Lasalocid Backgrounder

1. Permitted uses of the antibiotic lasalocid in the US

- CHICKENS (Chicken, broilers)
- CHICKENS (Chicken, fryers)
- CHUKAR PARTRIDGES (Chukar partridges, up to 8 weeks of age)
- Cattle (Cattle, calves, excluding veal calves)
- Cattle (Cattle, beef, on pasture)
- Cattle (Cattle, dairy, heifers on pasture) (not a permitted use in the EU)
- Cattle (Cattle, fed in confinement for slaughter)
- RABBITS (Domestic rabbit, young)
- SHEEP (DOMESTIC) (Sheep, confinement)
- TURKEYS (Turkey, growing)

http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=096-298

2. Lasalocid contaminant in Michigan was distributed primarily to farms where lasalocid is not a permitted use

Farm Type receiving Lasalocid	Number	Lasalocid an approved use
Swine Farms	35	No
Egg Producers	3	No
Turkey/Swine Farm	1	No for swine, Yes for Turkey
Dairy Farms	3	Yes
Cattle Farms	1	Yes
Turