European Food Safety Authority came a new committee structure and Mr Renshaw lost his seat in the reshuffle. He has, however, continued to advise the committee, something they recently acknowledged on their website.

Mr Renshaw, like Dr Kennedy, has remained tight-lipped on what he actually knows of the current level of understanding over whether or not the metabolites of lasalocid pose a health threat. However, we told him that our analysis of the limited data was that less than half the metabolites of lasalocid had ever been identified and that it appeared to us that a significant proportion of the total metabolites were potentially harmful. In reply he said,

If we're in the situation where 50% of the metabolites were unknown we'd not be wanting to approve the substance. We'd be wanting to find out a bit more about what is actually there (Renshaw 2003).

Failure of UK regulators to apply the ADI in a precautionary way

The failure of EU committees to set MRLs for residues of lasalocid in various foods so far clearly puts UK regulators in a difficult position. The FSA, for example, is waiting for an EU scientific opinion and will base its assessment on that. But do we really have to wait so long before acting in a more precautionary way? It is widely known that metabolites must be taken into consideration when setting MRLs, and UK regulators could surely make some allowance for this, before issuing statements on the drug's safety.

An example of this failing comes from the detailed notes of a meeting held by the pesticides campaigner Alison Craig with officials from the VMD in 2001. She asked about several reports of very high levels of lasalocid in

quail eggs (the highest being 4,300, 4,600, 5,300 and 5,400 µg/kg). She pushed the VMD to say exactly what toxicological advice it had received before it issued a statement saying 'that someone eating quail muscle or eggs containing the highest concentration found would be unlikely to suffer any adverse effect' (VMD 2000 p36).

Maggie Green from the VMD said the toxicologist had advised that the ADI for lasalocid is 300 µg per day [for an average adult weighing 60kg] so that the matter related to how many quail eggs you might eat. She said that eating five quail eggs would mean that 270 µg of lasalocid had been consumed and that this was below the ADI (Craig 2001).

It is apparent when one does the calculation, that the VMD have assumed that an average quail egg weights 10 grams. We decided to check this and bought some quail eggs from a local shop, cracked and weighed them individually to the nearest gram, and then weighed two random batches of five eggs. One batch weighed 58 grams, the other 60 grams. On this basis someone eating five quail eggs would consume between 313 µg and 324 µg of lasalocid, which is over, not under the ADI as suggested.

However, even if the calculation had been correct, what is clear is that the VMD is making no allowance for the possible presence of lasalocid in other food consumed on the same day, or for anyone eating more than five quail eggs, which should be done using the Veterinary Hypothetical Diet (see Chapter 5). This assumes a daily intake of 100 g of egg[3]. Anyone having a second helping of a typical quail egg dish would have consumed more than twice the ADI and might even have added to this through other foods containing egg on the same day.

The VMD's repeated reassurances over the safety of lasalocid residues in food also significantly make no allowance for metabolites of lasalocid, as will have to be done if and when MRLs are finally set. As far as we are aware no country has yet established an MRL for lasalocid in quail eggs. However, Australia, the only country so far to have published an MRL for hens' eggs, has set a limit of 50 µg/kg, less than one hundredth of the level found in the quail eggs.

Before we can see what all this means for the health of consumers in the UK it is necessary to look in detail at the incidence and level of residues found in recent years and why contamination continues to occur.

3 100 grams of egg is equivalent to two medium hens' eggs.

4 – Levels of contamination

Lasalocid has been licensed as a livestock feed additive for almost 30 years, and although its toxic effects were understood as early as 1975, it was believed then that any residues in food would be too small to pose dangers to humans (Pressman and deGuzman 1975; SCAN 1982a).

By the 1980s, however, American scientists had established that monensin, a related compound, could accumulate in poultry muscle and liver and expressed concerns about possible adverse reactions in humans, particularly in those suffering from coronary disease (Fahim and Pressman 1981, Pressman and Fahim 1983). Although their work focused on monensin, the most widely used ionophore at the time, government scientists in Northern Ireland have more recently referred to this work as being relevant to all ionophore residues in food, including lasalocid (Elliott et al 1998).

Because ionophores have never been permitted for use in laying-hen feed in the US and the UK, concern originally focused on animal tissues, rather than eggs. What was not realised at the time was that even small amounts of lasalocid getting into hen feed through lack of care at feed mills or other reasons, could concentrate in eggs. In the last decade, evidence has emerged showing that the most widespread lasalocid residues are in fact found in eggs: government surveillance schemes have been reporting significant lasalocid contamination of eggs laid by perchery, caged and free–range birds since at least 1993. In 2003, one sample of organic eggs was also contaminated.

Lasalocid is also found frequently in quail eggs and meat, and less often in chicken livers and meat. It could also be present in intensively reared turkeys and pheasants, but currently there is no testing of these species.

Lasalocid in eggs

If a bird ingests lasalocid, one might expect traces of the drug to be detectable throughout its tissues and organs. In fact, different parts of the body process lasalocid in different ways. Eggs, specifically egg yolks, tend to be residue traps because they are a major excretion route for the drug. They are also high in fat and lasalocid is fat-soluble. The Food Standards Agency acknowledges that ‘there is only minimal metabolism in the yolk, so clearance from the yolk is slow.’ (Renshaw 2002)

Record breaking lasalocid residues in eggs

In 2003, lasalocid contamination of eggs in the UK reached an all-time high: 12.4% of samples tested had residues in excess of 50 µg of lasalocid per kg of egg (µg/kg) (VMD 2004).

We refer only to samples with concentrations above 50 µg/kg because for 2003 these are the only results currently available. However, from a food safety point of view this concentration is also significant because, while no MRL for lasalocid contamination of eggs has been set in Europe or the US, Australia has set its MRL at 50 µg/kg (FSANZ 2004 p8).

The VMD undertakes 'targeted' testing. It is understood to involve increased sampling from producers supplied by feed mills where problems have previously been found, but it is not clear how representative positive samples are of the overall picture. If the figures published for 2003 are representative of the whole industry about 3 million eggs eaten every day would have been contaminated at a level which exceeded the Australian MRL. In Table 4.1 we provide all the data that has been published for lasalocid residues in eggs for the period between 1998 and 2003. In earlier years a greater amount of data was published, but this has been restricted in the past couple of years.

Table 4.1 Lasalocid residues in egg samples in the UK between 1998 and 2003

Year	No of samples	No of positives	Concentration detected (µg/kg)	Percentage above 50 µg/kg
2003[a]	250	31	50, 60, 60, 60, 70, 70, 70 70, 80, 90, 90, 100, 110, 130, 140, 145, 150, 180, 190, 200 220, 230, 250, 300, 310, 450 770, 810, 820, 3120, 3450	12.4
2002[b]	255	18	40, 50, 52, 60, 70 (2), 80 (2),110 (2), 120 (2), 150, 160, 230, 350, 560, 620	6.7
2001[c]	212	12	3, 4 (2), 7, 9, 40 (2), 60 (2), 90 (3)	2.4
2000[c]	212	10	2, 3, 10, 58, 70, 104, 130, 150, 710, 1400	3.3
1999[c]	208	21	2 (7), 3, 4 (3), 5, 6 (2), 7, 10, 16, 35, 36, 130, 150	0.96
1998[c]	221	5	10, 26, 29, 43, 60	0.45

Sources: VMD 1999a, VMD 2000, VMD 2001b, VMD 2004, VRC 2002a, VRC 2003a, VRC 2004

a Only samples above 50 µg/kg were recorded as positives

b Only samples above 40 µg/kg were recorded as positives

c All samples above 2 µg/kg were recorded as positives

In total 31 out of 250 samples[1] tested positive at over 50 µg/kg with 12 of these recorded at over 200 µg/kg. The previous record for samples over 200 µg/kg was four in 2002. Last year the highest ever residue from an egg

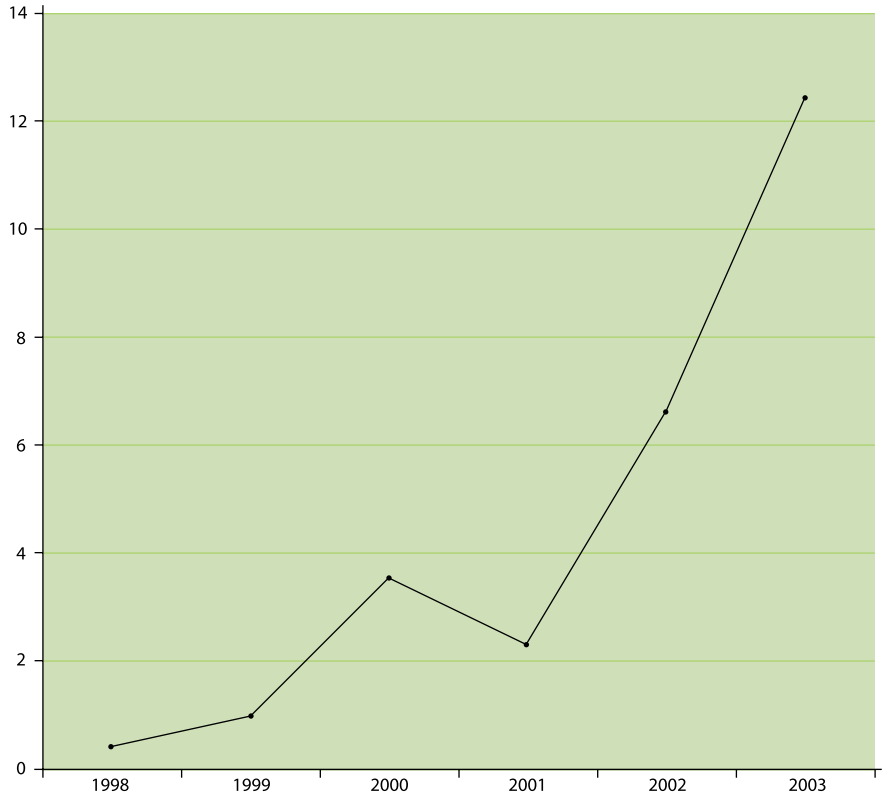
1 In April 2004, the VMD stated on their website that a further 25 samples had been tested, with 3 of these being recorded as positive. No concentrations were given for these positive samples.

sample was also recorded: 3,450 µg/kg. This is 69 times the Australian MRL. Another sample with a concentration of 3,120 µg/kg was also recorded. In previous years residues have been detected at concentrations as high as 1,400 µg/kg in 2000 and 620 µg/kg in 2002.

When a high residue is recorded government vets, scientists, and officials from the Royal Pharmaceutical Society of Great Britain and the Veterinary Medicines Directorate carry out a follow-up operation, visiting feed mills, farms and egg packing stations to establish, if possible, the source of the contamination. Last year there were a record number of follow-up investigations (31) and consideration is now being given to a proposal to raise the concentration at which a follow-up is required, presumably to reduce the workload (VRC 2003c p11).

The results for 2003 should not be seen as a one-off aberration. Since testing for lasalocid in eggs became part of the statutory surveillance scheme in 1998, contamination levels have been on a sharply increasing trend year on year: in 1998 0.5% of samples contained residues above 50 µg/kg, in 1999 the figure was 1%, 3.3% in 2000, 2.3% in 2001, 6.7% in 2002 and 12.4% in 2003.

Graph 4.1 Percentage of 12 egg samples contaminated at over 50 µg/kg



Sources: VMD 1999a, VMD 2000, VMD 2001b, VMD 2004, VRC 2002a, VRC 2003a, VRC 2004

Changes in surveillance scheme reduces chance of detecting high-level residues

These high-level residues are particularly surprising because changes to the testing method introduced in 1998 have made it less likely that these will be picked up. Until 1997, testing for lasalocid in eggs was carried out under an entirely British scheme, but since 1998 it has been carried out

under an EU-governed scheme, the UK National Surveillance Scheme.

The switch between the two schemes has reduced the chances of finding high-level residues for two reasons: firstly, because up until 1997 at least 425 egg samples were examined each year, whereas since 1998 at most 255 samples have been tested in one year. Secondly, because until 1997 an egg 'sample' for testing was just one egg, whereas since 1998 a sample has been 12 eggs mixed together. This means that the reported residues in recent years have only been averages of 12 eggs, which inevitably dilutes the highest residue concentrations.

On this point, the Food Standards Agency have argued that 'As poultry are treated with coccidiostats on a flock basis rather than as individuals, it is likely that a finding of lasalocid residues in a sample indicates that lasalocid was likely to be present in all of the 12 eggs.' Writing about a time when the record detected residue in eggs was 1,440 µg/kg, they admit, however, that

As a result of differences in the amount of lasalocid-containing feed eaten and differences in the pharmacokinetics of individual birds, it is likely that there will be a range of different concentrations of lasalocid in the 12 eggs. It is likely that some of the eggs making up the sample of eggs containing 1,440 µg/kg of lasalocid contained greater concentrations than this. Thus the estimate of the amount by which a high consumer of eggs might exceed the ADI may be too low. (Tudor 2003).

How high might residues in individual eggs be?

It seems clear, therefore, that concentrations in individual eggs will be higher than the reported levels for egg samples. How high could a concentration of a residue in an individual egg reach? The Veterinary Residues Committee is considering the possibility of using a farm where residues have been found in eggs to examine the variability of residues that might occur between eggs (VRC 2003d). However, a scientific feeding study is really needed to establish what the highest-level residues might be.

We can, however, make an estimate based on one published study. The scenario most likely to produce highly contaminated eggs is when laying birds are mistakenly fed medicated feed and, as we discuss below in this chapter, such errors are not uncommon. A paper published in the Veterinary Record reports on a similar case in Israel when broiler feed containing lasalocid was accidentally fed to broiler breeder chickens on two farms in Israel. Adverse effects on egg production and hatchability led to an investigation which revealed that eggs contained 2,500 µg/kg three days after the administration of lasalocid had begun, and 18,000 µg/kg after 14 days (Perelman et al 1993). This is more than five times higher than the highest average figure recorded in the UK.

Egg-laying birds eat about a third less than broiler breeders, but are also smaller. As such, it seems possible that similar concentrations would occur if broiler feed was given to laying birds for up to two weeks. One factor which may mitigate against this occuring very often is that egg production would fall if lasalocid were fed at full broiler concentrations which should trigger an investigation by the producer before the levels in eggs reached the maximum limit. Birds laying eggs contaminated at over 3,000 µg/kg may have been eating medicated feed for 4 to 5 days but levels would rise by over 1,000 µg/kg for every day that feeding continued.

Residue reporting restricted in recent years

Between 1997 and 2001 all lasalocid residues above 2 µg/kg were published but by 2002 only residues exceeding 40 µg were reported and in 2003 only those above 50 µg/kg. Justifying the shifting goal posts in their 2001 report, the Veterinary Residues Committee explained that publishing the lower level results 'made it more difficult to focus on the results that need to be considered more closely'. They also pointed out that '**all** the results are available from the VRC and VMD websites, or by request from the Secretariat' [their emphasis] (VRC 2002a p22). Although the complete 2001 results were published on the VRC website, we were told that the full results for 2002 and 2003 were not yet available.

The change means that many low-level and even some mid-level residues are no longer being reported as positives at all: only residues over 50 µg/kg are now being reported and since this is an average of 12 eggs, it is in theory possible that an egg sample could contain one egg contaminated at up to 599 µg/kg and the sample might still not show up as a positive if the average contamination fell below 50µg/kg.

Lasalocid in meat and chicken livers

Lasalocid residues are found less often in chicken tissues than eggs. When they are found, the residue concentrations tend to be lower than in eggs. Nonetheless, over 0.5% of chicken livers tested between 1997 and 2002 were contaminated with lasalocid residues, and most of those were in the 60 to 140 µg/kg range. Compounding this problem are residues of monensin, another ionophore in over 1% of chicken livers tested between 1997 and 2003. The levels of monensin residues are lower, typically in the 1 to 25 µg/kg range, although since the drug is often considered to be more toxic than lasalocid, this contamination may be as important as the lasalocid contamination.

Table 4.2 Ionophore residues in broiler livers in Great Britain

	Lasalocid residues in broiler livers			Monensin residues in broiler livers		
Year	No of samples	No of positives	Concn of positives (µg/kg)	No of samples	No of positives	Concn of positives (µg/kg)
2003	-	-		269	2	3,25
2002	312	2	80,100	335	5	1,2.5,3,4,5
2001	210	0	-	204	0	
2000	197	1	12	182	1	30[a]
1999	176	0	-	185	0	
1998	236	3	62,63,140	231	3	3,5,6
1997	100	1	120	40	2	6,24

a This residue is identified as an 'ionophore', but report does not indicate whether it is monensin, narasin or salinomycin

In Northern Ireland a higher rate of contamination has been observed. In 2001, the Department of Agriculture and Rural Development (DARD) found nine cases of lasalocid contamination in 194 chicken liver samples (all below 100 µg/kg), i.e. 4.6 % positive samples (VRC 2002b).

However, these data undoubtedly underestimate the real level of contamination. Firstly, a proportion of the lasalocid is likely to be 'tissue-bound' (see Chapter 3) and this quantity will not be picked up by the testing methodology. Secondly, there is no testing for lasalocid metabolites since surveillance only detects the parent compound. Very little is known about the lasalocid metabolites in chicken liver - only two of the metabolites have ever been identified. We do know that while lasalocid and some of its metabolites are microbiologically active[2], they only account for 3 to 4 % of all residues in the liver (SCAN 1982a). This means that if some of the residues which are not microbiologically active are nonetheless toxic, the total amount of toxic residues may be vastly underestimated by standard testing which is only for the parent compound.

Thirdly, as with egg sampling, one chicken liver sample is in fact a mixture of 12 different livers taken from two separate batches of birds

2 This means they have an effect on microorganisms.

(Crutcher 2003). As a result, the likelihood of recording high-level individual residues is reduced.

The reason that testing is undertaken for lasalocid in chicken livers is that more tends to accumulate there than in muscle and so testing the liver gives a better idea of the total level of contamination. But as well as being a convenient organ for laboratory samples, chicken livers are also used for human consumption. While most chicken livers are thrown away or used in dog food, a proportion are sold in butchers, turned into pâté or used in processed food.

The lack of testing for residues in chicken muscle (no testing has been undertaken since 1997) should not be interpreted as an indication that there are no residues in chicken muscle. Experiments show that residues do in fact occur in liver, kidneys, skin, fat and muscle (SCAN 1982a). Furthermore, the highest concentrations of total lasalocid residues can be detected in skin and fat if a microbiological test is used. Only when a radioactivity measurement is used is the highest concentration detected in the liver (ibid.). Despite this, there is no testing for lasalocid or any of the ionophore feed additives in chicken skin, fat or kidneys.

Consumers are therefore being exposed to lasalocid residues, not just through chicken livers as might be deduced from a hasty reading of the surveillance data, but through a variety of chicken tissues. Since chicken is Britain's most popular meat – annual consumption is 800 million chickens a year - even occasional low-level residues are of concern.

Quail

Quail eggs are no longer a delicacy saved only for the rich and famous. Increasingly, they are available in supermarkets and delicatessens. However, if the current level of lasalocid contamination of quail eggs were widely known, consumers might think twice before buying them. Quail eggs have the highest lasalocid contamination of all foods tested.

The problem with quail eggs became apparent in 2000 when the Veterinary Residues Committee tested quail eggs and meat for the first time. The level of contamination they found was shocking. Out of only ten samples taken, six contained lasalocid residues and four of those had concentrations in excess of 4,000 µg/kg. The highest residue concentration was a massive 5,400 µg/kg.

One member of the VRC described the results as 'disturbing' (FSA 2002 p47). However, attempts to remedy the situation have clearly been unsuccessful. Testing in subsequent years has continued to disclose a pattern of widespread and high-level residues. In 2003, 12 of 30 samples (i.e. 40% of samples) contained residues, the highest of the six concentrations published to date being 1,700 µg/kg.

Quail meat too, tends to contain residues. In 2000, nearly a third of muscle samples contained traces of lasalocid and in the following year 16.7% showed a positive result. There was no testing in 2002 and it is unclear whether there was any testing in 2003 either.

The 'reporting limit' for lasalocid residues in quail eggs and muscle is 40 µg/kg. It therefore seems probable that many of the samples which are currently being reported as negative, do in fact contain residues at lower levels.

Table 4.3 Lasalocid residues in quail eggs and muscle in Great Britain between 2000 and 2003

	Lasalocid residues in quail eggs			Lasalocid residues in quail meat		
Year	No of samples	No of positives	Concn of positives (µg/kg)	No of samples	No of positives	Concn of positives (µg/kg)
2003	30	12	41,77, 110,150, 900,1700, other 6 concns not yet available	No data available	-	-
2002	40	6	41,92, 130,430, 450,520	Not tested	-	-
2001	30	14	40,42, 44,66, 70,72, 98,210, 240,330, 410,550, 630, 740	30	5	43,45, 88,290, 400
2000	10	6	80,120, 4300,4600, 5300, 5400	20	6	50,85, 90,95, 130,250

Sources: VMD 2001a, VMD 2004, VRC 2002, VRC 2003a

Since lasalocid residues are found in high concentrations in quail eggs and meat, how confident can we be that other niche market game, poultry and eggs are free from residues? The answer is, we cannot. Goose, duck, pheasant and partridges either escape testing or are subject to minimum surveillance with small sample sizes, despite the fact that lasalocid is used as a feed additive for pheasants and partridges and may be prescribed by vets for geese and ducks.

The only other animal that has been tested systematically for lasalocid is rabbit and no residues have yet been detected. However, between 1999 and 2001 only 12 to 15 samples were tested a year, and it is unclear whether any samples have been tested since then.

Baby food and infant formula

No lasalocid residues have ever been reported in baby food. This sounds reassuring, but does not necessarily mean that all is well.

In both 1999 and 2002, 50 samples of chicken-based baby foods were tested for lasalocid. In 1999 testing was undertaken by the Central Science Laboratory using HPLC (a type of chromatography) with fluorescence detection. However, as the scientists undertaking this analysis explain,

It was found that standard methodology using a silica-based clean-up was unable to cope with the level of co-extractives and interferences and, therefore, was not

suitable for the determination of lasalocid in those matrices. (Tarbin et al 2002).

During 2000, they developed a successful modification to this method, which 'allows the determination of this analyte [lasalocid] which had previously been shown to be not possible via standard methodology.' (Sharman, 2004, ibid.). This is clearly shown in Graph 4.2.

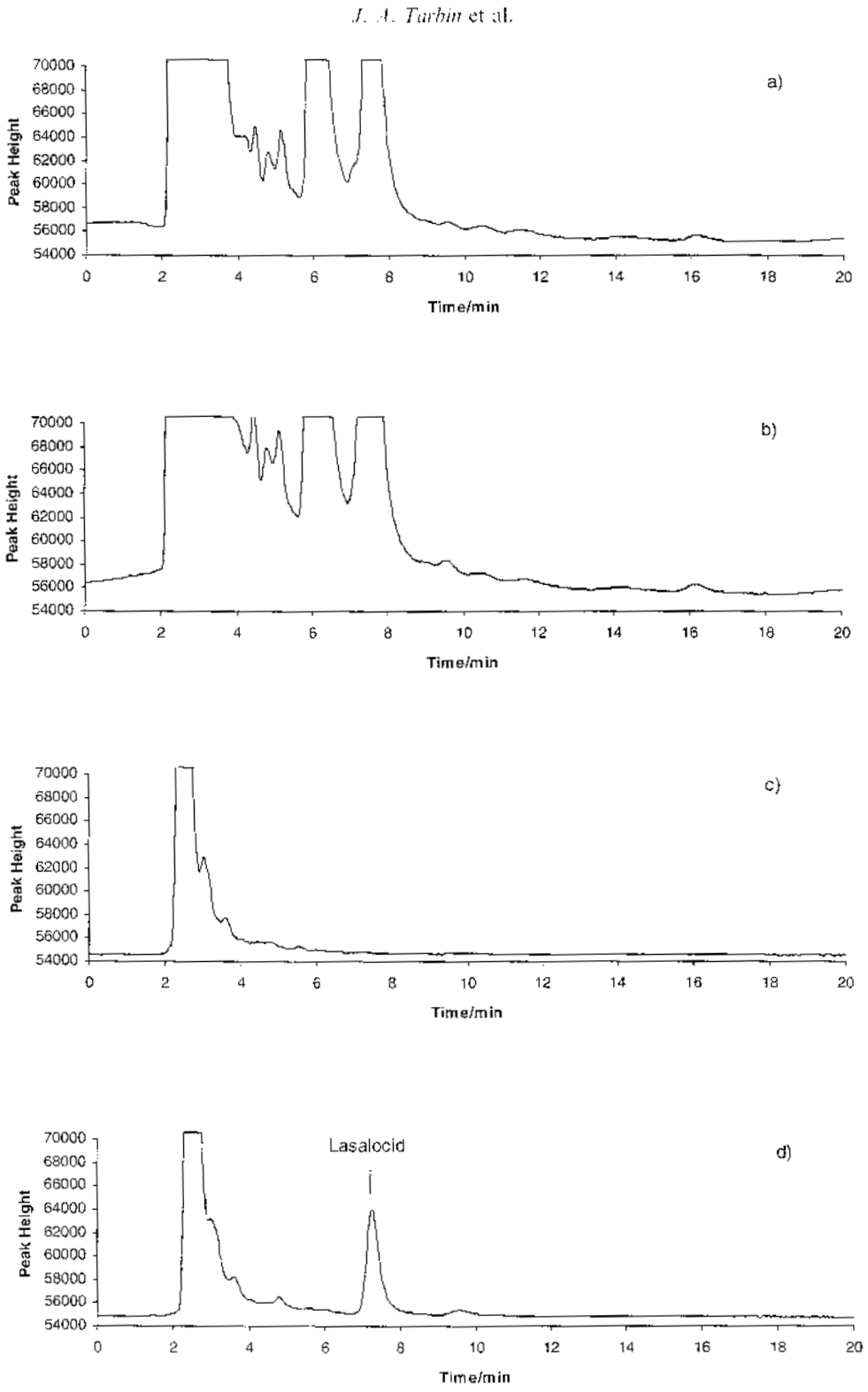
The technique would almost certainly have been used in 2002. The fact that no positive samples were found is not particularly surprising since we know that only one in every 156 batches of chickens tested in the UK in 2002 were reported to have livers contaminated with lasalocid (see page 32). However, while the logical response to this would be to increase the number of samples and test every year, no such tests at all were undertaken in 2003. According to Eric Crutcher, Head of Residue Surveillance at the VMD, the Veterinary Residues Committee reviewed the foods collected under the scheme and recommended that baby foods and processed foods be dropped, because they had 'not had many positive results in such foods' (Crutcher 2003).

Significantly, the last time testing was undertaken for residues in egg-based baby foods in 1998 and 1999, the 'reporting level' was 40 µg/kg, meaning that any residues detected below this level were not reported as positive (VMD 1999a, VMD 2000). However, as we explain in the next chapter, even residues below 40 µg/kg could be dangerous to babies.

There is also reason to be concerned about the possibility of residues in infant formula. Since 1997 it has been legal to add egg-yolk lipid to infant formula (Statutory Instrument 1997). However, infant formula containing egg-yolk lipid has never been tested under the surveillance scheme (Fitzgerald 2004c). Alarmingly while 2003 saw the highest levels of lasalocid contamination in eggs since the introduction of the National Surveillance Scheme, there was no testing at all for any baby foods containing egg.

Even more sensitive methods are now available which are able to detect lasalocid residues as low as just 1 µg/kg, though it is not clear if these have yet been validated on egg-based baby foods and infant formula. (Matabudul et al 2000).

Graph 4.2 Comparison of two methods for detecting lasalocid residues in chicken-based baby food



(a) Blank sample extract without additional clean-up

(b) 40 µg kg-1 spiked extract without additional clean-up

(c) Blank sample extract with additional clean-up

(d) 40 µg kg-1 spiked extract with additonal clean-up

Source: Tarbin et al 2002

The sources of lasalocid residues

How does lasalocid get into the eggs of laying birds, into the livers and muscle of broilers and into such a large proportion of quail eggs and meat? Since the drug is not even licensed for use in laying birds, it appears at first to be a mystery why it is found in such a large proportion of eggs. It is unlikely that many of the residues in hens' eggs are caused by deliberate lasalocid-feeding by farmers, since there is good evidence that lasalocid actually reduces egg production by laying birds.

Hundreds of millions of broiler birds on intensive poultry farms receive feed containing 75 to 125 mg/kg of lasalocid. This medicated feed is supposed to be withdrawn five days before slaughter to allow traces of the drug in muscle, fat and liver to be metabolised. Turkeys and pheasants receive between 90 and 125 mg/kg, with a withdrawal period of seven days. Observation of the withdrawal period is absolutely vital to prevent residues. Scientists from the Department of Agriculture (DARD) in Northern Ireland explain:

What is clear…is that following withdrawal of medicated feed, residue concentrations fall quickly and that the time periods specified in manufacturers' guidelines will normally ensure that high residue levels will not reach the food chain. This is assuming that the correct level of medication has been given for the correct time period and that possible sources of cross-contamination of the drug have been removed. If any of these factors are not adequately controlled, then the likelihood of high residue concentrations in edible tissues increases sharply (Elliott et al 1998).

There are probably a variety of explanations for the persistent lasalocid residues in the food chain. Several, but not all, of these contamination routes have been recognised by the regulators, but none has yet been blocked.

Cross-contamination at feed mills

Regulators have identified cross-contamination at the feed mill as a major cause of residues.

Medicated and un-medicated feed are commonly produced at the same mill. Mixing bins, pre-cubing bins, pipes and ducts are supposed to be flushed and thoroughly cleaned between additive-containing and additive-free batches, but, even so, some additives inevitably get through. This is hardly surprising as in some mills metal pipes and ducts carrying feed to pre-cubing bins can be 50, 60 or 70 feet long (FSA 2002 p59). In its original powdered form lasalocid was electrostatic and tended to stick to metal. Lasalocid premix also becomes airborne easily, increasing the chances of cross contamination (Alpharma n.d.).

The manufacturers have tried to address these problems by producing Avatec in a granular form, which is less likely to cling to metal tubing and become airborne, but the problems still persist: scientists in Northern Ireland have found that when the granular form is used, lasalocid residues can still be detected in feed up to four batches after Avatec (lasalocid-medicated feed) has been through the system, an improvement on the situation with the powdered formulation where the drug could be detected in the ninth batch, but hardly encouraging (Kennedy et al 1998).

Nor does the problem seem to be resolved by careful scheduling of feed production to prevent additive-free feed from being made immediately after a batch of feed containing a high percentage of a drug such as lasalocid.

Modern feed mills are automated and computer-controlled so in theory operator error should not be a possibility.

One possible explanation for the increase in lasalocid residues in the last couple of years is that feed containing the antibiotic is being promoted to the game industry as an alternative to Emtryl, a medicated feed which contained the now-banned drug dimetridazole (Grain Harvesters 2003). If more of the feed containing lasalocid is being sold to the game industry, more of it will be prepared at the feed mill and there will be greater opportunity for feed contamination.

Inadequate feed management and 'litter recycling' on farms

Silos and feed bins on intensive poultry farms have also been identified by regulators as a potential source of contamination. The problem arises if the same feeding bin is used for birds at different stages of growth and maturity, as birds move from a normal broiler diet (e.g. feed with lasalocid additives) to the five-day additive-free withdrawal period before slaughter.

Farmers routinely calculate how much chickens are eating and anticipate when feed hoppers need to be refilled. It appears to be common practice on many farms to 'top up' feed bins two or three days in advance, if necessary with an un-medicated feed lying on top of feed containing additive. Logically, one would expect the additive-containing feed to be consumed first, before the birds began to receive the upper layers of additive-free feed for the last five days of withdrawal before slaughter. Surprisingly, this is not always the case. An experiment in 2002 with three tonnes of nicarbazin-laced feed, topped up with six tonnes of un-medicated feed showed that bins can deliver feed on a 'first in last out' basis. (VRC 2003d). Because of its electrostatic properties, feed containing additive can stick to the sides and, depending on the design of the bin, additive-free feed can tumble through to be delivered to the birds earlier than expected. Quantities of medicated feed are then left until last, giving birds an unexpected lasalocid boost towards the end of the withdrawal period.

Clearly, only more careful farm management practices, with separate feeding bins, can reduce the risk of exposure to cross-contamination of this sort. Spillages of additive-containing feed that are not promptly cleared away in areas housing birds in withdrawal are another potential source of unexpectedly high residues in individual birds.

Another possible source of lasalocid ingestion by chickens during the withdrawal period is 'litter recycling' - a term used to describe the re-ingestion that occurs when birds peck at faeces on the floor. This is common under crowded conditions and during the eight-hour 'thinning' period towards the end of a bird's life when it receives no feed at all and is consequently very hungry. Faecal recycling has been blamed for high residues of the coccidiostat nicarbazin, where an experiment showed that birds kept in wire cages had much lower residues than birds kept on litter (Vernon and Kennedy 2002). Could this also account for some high concentrations of lasalocid?

Feeding the wrong feed

It appears, from the number of VMD reports, that feeding the wrong feed to an animal is a relatively frequent occurrence. This is suspected by the VMD to have possibly happened in two cases in 2003 when residues were

recorded at over 3,000 µg/kg (VRC 2004). In one case of lasalocid contamination in 2002, they also admitted that there was 'evidence that feed containing lasalocid had been fed to laying birds by the farmer' (VMD 2003a p14). In other cases, they explained that a monensin residue in broiler liver was probably caused by delivery of the wrong feed, and monensin residues in sheep occurred because the animals had received cattle feed (VMD 1999b p10, VMD 2004 p18). Officials from the VMD have also stated that they regularly receive reports in the lead up to Christmas of ionophore poisoning in turkeys and that one of the main causes is inadvertent use of broiler or other feed containing the ionophore (Sharpe and Crutcher 2001).

If the small amount of surveillance and follow-up investigation is already highlighting cases where this is happening, it must be concluded that such errors are frequently going unnoticed.

Although the VMD has been reporting serious breaches it does not appear that the industry as a whole has been fully made aware of the potential dangers of lasalocid residues. Instances where laying birds are incorrectly fed lasalocid-medicated feed are likely to lead to the highest residues in eggs.

Feeding lasalocid to layer replacers

Another way in which lasalocid may be getting into eggs has only recently been mentioned for the first time by the VMD (VRC 2004). It can be explained as follows: birds known in farming circles as 'layer-replacement pullets' (i.e. baby chickens raised over a period of 16 weeks to become mature egg-laying birds) can be fed lasalocid for the first 16 weeks of their life. In theory, young birds start laying three or four weeks later, which, regulators believe, gives plenty of time for the lasalocid to leave their systems, reducing the likelihood of residues passing to eggs.

In practice, however, regulators and egg producers know that birds can begin laying long before 20 weeks. When the European Union's Scientific Committee on Animal Nutrition (SCAN) gave its opinion on the inclusion of monensin in layer-replacement pullets feed it mentioned that 'under poor technical conditions and in countries where the sky is brighter, laying may start as early as in the 16th week because of stimulation of the reproductive tract' (SCAN 1981 p29). SCAN reported that one of the two breeds of chicken involved in the experiment began laying just three days after the withdrawal of another ionophore, salinomycin, which had been fed for 16 weeks (SCAN 1997). As the experiment was presumably carried out by Hoechst, the manufacturers of salinomycin, it seems reasonable to assume that it was carried out under good technical conditions. Other experiments have shown that chickens can in fact lay as early as the 14th week (Lewis et al 1997). Amazingly, it is not illegal to collect and sell such eggs for human consumption (NOAH 2001a).

But regulators and egg producers will point out, quite correctly, that eggs laid too early are of poor quality and, therefore, they do not seek to encourage the chickens to begin laying before they have reached maturity. However, some breeds can begin laying significantly earlier than others (SCAN 1997, Lewis et al 1997) and 'genetic improvement in performance and advancement in maturity' have also occurred over the decades (Lewis et al 1997), increasing the likelihood that chickens lay their first eggs when lasalocid is being fed to layer-replacement pullets, or shortly afterwards,

while the drug is still in the birds' system.

In practice, layer-replacement pullets are raised by specialist breeders for the first 16 weeks of their life and then delivered to egg producers who aim to encourage the birds to start laying several weeks later. However, if some birds begin laying very soon after delivery (and it is clear that some breeds begin laying significantly earlier than others), then the egg producer will have an obvious economic advantage in collecting and selling the eggs, even those that may be highly contaminated with lasalocid. The VMD claim that eggs from birds laying at 18-19 weeks are usually broken, however there is no legal requirement to do this and the VMD suspect that the highest residue from 2003 of 3,450 µg/kg may have been caused by birds laying early if it was not caused by the wrong feed being fed (VRC 2004).

Cascade prescribing – a likely explanation for quail residues?

The cause of the persistent high-level quail residues has been attributed to feed contamination by a member of the VPC (FSA 2002 p54). However, a more likely explanation may be that although lasalocid is not licensed as feed additive for quail in the UK, it is nonetheless being used. Lasalocid is licensed in some countries for use in quail, so it clearly has some desirable effects in the animal, such as controlling coccidiosis which can be a big problem.

Despite lasalocid not being licensed in the UK for quail, vets can prescribe it under the 'cascade' arrangement, which allows them to prescribe medicines licensed in another species if all licensed medicines are inappropriate for treating a particular disease. Given that residues in quail are widespread, it seems likely that cascade prescribing is occurring on a very regular basis. But since lasalocid has not been subjected to the EU regulatory process for use in quail, it is unlikely that much is known about how the drug accumulates in quail eggs and tissues. If the drug is being used regularly in quail farming, as would seem to be indicated by the residues figures, then it should be subjected to the full regulatory process. The present arrangement would appear to be the worst of all worlds: possible widespread use, but little or no knowledge as to the consequences. It is, however, a problem the VMD has yet to recognise or take action on.

Establishment of VRC fails to solve problem

The Veterinary Residues Committee (VRC) is a panel of advisors, drawn from consumers, farmers, veterinarians, toxicologists and representatives of the pharmaceutical, animal feed and retail industries. It advises the VMD and the FSA on drug residues in all kinds of food. It was established in January 2001, replacing the highly secretive and widely criticised Advisory Group on Veterinary Residues (AGVR). The VRC conducts its business openly and appeared at first to take effective steps towards addressing the problems of lasalocid residues.

Straight away it set up a food additives sub-group to recommend strategies for reducing the residues of lasalocid and two other ionophores (VRC 2002a).

At its first meeting in 2001 the subgroup also considered strengthening the impact of surveillance programs by introducing a policy of 'brand naming' or, as it is sometimes referred to, 'naming and shaming'(VRC 2001a). This would involve publishing the name of a food product and the

manufacturer/supplier in the case of positive samples. If poor practice in one or two companies was responsible for a significant number of positive samples, sharing the information might lead to swift identification of, for example, contamination at critical points in the feed manufacturing process. Arguably, the release of the information would be in the public interest. The VRC also established a working group to address the brand naming question.

A third encouraging move was the removal of the 'Differential Action Level' for lasalocid and other coccidiostats in 2002 (VRC 2003a p21). In practice the VRC's recommendation means that whereas before the VMD only followed up cases where residues had occurred at concentrations above 100 µg/kg, it is now required to investigate all residues of lasalocid above 50 µg/kg.

Unfortunately, despite the encouraging early activity, VRC initiatives have had no meaningful impact upon lasalocid contamination of eggs. Remarkably, after several meetings in 2001, the feed additive sub-group failed to meet at all in 2002 (VRC 2003a p9). It did manage one meeting in 2003, but its most significant suggestion was that the VRC should consider the re-introduction of a 'Differential Action Level' specifically for lasalocid residues in eggs (VRC 2003c p11). There are indications that this was motivated by a wish to reduce demands on the VMD to carry out follow-up investigations, as the need for these rose due to the increasing occurrence of lasalocid residues in eggs in 2002 and 2003.

The VRC's brand naming policy has also made little progress. Various legal obstacles to the implementation of the scheme were identified early on: VMD legal advice was that it would not be possible to introduce brand naming for the statutory surveillance scheme unless there were to be an amendment to the EU Council Directive 96/23/EC (VRC 2001a p2). The VRC considered that even if other member states supported the policy, the change to EU law could take years.

They decided, therefore, to focus on brand naming for the non-statutory scheme (VRC 2001b), but since lasalocid testing for eggs now comes under the statutory scheme, this would fail to be of any benefit for dealing with the principal lasalocid residue problem. The only lasalocid testing which comes under the non-statutory scheme is for residues in quail eggs and meat. Yet even with the non-statutory scheme, progress has been very slow. In November 2001 the VRC decided to examine the criteria which the scheme would have to meet, 'with the aim of introducing it with six months' (VRC 2001c). But two years later the VRC were still at the stage of circulating proposals for a pilot scheme on brand naming for the presence of malachite/leucomalachite green in farmed fish (VRC 2003c) and there was little prospect of brand naming being introduced for lasalocid residues in the near future.

5 – Consumer exposure

Estimating egg consumption

In order to evaluate the risks posed by chemical residues in food, regulators need reliable estimates of food consumption, particularly for high-level consumers. It is for this purpose that the Veterinary Hypothetical Diet (VHD) was originally proposed by the Joint Expert Committee on Food Additives (JECFA) of the UN Food and Agriculture Organisation and the World Trade Organisation. It is now used almost universally by advisory and regulatory bodies to establish 'maximum residue limits' (MRLs) for veterinary residues in food and to ensure that consumers do not exceed the 'acceptable daily intake' (ADI).

The VHD makes 'conservative' assumptions for consumption of various foodstuffs - estimates which consumers are not expected to exceed on a consistent basis. These are set out in Table 5.1.

Table 5.1 The Veterinary hypothetical diet for an adult assumed to weigh 60 kg

Food	Consumption	
	Absolute Intake (g/person/day)	Relative Intake[1] (g/kg bw/day)
Lean muscle	300	5.00
Fish (muscle and skin in natural proportions)	300	5.00
Liver	100	1.67
Kidney	50/10[a]	0.83 / 0.17[a]
Fat and skin	50/90[a]	0.83 / 1.5[a]
Milk or milk products	1500	25
Eggs	100	1.67
Honey	20	0.33

a. Second figure is for poultry

Source VRC 2002c

1 Consumption of egg per kilo of bodyweight

As can be seen from table 5.1, the VHD estimates that an adult (assumed to weigh 60 kg) will not consume more than 100 g of egg (two medium-sized eggs) per day and that children and babies will not consume more than 1.67 g of egg per kilo of their bodyweight.

However, a recent critique of the VHD prepared by the Food Standards Agency (FSA) has argued that the VHD 'may not be a suitable tool for estimating consumer exposure to veterinary medicine residues as part of any meaningful risk-assessment process'. The authors argue that it 'vastly underestimates milk, eggs and honey and total diet consumption for those aged 6 months to 6 years' and warn that 'any underestimate of exposure may compromise the safety of important subgroups of the UK population'. This warning clearly has implications for assessing the risks posed by lasalocid residues, since eggs are involved in this underestimate.

The paper goes on to claim that the VHD 'makes no distinction between chronic [average long term] and acute[a single day's] consumption, for which dietary patterns can differ significantly' (VRC 2002c.). Because daily consumption has the potential to be significantly higher than average consumption, the maximum levels assumed in the VHD may not be sufficient to protect the whole population, as they may underestimate actual exposure for some people

The FSA suggests therefore that, instead of using a model diet, figures for actual UK consumption should be used. The figures are available from the UK National Diet and Nutrition Survey (NDNS) which provides data on weekly egg consumption by adults and children. Adults aged between 16 and 64 consume on average 200 grams (g) of egg (4 medium egg) per week, whereas toddlers aged between 1.5 and 4.5 years consume 127 g (Gregory et al 1990, Gregory et al 1995).

Derek Renshaw, a toxicologist at the Food Standards Agency (FSA) has provided data on the chronic consumption (i.e. the daily average, calculated from consumption over several days) for the upper 97.5th percentile of consumers for different age groups using further data from the NDNS and other sources (see Table 5.2). This is the figure for the average egg consumption of the 25th highest intake consumer out of every thousand.

Table 5.2: Chronic egg consumption (average consumption) of the upper 97.5th percentile of consumers

Sub-population	Chronic consumption	
	Absolute intake (g/person/day)	Relative intake (g/kg bw/day)
Adults, 16–64 years	79.3	1.11
Young people, 4–18 years	54.5	1.74
Young people, 15–18 years	60.7	0.98
Young people, 11–14 years	69.0	1.36
Young people, 7–10 years	49.1	1.82
Young people, 4–6 years	47.6	2.09
Toddlers, 1.5–4.5 years	49.9	3.52
Infants, 6–12 months	41.3	4.31

Source: Renshaw 2002,

This means that 25 out of every 1000 people consume, on average, at least 79.3 g of egg (roughly two small eggs) each day. Since there are over 38 million people in the UK aged between 16 and 64, it can be estimated that nearly 1 million people will be eating this much or more. The NDNS does not provide information on the diet of those aged over 65, but since they number nearly 10 million in the UK, it is possible that another 200,000 people or so consume over 80 g of egg a day.

The figures provided by Mr Renshaw were based only on chronic consumption patterns, i.e. on long-term averages of egg consumption, and provide no information on short-term consumption patterns. While the chronic figures do give an idea of high levels of consumption averaged over several days, they tell us nothing about how much an individual might eat on a single day. Clearly, even an average egg consumer will sometimes eat more than two small eggs on a single day.

However, the NDNS also provides some data on acute consumption (a single day's consumption). One of the tables in the FSA paper gives this information for adults and toddlers.. The relevant figures are set out in Table 5.3.

Table 5.3 Acute consumption (a single day's consumption) of egg of the upper 97.5th percentile of consumers

Sub-population	Acute Intake (g/kg bw/day)
Adults, 16–64 years	2.24
Toddlers, 1.5–4.5 years	5.57

Sources: VRC 2002c Annex 1, Table 5

As can be seen from the table, consumption on a single day can be substantially higher than the average daily consumption and higher still than the upper limit estimated by the VHD. For example, if we consider the consumption of the upper 97.5th percentile of toddlers weighing 15 kg, then consumption on a single day would be 83 g (15 x 5.57) or approximately two small eggs, while average daily consumption would be 53 g and the upper limit suggested by the VHD would be just 25 g.

Table 5.4 Estimates of upper limit for egg consumption in a toddler weighing 15 kg (in grams)

VHD	Average Daily Intake (from NDNS)	Maximum Daily Intake (from NDNS)
25	53	83

Source: VRC 2002c, Renshaw 2002

A major limitation of all these tables, however, is that they tell us nothing about the consumption of the very highest intake consumers, the top two or three consumers out of every 1000 for example - a population grouping which accounts for well over a 100,000 individuals in the UK. People on special diets such as the high-protein Atkins Diet or muscle-building diets, are likely to consume many eggs each day, often over long periods of time, yet this is not acknowledged in this data.

In an attempt to establish what the highest consumption on a single day might be, we sent an electronic survey to all Soil Association staff members. We recognised that the results would not be representative of the population and could even be biased, but we felt they might give us an idea of possible maximum egg consumption in a single day. In total 61 people responded. 38% of men and 15% of women claimed to have eaten the equivalent of six or more medium-sized eggs in one day. The highest consumption amongst men and women was eight and seven respectively (See Appendix).

Regulators indicate all is safe, but rely on dubious calculations

In order to assess whether the level of contamination in food by a particular chemical is acceptable or not, regulators usually rely on the MRL (see Chapter 3). As long as the concentration of the chemical is below the MRL for that particular food, the residue is deemed safe.

However, for veterinary drugs, such as lasalocid, no MRL has been set. In these cases, regulators undertake a calculation, based on the ADI of the chemical, which is supposed to yield an equal level of protection. For lasalocid the ADI in the UK has been set at 5 micrograms of lasalocid per kilo of bodyweight (µg/kg bw), in the US it is 10 µg/kg, but in Australia it is just 1 µg/kg bw (see Chapter 3).

The calculation multiplies the level of contamination by the estimated daily consumption of the food in question given by the VHD. If the figure obtained is lower than the ADI, the food is declared safe.

As an example, consider a typical 'low-level' residue of 50 µg/kg. The VHD allows for a 60 kg adult to consume at most 100 g of egg in a day. At this level of contamination the total consumption of lasalocid over one day in micrograms per kilogram bodyweight (µg/kg bw) would be:

$$\frac{50 \times 100}{(1000 \times 60)} = 0.07 \text{ µg / kg bw}$$

which is well below the UK ADI of 5 µg/kg bw.

Even if the eggs were to be contaminated at a much higher level of 1,000 µg/kg then an adult's total consumption in one day would be:

$$\frac{1000 \times 100}{(1000 \times 60)} = 1.67 \text{ µg / kg bw}$$

which is still below the UK ADI, although it would breach the Australian ADI.

On the basis of calculations such as these, the VMD frequently issues public statements to the effect that its toxicological advice is that any reported residues are of no danger to human health.

However, despite these reassurances, calculations such as these are not equivalent to an assessment using an MRL. This is because it is based entirely on detectable residues of lasalocid in eggs and takes no account of tissue-bound residues of lasalocid or of lasalocid metabolites, neither of which show up in standard tests (see Chapter 3).

By contrast, when scientists establish an MRL, they make allowances for all residues, detectable and undetectable, of both the parent drug and its metabolites: having first established experimentally, using radioactive

carbon, what proportion of the total residues will be undetectable metabolites or tissue-bound residues and what proportion of these are likely to cause harm, they then adjust the permitted concentration in various foodstuffs of detectable parent drug accordingly. Assessments using an established MRL rather than an ADI-based calculation as above, are therefore more stringent, and in some cases, much more stringent. Where there are no MRLs however, it is simply not right to give assurances, just because detectable residues fail to breach the ADI.

A further problem with the regulators' calculation is that it relies on the dietary estimates from the VHD which, as we have seen, 'vastly underestimates' egg consumption (both chronic and acute) in children and also underestimates acute egg consumption in adults. As we shall see in the rest of this chapter, when higher estimates for egg consumption are used, significant breaches of ADI occur in adults, children and babies.

Breaches of the ADI in adults

In 2003, one sample of 12 eggs was recorded to be contaminated with lasalocid at 3,450 µg/kg. Should an adult consume two (medium-sized) eggs contaminated at this level in a day, they would exceed the ADI:

$$\frac{3450 \text{ x } (2 \text{ x } 50)}{(1000 \text{ x } 60)} = 5.75 \text{ µg / kg bw}$$

An adult eating four such eggs contaminated at this level would exceed the UK ADI twice over. Table 5.5 gives the intake of lasalocid, in terms of bodyweight, for an adult consuming two, three or four eggs a day contaminated at a range of levels.

Table 5.5 Lasalocid intake of adult weighing 60 kg at various levels of residue

No of eggs eaten	Lasalocid residue (µg/kg)	Weight of egg (g)	Intake (µg/kg bw)
2	50	50	0.08
3	50	50	0.13
4	50	50	0.17
2	500	50	0.83
3	500	50	1.25
4	500	50	1.67
2	1000	50	1.67
3	1000	50	2.5
4	1000	50	3.33
2	2000	50	3.33
3	2000	50	5
4	2000	50	6.66
2	3450	50	5.75
3	3450	50	8.63
4	3450	50	11.5

Breaches of ADI in children

Young children may be much more susceptible than adults to toxic effects from lasalocid. Residues of lasalocid are principally broken down into less complex molecules in the liver and while in very young children the liver is proportionally much larger than in adults, accounting for one-eighth of the total weight of a newborn baby, it is much less developed and therefore less able to deal with toxic substances. Furthermore, young children are more likely to have a higher relative consumption of food since their food intake to bodyweight ratio is much higher than for adults.

In theory the ADI has been calculated in a way which allows for this, since a proportion of young rats will have been included in the long-term feeding studies used to calculate the 'no-observed effect level' (NOEL) which is used to establish the ADI (see Chapter 3). However, because children have combined higher susceptibility and higher relative consumption, 'public opinion in some countries is leading towards legislation requiring routine use of extra safety factors to "protect" infants and children' (Herrman and Younes 1999).

An example of this is legislation introduced in the US in 1996 to protect infants and children from pesticide residues. The acceptable daily intake for pesticides is 10 times lower for infants and children than it is for adults. However, this extra safety factor is not yet applied to veterinary medicines. (FQPA 1996)

However, it is arguable that an extra safety factor for infants and children should be applied to residues of both pesticides and veterinary medicines if they are similarly harmful. Lasalocid's toxicity is comparable to that of many pesticides (see Table 3.1) and experiments show that weanling rats for example are significantly more sensitive to lasalocid than adult rats: the lethal dose is only about a quarter of the lethal adult dose. Doses of lasalocid between 1 mg/kg bw and 10 mg/kg bw had no significant effect on mothers, while a dose of 1 mg/kg bw to weanlings reduced body and organ weight gain, changed blood and body chemistry, and increased levels of haemosiderin[2] in liver and kidneys (FOI 1994).

If we consider a four-year-old-child weighing 20 kg eating in a day a total of two medium-sized eggs (each 50 g), where the eggs are contaminated with lasalocid at a level of 3,450 µg/kg, the total consumption of the drug per kilo of bodyweight becomes:

$$\frac{3450 \text{ x } (2 \text{ x } 50)}{1000 \text{ x } 20} = 17.25 \text{ µg / kg}$$

This is three times higher than the acceptable daily intake in the UK and 17 times higher than the Australian ADI.

In fact, as Table 5.6 shows, consumption of eggs contaminated at much lower concentrations can lead to significant amounts of lasalocid being consumed: eating two eggs contaminated at 200 µg/kg will lead to a breach of the Australian ADI and if the eggs are contaminated at 1,000 µg/kg, the British ADI will be breached.

According to one British scientist because of the higher food intake of children on a body weight basis, specific risk management measures may be needed to ensure that the ADI is not exceeded (Walker 1998). However no such measures have been taken in the UK.

2 A substance composed of ferric oxide which can be a sign of disturbed iron metabolism

Table 5.6 Lasalocid intake of child weighing 20 kg

No of eggs eaten	Lasalocid residue (µg/kg)	Weight of egg (g)	Intake (µg/kg bw)
1	50	50	0.13
2	50	50	0.25
1	200	50	0.5
2	200	50	1
1	500	50	1.25
2	500	50	2.5
1	1000	50	2.5
2	1000	50	5
1	2000	50	5
2	2000	50	10
1	3450	50	8.63
2	3450	50	17.25

Breaches of the ADI in babies

The situation may be worse still in babies.

Any lasalocid residues that babies consume would be particularly worrying for several reasons:

- the maturing organs of infants can be sensitive to chemical injury (Brukner 2000). This is particularly true of the brain, which develops over a much longer period than other organs (Scientific Committee on Food 1998)
- an infant only acquires adult levels of most enzymes by two to three months of age, before which it is less able to detoxify chemicals and consequently more susceptible to toxicants (Scientific Committee on Food 1998)
- protein-binding in the newborn is low, which means that the amount of 'active' free chemical could be greater (Scientific Committee on Food 1998)

For these reasons, and because animal experiments 'do not mimic the situation of a baby receiving infant formula' ADIs established for adults and children do not apply to babies under the age of 12 weeks (Walker 1998).

It has been assumed that very young children are unlikely to be at risk from lasalocid residues in the UK because they do not usually consume foods contaminated by lasalocid. We have, however, identified at least three ways in which infants might consume more than the ADI:

- cooked egg yolks used as a weaning food
- maternal breast milk
- infant formula and baby food

Consumption of cooked egg yolk as a weaning food

The Food Standards Agency recommends that eggs are not fed for the first six months of a baby's life as they can sometimes cause allergies (FSA n.d.). However, the allergenic nature of egg is thought to come from the white, not the yolk, which is now considered a very healthy food for young babies (Hedstrom n.d.). This is in part because egg yolk contains significant quantities of two omega fatty acids, docosahexaenoic acid (DHA) and arachidonic acid (ARA) which are important phospholipid fatty acids used in the formation of the retina and brain (Carlson et al 1996).

Recent research has confirmed the beneficial effect of feeding four egg yolks per week to babies during the weaning period from four to six months onwards (Makrides et al 2002). The BBC promoted this finding in a report entitled 'Egg boost for babies' (BBC 2003). Previously, research by the Child Nutrition Research Centre in South Australia had also suggested that babies aged between six and twelve months benefited from consuming four eggs per week and the Australian government promoted this research in an article entitled 'Egg yolks: nature's "wonder food" for babies' (RIRDC 1998).

Consequently, many nutritionists now recommend feeding cooked egg yolk to babies under one year of age. Mothers looking for advice from nutrition research bodies (e.g. on the internet) find a considerable variation in the suggested age (from four months to eight months) for starting to feed egg yolk.

However, using egg yolks in weaning food is of potential concern because the yolk is where lasalocid accumulates: Mr Renshaw from the FSA has confirmed to us that because lasalocid is lipophilic, the residues are found in the egg yolk which has a much higher fat content than the egg white (Renshaw 2002).

If a baby aged six to eight months and weighing 7 kg eats one medium-size egg yolk, a contamination level of just 150 µg/kg would be sufficient to breach the Australian ADI since:

$$\frac{150 \times 50}{1000 \times 7} = 1.1 \text{ µg / kg}$$

(we assume that all lasalocid residues are contained in the egg yolk).

A contamination level above 700 µg/kg is sufficient to breach the British ADI since:

$$\frac{700 \times 50}{1000 \times 7} = 5 \text{ µg / kg}$$

Similarly, if the baby weighed 5 kg, a contamination level above 500 µg/kg would be sufficient to breach the British ADI.

If a 7 kg baby had eaten an egg yolk which was contaminated at the highest level of 3,450 µg/kg, the consumption of lasalocid per kilo of bodyweight would be

$$\frac{3450 \times 50}{1000 \times 7} = 24.6 \text{ µg / kg}$$

which is approximately five times the British ADI and over 24 times the ADI in Australia.

Table 5.7 Lasalocid intake of baby weighing 7 kg eating one egg or egg yolk in a day

Lasalocid residue (mg/kg)	Weight of egg (g)	Intake (mg/kg bw)
50	50	0.36
100	50	0.71
150	50	1.07
300	50	2.14
500	50	3.57
750	50	5.36
1000	50	7.14
1500	50	10.71
2000	50	14.29
3450	50	24.64

Lasalocid through breast milk

Might a young child ingest lasalocid residues via its mother's milk? Dr David Atkins of the Food Standards Agency acknowledges that prescribed antibiotics taken by a breast-feeding mother can give rise to levels in breast milk which are a cause for concern, but nonetheless believes that residues of lasalocid in food would give rise to such small traces in breast milk as to be insignificant (Atkins 2003).

However, as far as we have been able to establish, no studies have ever been undertaken to determine what proportion of the lasalocid ingested as residues in food is excreted in human breast milk and whether this may vary according to stage of lactation or other factors.

As Dr Atkins indicated, there has, though, been a large amount of research into medicinal antibiotics passing into breast milk. According to a review, the physiochemical properties which influence drug distribution into breast milk include molecular size and water-and lipid-solubility: the more lipid-soluble antibiotics are more likely to accumulate in breast milk fat, whereas drugs composed of large molecules are less likely to do so (Chung et al 2002).

Since lasalocid is lipid-soluble (particularly so in the phospholipids that are a major constituent of the fat of breast milk), there is reason for concern. Lasalocid's molecular weight of 613 is quite high, and it may mitigate against residues in milk, although this might not apply to toxic metabolites of lasalocid.

Using published data by Chung and her colleagues, we have calculated the potential percentage of antibiotic which a 2 kg baby would take in if it consumed 450 ml of breast milk a day and its mother was taking a course of antibiotics (Table 5.8).

Table 5.8 Percentage of antibiotic which a 2 kg baby would potentially take in if it consumed 450ml of breast milk a day and its mother was taking a course of antibiotics

Ampicillin	0.025%
Ceftazidime	0.04%
Chloramphenicol	0.09%
Ciprofloxacin	0.08%
Clindamcyin	0.21%
Erythromycin	0.05%
Gentamycin	0.10%
Metronidazole	0.69%
Nitrofurantoin	0.22%
Ofloxacin	0.06%
Pefloxacin	0.09%
Sulfafurazole	0.20%
Sulphamethoxazole	0.20%
Tetracycline	0.03%
Trimethoprim	0.25%
Vancomycin	0.19%

Percentages calculated by the Soil Association on the basis of Chung et al (2002)

For these 16 antibiotics the percentage varies from 0.025% to 0.69%. If we were to take a hypothetical figure of around 0.25% (below the middle of the range) for lasalocid, we can then calculate a possible exposure to lasalocid in the worst case scenario of a breast-feeding mother eating four large eggs (each weighing 60 g) contaminated at 3,450 µg of lasalocid per kg of egg, the highest levels measured in 2003. The mother would then consume:

$$\frac{3450 \times 60 \times 4}{1000} = 828\ \mu g \text{ of lasalocid.}$$

For an average 60 kg adult this would equate to a daily intake of 13.8 µg per kg of body weight, which is over twice the ADI.

Assuming then that the 2 kg baby consumes 0.25% of this lasalocid in the breast milk, it will have consumed

$$\frac{828 \times 0.25}{100 \times 2} = 1.035\ \mu g\ /\ kg$$

which is slightly above the Australian ADI of 1 µg/kg bw.

The ADI however, is not applicable to babies below 12 weeks of age (see above). Therefore the possibility that young babies could be consuming this

much lasalocid should be cause for concern. Clearly research is required but as a precautionary measure nursing mothers should be advised to limit their daily consumption of egg.

Infant formula, baby food and lasalocid

Many infant formulas do not include any ingredients from egg. However, nowadays a significant number of formulas do contain some egg yolk in order to provide the quantities of the fatty acids DHA and ARA that are found in breast milk. Since premature babies benefit from this supplementation it is particularly common (but not universal) to include egg yolk in infant formula specially formulated for premature babies (Jewell et al 2004).

In addition, egg yolk contains a variety of phospholipids (Scientific Committee on Food 1999). European Union regulations currently allow for the use of 5 g of egg yolk lecithin to be added to each litre of infant formula (Scientific Committee on Food 1999, Carlson et al 1996).

The fact that lasalocid dissolves in phospholipids, including lecithin, suggests that a significant part of any lasalocid surviving processing may be present in the lecithin when it is extracted from the yolk. Professor Ronquist of Uppsala University in Sweden, has expert knowledge in the biochemistry of ionophores. He states that 'lecithin in egg yolk may well be an excellent vehicle of lasalocid or any other ionophore', although he acknowledges that he does not know how much could be transferred that way on a quantitative basis (Ronquist 2004b).

Egg yolk only makes up approximately a third of the liquid part of the egg and lecithin only makes up a ninth of the egg yolk. If a significant proportion of any lasalocid residues were to remain in the lecithin, then it is possible that the concentration could become very high. This danger would be increased if all the eggs came from one supplier for one brand of formula.

Some baby foods also contain egg, but what the VMD calls 'egg-based baby food' has not been tested for lasalocid residues under the either the statutory or non-statutory surveillance schemes since 1999. No samples of infant formula were ever included in the testing (FitzGerald 2004c).

Significantly, the last time testing took place for residues in egg-based baby foods in 1998 and 1999, the 'reporting level' was 40 µg of lasalocid per kilo of baby food. This means that any residues occurring below this level would not have been reported as positive, even if they had been detected (VMD 2000). However, as we detail in Chapter 4 analytical methods prior to 2000 were much less sensitive than they are today and could not easily detect residues in processed food. A reporting level of 40 µg/kg, in any event, does not provide a guarantee that the ADI was not being breached, even when samples were reported as negative. If we assume, for example that a baby consumes 150 g per day of infant formula per kilo of bodyweight and that this food is contaminated with lasalocid at a concentration of 35 µg/kg then, the baby will have consumed:

$$\frac{35 \times 150}{1000} = 5.25\ \mu g$$ of lasalocid per kg of bodyweight[3]

3 We assume that a litre of infant formula weighs 1 kg.

This is in excess of the ADI. Since babies and young children may well be more sensitive to lasalocid than adults, even values below this would be of concern.

The present lack of surveillance and previous limited testing provides no reassurance that infant formula or baby foods are not contaminated with lasalocid at unacceptable levels.

Testing for lasalocid residues in egg-based baby foods should be re-introduced immediately. In addition research is needed into the fate of lasalocid residues in eggs being processed for use in infant formula feeds.

Lasalocid and the foetus

A further major concern is the possibility of lasalocid residues reaching the unborn foetus. Given that lasalocid produces damaging effects in rat foetuses, this transmission route must be of concern (FOI 1994).

Most drugs below a molecular weight of 1,000 will readily cross the placental membranes into the foetal circulation and attain blood levels comparable to those measured in the mother (Ecobichon 1987). Lasalocid's molecular weight of 613, suggests it will enter into the foetus' blood stream when a mother consumes lasalocid-contaminated food.

How well-equipped would the foetus then be to cope with this lasalocid contamination? Would it be able to metabolise the lasalocid in order to eliminate it?

The main process which occurs when chemicals are metabolised is to render them sufficiently water-soluble to be eliminated from the body in urine or faeces. This involves two metabolising phases known as phase 1 and phase 2. Phase 1 reactions are relatively simple reactions such as oxidation, reduction and hydrolysis. A foetus can carry out these processes efficiently, but it cannot carry out phase 2 metabolism, which involves more complicated reactions. Instead, it depends on the mother for phase 2 metabolism. Because the foetus has a much higher metabolic rate than the mother, the concentration of phase 1 metabolites in the foetus can be up to five times higher than in its mother (Howard 2004).

This is significant, because simple metabolites of chemicals tend to have similar toxicity to the parent chemical – it is only when the parent chemical is broken into several molecules that metabolites' properties greatly differ from the parent chemical (Renshaw 2003).

Known breaches of the ADI from UK national diet and nutrition survey

The data for chronic egg consumption from the UK National Diet and Nutrition Survey (NDNS) provided by the Food Standards Agency (see Table 5.2) show that the young are at greatest risk in terms of their intake of lasalocid per kilo of bodyweight. Despite the fact that these figures are based on long-term averages, it points to very significant breaches of the ADI in babies and children.

Table 5.9 Lasalocid intake of upper 97.5th percentile of consumers of eggs (based on chronic consumption of eggs)

	Relative egg consum-ption (g/kg bw/day)	Intake (µg/kg bw) when residue 250 µg/kg	Intake (µg/kg bw) when residue 500 µg/kg	Intake (µg/kg bw) when residue 1,000 µg/kg	Intake (µg/kg bw) when residue 2,000 µg/kg	Intake (µg/kg bw) when residue 3,450 µg/kg
Adults, 16—64 years	1.11	0.28	0.56	1.11	2.22	3.83
Young people, 4–18 years	1.74	0.46	0.87	1.74	3.48	6.00
Young people, 15–18 years	0.98	0.26	0.49	0.98	1.96	3.38
Young people, 11–14 years	1.36	0.34	0.68	1.36	2.72	4.69
Young people, 7–10 years	1.82	0.46	0.91	1.82	3.64	6.28
Young people, 4–6 years	2.09	0.52	1.05	2.09	4.18	7.21
Toddlers, 1.5–4.5 years	3.52	0.88	1.76	3.52	7.04	12.14
Infants, 6—12 months	4.31	1.08	2.16	4.31	8.62	14.86

However, older people may also be at risk of adverse effects from residues in food since a greater percentage suffer from heart and other health problems on which lasalocid may have an effect (see Chapter 6).

Table 5.10 Lasalocid intake of upper 97.5th percentile of consumers of eggs (based on acute consumption of eggs)

	Relative egg consump-tion (g/kg bw /day)	Intake (µg/kg bw) when residue 250 µg/kg	Intake (µg/kg bw) when residue 500 µg/kg	Intake (µg/kg bw) when residue 1,000 µg/kg	Intake (µg/kg bw) when residue 2,000 µg/kg	Intake (µg/kg bw) when residue 3,450 µg/kg
Adults, 16—64 years	2.24	0.56	1.12	2.24	4.48	7.73
Toddlers, 1.5–4.5 years	5.57	1.39	2.79	5.57	11.14	19.22

Using the limited data we have from the NDNS on acute daily consumption of eggs (see Table 5.3), we may also compare the acute lasalocid intake for the upper 97.5th percentile of consumers in both adults and toddlers.

Since the chronic consumption of egg is highest of all in infants between 6 months and one year, it is reasonable to assume that the acute consumption will also be significantly higher in these babies than it is in toddlers. If this is the case, then breaches of ADI well in excess of 20 µg/kg bw will be occurring in babies when eggs are contaminated at 3,450 µg/kg.

Is the problem worse than we think?

While such residue levels are worrying enough, even greater breaches of the ADI are possible and probably occurring.

This is because under the national surveillance scheme, the concentrations quoted for residues are averages of the concentrations of 12 eggs from a single source. The highest concentrations occurring are therefore probably much higher than 3,450 mg/kg, the highest concentration published to date. As detailed in Chapter 4, concentrations as high as 18,000 µg/kg may be occurring.

The consumption of just one egg, or egg yolk, contaminated at this level by a baby weighing 7 kg would lead to an intake of 128.6 µg/kg of lasalocid per kilo of bodyweight, which is over 25 times the British ADI and over 128 times the Australian ADI

As Table 5.11 shows, even adults consuming just 1 egg would be consuming far more lasalocid than is allowed for under the ADI.

Table 5.11 Lasalocid intake when eggs contaminated at 18,000 µg/kg

	No of eggs eaten	Lasalocid Residue (µg)	Weight of egg (g)	Intake (µg/kg bw)
Baby 7 kg	1	18,000	50	128.6
Child 30 kg	1	18,000	50	30
	2	18,000	50	60
Adult 60 kg	1	18,000	50	15
	2	18,000	50	30
	3	18,000	50	45
	4	18,000	50	60

To all these calculations needs to be added a reminder that they are based only on detected (and, assumed likely on the basis of studies) residues of lasalocid itself and make no allowance for metabolites. In chicken liver we know that detectable lasalocid residues account for only 3.8% of total residues, however there is no available information on the metabolites of lasalocid in eggs.

6 – Possible effects of lasalocid on human health

Why the ionophores have toxic effects on the heart

The term 'ionophore' means 'ion-bearer'. The toxicity of lasalocid and other ionophores is linked to their ability to carry ions (electrically charged atoms) across biological membranes (including cell membranes and membranes of structures within cells). The molecules of antibiotic embed themselves in the membrane, form chemical complexes with ions on the outside, carry the ions across the membrane, and release them on the inside.

This is no marginal issue: the abnormal movement of ions across cell membranes induced by the ionophores can have profound effects on the health of cells and may ultimately lead to cell death. This is because a healthy cell will always maintain an 'ion gradient' on either side of its membrane – in other words, the concentration of particular ions is greater on one side of the membrane than on the other. When ionophores cause ions to 'leak' across the membrane, the cell must work harder to maintain the ion gradients and in doing so it uses up more of its energy. Even in healthy cells, maintenance of ion gradients takes up 30-70% of the energy produced in the cell. When extra work is required to maintain the gradients, energy levels fall and, in extreme cases, cell death occurs. When the ionophore's effect on ion gradients is not sufficient to cause actual cell death there are nonetheless symptoms at the level of the whole organism.

Effects of carboxylic ionophores on the heart

The cardiovascular toxicity of carboxylic ionophores (a subgroup of ionophores which includes lasalocid, monensin, salinomycin and narasin) was reviewed in 1983 by Pressman and Fahim, two scientists from the University of Miami. They found that the principal effect in dogs was an increase in blood flow, indicating expansion of blood vessels in the heart. While their review was concerned mainly with monensin – the ionophore most widely used in agriculture at the time – they point out that lasalocid, salinomycin and other carboxylic ionophores have 'very similar cardiovascular effects'.

Pressman and Fahim explained why this means that consumption of even small quantities of ionophore residues by those with coronary heart disease poses special problems:

If a given coronary vessel becomes partially occluded[1] through disease, the resultant flow impairment would produce some degree of hypoxia[2] which would trigger the autoregulatory process causing the vessel to dilate. Such a vessel, if dilated close to its limit, cannot respond further to a coronary vasodilator[3] to the same degree as normal, unoccluded vessels possessing normal tone. Thus, dilatation by a coronary vasodilator of normal vessels in parallel with less responsive occluded vessels would divert blood flow away from the latter to the normal vessels, thereby exacerbating hypoxia in the myocardium[4] fed by the occluded vessels (Pressman and Fahim 1983).

This phenomenon is termed 'coronary steal' as it takes blood away from heart muscle. They went on to say:

Since an appreciable fraction of the population at large suffers from some degree of coronary disease, ingestion of even small amounts of dietary monensin could produce an appreciable incidence of adverse effects such as hypoxia with attendant angina. Such responses to dietary monensin might well escape clinical detection as they would be swamped by the spontaneous incidence of adverse episodes among victims of coronary disease. Moreover, coronary steal would not present a problem to the large segment of the population not predisposed to a deleterious response by coronary disease.

1 Blocked
2 Oxygen deficiency
3 Substance causing blood vessels to dilate
4 Heart muscle

Nevertheless, in view of the significant incidence of coronary disease within the population at large, and the number of people who consume poultry (perhaps beef should also be considered), the incidence of adverse human reactions to dietary monensin may be appreciable. A number of human adverse reactions to monensin are already on file with the FDA although these may represent mainly industrial exposure to younger workers and not be directly pertinent to the hazards posed to the older population by dietary monensin. (ibid.).

In their experiments on dogs, the scientists found that a dose of just 2.5 µg per kg of bodyweight doubles coronary flow, from which they deduce that 'a threshold dose is about 1 µg/kg'. They point out that 'a 1 kg chicken consuming 8.5% of its weight daily of feed containing 120 ppm [parts per million] monensin would take in 10,000 µg per day of ionophore' (Pressman and Fahim 1983). Broiler chickens in the UK can have up to 125 ppm of lasalocid added to their feed (NOAH 2001a).

In earlier experiments the same scientists had shown that because monensin is lipid-soluble, when it is fed to various animals (including chickens), 'it easily passes through the gut into the blood and ultimately into the tissues', thus leaving significant residues. They concluded that since monensin has 'extremely potent cardiovascular effects', 'the impact on man of continuing exposure to monensin in the food supply requires careful re-evaluation' (Fahim and Pressman 1981). Lipid solubility is also a characteristic of lasalocid.

Given the substantial use of both monensin and lasalocid in agriculture in the UK and many other developed countries, and given the potentially enormous health implications identified two decades ago, it seems incredible that no further research has been undertaken and that there has been no recent re-evaluation of the consequences of ionophore exposure through the food chain. In 1998, Pressman and Fahim's work was still being quoted by the Principal Scientific Officer of the Veterinary Sciences Division, Belfast, a European national reference laboratory, as being the most up to date review of this issue (Elliott et al 1998).

Lasalocid's harmful effects on the heart

Perhaps because lasalocid was licensed more recently than monensin and is less commonly used in agriculture, no specific review of lasalocid's cardiotoxicity has been published in the scientific literature. Nonetheless, its effects are very similar to those of monensin, as has been shown in many experiments with animal tissues or live animals.

Experiments on human-, rabbit-, rat- and dog-heart muscle confirm that lasalocid increases the force of contraction of heart muscle (Levy and Inesi 1974, Rodgers et al 1979, Singal and Prasad 1976). With human heart muscle the effect can last for up to an hour after even a low dosage of lasalocid had been added to the solution in which the muscle is suspended.

Numerous ionophore toxicity studies have been carried out on live rats, mice, rabbits, dogs, cats, cattle, sheep, horses, chickens and pigs (Gad et al 1985, Galitzer et al 1982, Galitzer et al 1986, Hanley et al 1975, Melville et al 1977, Novilla 1992, Prasad 1983, deGutzman and Pressman 1974, Schwartz et al 1974). These experiments have all confirmed the cardiotoxicity of ionophores, namely their effects of increasing heart rate and the force of contraction of heart muscle (albeit at generally higher doses than

Some ionophores such as monensin, narasin or salinomycin only bind with monovalent (single-charge) positive ions (cations) such as potassium (K^+) or sodium (Na^+), whereas lasalocid can also bind with divalent ions such as calcium (Ca^{++}), magnesium (Mg^{++}) and barium (Ba^{++}).

Lasalocid is particularly effective at carrying calcium ions across biological membranes and is often referred to as a 'calcium ionophore'. It has an effect on calcium flows even at low concentrations: just 25 nMol (=15 mg per litre) of lasalocid inhibited calcium efflux in rat liver cells mitochondria[5] (Pereira da Silva et al 1984).

A vital aspect of heart function relies on the movement of calcium ions across the membrane of a small structure within individual heart cells, called the sarcoplasmic reticulum. The heart contracts and relaxes as calcium ions are shuttled in and out of the sarcoplasmic reticulum, varying the concentration of calcium ions. Lasalocid, as a calcium-ionophore, can interfere in these calcium flows, which explains why it has marked effects on cardiac muscle (Levy et al 1973, Levy and Inesi 1974, Entman et al 1972).

5 A specialised structure in cells which is sometimes referred to as a 'cellular power plant' as it manufactures the substance which is used as the cell's energy source

those which occur as residues in food). One study of 13 different ionophores found that lasalocid and another closely related calcium ionophore A23187, were particularly cardiotoxic (Gad et al 1985).

There are also many reports in the literature of cases of accidental ionophore poisoning which have caused cardiomyopathy (disease of heart muscle) or cardiac failure. These have occurred in turkeys (Pritchard et al 2001), deer (Glover and Wobeser 1983 quoted in Gallitzer and Oehme 1984), sheep (Newsholme et al 1983 quoted in Gallitzer and Oehme 1984), pigs (van Halderen et al 1993 quoted in Oehme and Pickrell 1999) and cattle (Perl et al 1991) (see also Chapter 3).

It is worth mentioning at this point the experience of one member of the public who has contacted the Soil Association. Richard Gee had been suffering for five years from a condition known as 'atrial fibrillation', a potentially severe form of heart arrhythmia (irregular heartbeat). Every couple of months he would have a serious attack of atrial fibrillation which would last for about 18 hours. On hearing about the issue of lasalocid residues in eggs and ionophore residues in meat, he decided to adopt a vegan diet, giving up meat and dairy produce, and also his normal daily consumption of approximately two eggs. Since adopting this diet 17 months ago, he has not had an occurrence of atrial fibrillation which has lasted more than half a minute. This sudden improvement, corresponding with the removal of eggs from the diet, may of course be no more than coincidence, but the anecdote is interesting because of the scale and cost to the NHS of this type of heart complaint, and because it indicates an area for possible research.

Atrial fibrillation is estimated to affect over half a million people in the UK. One in 100 people have the condition, with the figures rising to one in 10 in those aged over 65. Researchers at the Western Infirmary in Glasgow have found that the cost of treating the disease almost doubled between 1995 and 2000 to £459 million, which is approximately 1% of the entire National Health Service budget (BBC 2004, Stewart et al 2004). An additional £111 million is spent treating the disease in nursing homes. The reasons given for the rise in the prevalence of atrial fibrillation are an ageing population and an increased survival rate from conditions closely associated with atrial fibrillation (Stewart et al 2004).

Experiments carried out with cells taken from the hearts of human sufferers of atrial fibrillation have shown abnormal activity of some calcium 'ion channels'[5] (Klein et al 2003). Could this mean that sufferers of atrial fibrillation would be adversely affected by ingesting lasalocid, a calcium ionophore? Unfortunately, no scientists have yet considered the possibility that residues of lasalocid in eggs and poultry meat may be contributing to atrial fibrillation.

The current British Prime Minister is a sufferer of supraventricular tachycardia, a similar heart arrhythmia involving rapid heart beats (atrial fibrillation is in fact a form of supraventricular tachycardia). It might eventually benefit a significant proportion of the population if the high-profile nature of the Prime Minister's heart condition encouraged government scientists to look at the possible health effects of lasalocid residues on human health.

5 Proteins embedded in biological membranes that control the flow of particular ions across membranes (see box)

Lasalocid and sudden-death syndrome

While sudden-death syndrome is not well understood, the main causes are believed to be cardiomyopathy[6], in particular hypertrophic cardiomyopathy[7], and myocarditis[8]. An estimated one in 500 young adults suffer from hypertrophic or dilated cardiomyopathy (Medical News Today 2004). The syndrome has received unwelcome publicity in recent months as two young high-profile Irish sportsmen have died from it: the captain of the All Ireland winning gaelic football team and the captain of the under-19 Irish rugby team. In both cases heart failure was diagnosed.

There is significant scientific evidence suggesting a possible link between these conditions and ionophore consumption. Experimentally-induced lasalocid and monensin toxicosis causes mild to marked cardiomyopathy in cattle (Galitzer et al 1986). Accidental ionophore poisoning (with maduramicin or salinomycin) is believed to have caused cardiomyopathy leading to sudden death in cattle (Perl et al 1991). Accidental lasalocid toxicosis in turkeys, which occurs regularly, can also reveal myopathy of the cardiac muscle (Pritchard et al 2001). Fatal cardiomyopathy has occurred in sheep following accidental monensin poisoning (Newsholme et al 1983 quoted in Gallitzer and Oehme 1984). Lasalocid-fed horses have developed toxic myocarditis (Oehme and Pickrell 1999) and sudden death was noted in 70% of cattle and sheep fed poultry litter containing 2.5–6.1 ppm of the ionophore maduramicin (Fourie et al 1991 quoted in Oehme and Pickrell 1999). British scientists have also shown that another calcium ionophore closely related to lasalocid, A23187, can induce hypertrophic cardiomyopathy in pregnant rats (Pearce et al 1985).

One Eli Lilly scientist has drawn attention to the fact that with ionophore toxicity 'the syndrome of sudden death with myocardial necrosis is common, but sporadic in occurrence in cattle, especially calves. It produces unexpected deaths, and lesions have been described in the heart but not skeletal muscles' (Novilla 1992).

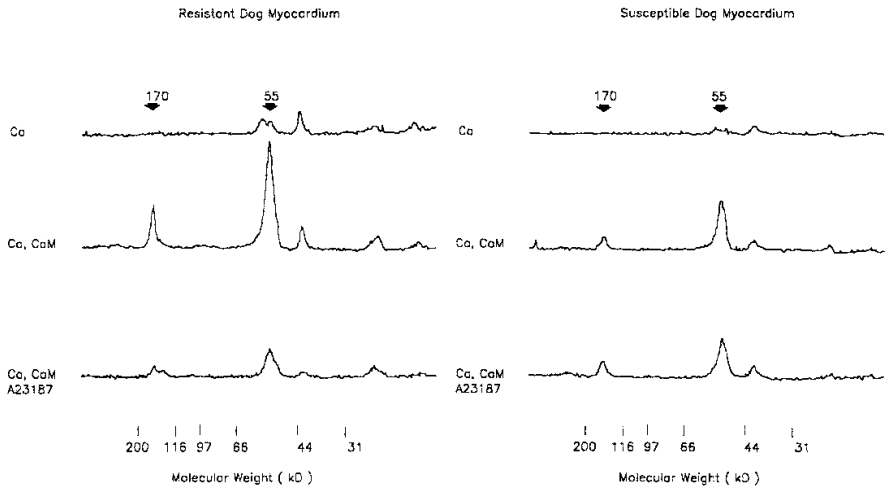
A Norwegian scientist has suggested that hypertrophic cardiomyopathy and high blood pressure are both caused by systemic disorders of calcium ion channels and calcium uptake and binding by muscle membranes. He also points out that the hypercontractile state in hypertrophic cardiomyopathy has often been linked to calcium-ion overload in cells (Landmark 1986). Lasalocid, as a calcium ionophore (see side panel page 56), interferes with calcium channels and causes calcium overload in cells (Satoh et al 1992, Satoh and Uchida 1993). Swedish scientists have also suggested that an ionophoric effect may be important in the occurrence of myocarditis (Waldenstrom et al 1993).

Ventricular fibrillation (fibrillation of the lower part of the heart) is another condition which is linked to sudden death: left untreated it can cause sudden cardiac death within minutes. Evidence provided by a particularly gruesome study carried out on dogs shows that calcium ionophores could be linked with the condition: after various experiments had been carried out, hearts taken from dogs were classified as being either 'susceptible' or 'resistant' to ventricular fibrillation. Examination of the dogs heart muscle showed different patterns of 'phosphorylation'[9] of two particular proteins in susceptible and resistant hearts. This was thought to

6 Disease of heart muscle
7 Enlarged heart muscle
8 Swollen heart muscle
9 The binding of phosphate group to a protein or small molecule

be indicative of higher free calcium concentrations inside the cells in the susceptible hearts. Pretreatment of heart tissue from a dog resistant to ventricular fibrillation with the calcium ionophore A23187 converts the resistant phosphorylation pattern to a sensitive one, as Graph 6.1 shows. (Billman et al 1991).

Graph 6.1



Source: Billman et al 1991

While there are countless theories about the causes of Sudden Infant Death Syndrome (SIDS) in children (commonly known as 'cot death'), some researchers have suggested a cardiac origin, based on a 19-year survey of over 33,000 babies (Schwartz et al 1998). Cot death most frequently occurs between one and three months of age, an age at which babies are not consuming eggs directly. However, because of the inclusion of egg yolk lecithin in many infant formulas (see Chapter 4 and 5), the possibility of babies consuming residues of lasalocid or its toxic metabolites remains. Similarly, babies could be receiving lasalocid through their mother's milk or in utero during development (see Chapter 5).

It is important to note that the dosages of lasalocid and ionophores which have been shown to cause cardiomyopathy in healthy animals are significantly higher than those which humans could be getting as residues in food. It is therefore unlikely that even the high-level residues which are currently occurring in eggs could cause a healthy adult to develop cardiomyopathy. However, for people who are already suffering from cardiomyopathy or myocarditis there remains the possibility of serious adverse reactions to lasalocid/ionophore residues. In a situation where a patient is suffering from life-threatening cardiomyopathy, it would seem highly advisable to eliminate all known potential sources of ionophore residues from their diet. Unfortunately sufferers of hypertrophic cardiomyopathy or other forms of cardiomyopathy are often unaware that they have the condition until it is too late. As a result many people who do not realise that they have a heart problem, may also be at risk.

The Royal College of Pathologists has confirmed that tests are not undertaken during post-mortem examintaions in the UK to see if lasalocid residues are present in the livers of those who die unexpectantly (Macaskill 2004).

Despite all the indications of a possible link between the consumption of ionophores and sudden-death syndrome, the matter has not yet received serious scientific attention. In view of the fact that residues in eggs reached record levels last year (see Chapter 4), a proper scientific enquiry into possible links between these residues and a variety of heart conditions is now urgently required. The Public Health Minister, Melanie Johnson, recently set up a new advisory body to focus on adult sudden deaths and heart arrhythmias such as atrial fibrillation (Medical News Today 2004, Mead and Churcher 2004). We strongly recommend that this new body examine what role lasalocid residues may be playing in these conditions.

Lasalocid's neurotoxicity

Some of the most common symptoms of ionophore poisoning in animals such as dogs, horses, sheep and chickens are neurological or neuromuscular in nature: loss of control of movement, paralysis, leg weakness and impaired reflexes (Espino et al 2003, Hanson et al 1981, Novilla 1992, Perelman et al 1993, Safran et al 1993, Shlosberg et al 1985). The neurological signs of accidental lasalocid toxicosis in dogs have been described as being consistent with a 'generalised lower motor neuron deficit' (Safran et al 1993, Suarez et al 2003).

In one study, scientists determined that dogs showing signs of intoxication had accidentally been fed lasalocid at between 166 and 210 ppm in their feed. In subsequent experiments, they found that feeding as little as 10 to 15 ppm caused a similar neuromuscular effect. This surprised the scientists, who observed that there is a 'marked difference in the species susceptibility to lasalocid' and warned that 'the routine use of lasalocid as an anticoccidial agent in poultry feed also has the potential for leaving toxic residues of this substance in human food. This is especially important in the light of the unexpectedly low dose of lasalocid that caused clinical signs in dogs. Although we do not have data on the concentrations of lasalocid that would cause clinical signs in human beings, we speculate that if the toxin has a cumulative effect, small residues in food for human consumption may potentially lead to subclinical effects' (Safran et al 1993).

Ionophores and other diseases

Even back in 1983, US researchers Pressman and Fahim drew attention to the fact that monensin residues in food might not just affect people with coronary heart disease but could also be 'deleterious to diabetics'.

More recent research has linked abnormal movements of ions across biological membranes with a wide range of diseases. Scientists have pointed out how similar this disease mechanism is to the effect that ionophores have on membranes and their ion gradients.

Research by Swedish scientists published in December 2003 has suggested that 'excess leakage of ions across the plasma membrane seems to be a major component of certain diseases such as syndrome X, Tarui's disease, myocarditis and Alzheimer's disease (and possibly also prion disease)'. They found that 'an ionophore or ionophore-like mechanism may be the underlying cause of syndrome X' and that 'the enhanced erythrocyte [red blood cell] haemolysis[10] in Tarui's disease is...due to enhanced leakage of Ca^{++}' (Ronquist and Waldenstrom 2003, Waldenstrom et al 1993).

10 The excessive breakdown of red blood cells which causes a form of anaemia

Furthermore Swedish scientists found that amyloid beta peptide, which is the major component of 'senile plaque' in the brains of Alzheimer's patients, had an ionophoric action on human red blood cells which was qualitatively similar to the action of the calcium ionophore A23187. American scientists had previously found that the same calcium ionophore actually increased the production of the amyloid beta peptide three-fold (Querfurth and Selkoe 1994).

It has also been proposed by scientists from Glasgow and Brisbane that chronic-fatigue syndrome is related to abnormal ion channel function. They point out that organochlorines, lead, insecticides and pesticides are known to target ion channels and that chronic exposure to these chemicals can lead to symptoms similar to those of chronic-fatigue syndrome (Chaudhuri et al 2000). Might exposure to lasalocid residues in food also cause deterioration in sufferers of chronic-fatigue syndrome?

While the mechanisms of these diseases have many similarities with the mode of action of the ionophores, these are nevertheless only theoretical links which should be investigated. The effects could be caused by other factors such as viruses or even other chemicals in the environment with similar effects. However, in view of the ionophoric profiles of the diseases, we asked Professor Ronquist of Uppsala University whether residues of lasalocid occurring at the levels found in the UK in 2003 would cause him concern. In his opinion we have insufficient knowledge about the modifications of ionophores through cooking and stomach acidity. However, he also says that 'we cannot rule out the possibility that the ionophores in question can come out unharmed and appear in the circulating blood and even reach some target cells and the concentrations you mention are in my judgment enough to be relevant in a pathophysiological context' (Ronquist 2004a).

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Abbreviations (used in this report)

ADI	Acceptable Daily Intake
AGVR	Advisory Group on Veterinary Residues
DARD	Department of Agriculture and Rural Development
DEFRA	Department for Environment Food and Rural Affairs
EFSA	European Food Safety Authority
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FOI	Freedom of Information
FSA	Food Standards Agency
MRL	Maximum Residue Limit
NOAEL	No Observed Adverse Effect Level
NOAH	National Office of Animal Health
NOEL	No Observed Effect Level
SADS	Sudden Adult Death Syndrome
SCAN	Scientific Committee on Animal Nutrition
SCAN	Standing Committee on Animal Nutrition
SIDS	Sudden Infant Death Syndrome
VMD	Veterinary Medicines Directive
VPC	Veterinary Products Committee
VRC	Veterinary Residues Committee

Appendix –

Soil Association electronic survey of staff on egg consumption

Total respondents 61

Answers have been adjusted and all refer to medium-sized eggs on the basis: large eggs 60 grams, medium-sized eggs 50 grams, small eggs 40 grams rounded to the nearest half egg.

1. On average how many eggs would you consume on a day when you eat food containing egg?

No. of Eggs	Male	%	Female	%
0	0	-	1	3
0.5	1	5	2	5
1.5	0	-	1	3
1	9	43	17	43
2	6	29	14	35
2.5	4	19	3	8
3	0	-	1	3
3.5	1	5	2	5

2. Taking account of all possible sources, what is the highest number of eggs you might ever have consumed in one day?

No. of Eggs	Male	%	Female	%
1	1	5	3	8
2	0	-	1	3
3	2	10	9	23
3.5	1	5	4	10
4	5	24	12	30
4.5	3	14	0	-
5	1	5	5	13
6	3	14	2	5
7	4	19	4	10
8	1	5	0	-

3. What about over two consecutive days?

No. of Eggs	Male	%	Female	%
1	1	5	1	3
2	0	-	6	15
2.5	0	-	1	3
3	0	-	2	5
3.5	1	5	1	3
4	5	24	6	15
5	2	10	4	10
6	2	10	10	25
7	4	19	1	3
8	0	-	3	8
8.5	2	10	1	3
9.5	1	5	1	3
10	1	5	1	3

Several vegetarians commented that they sometimes ate more eggs in a day than they intended because it was often the only vegetarian option when away from home.

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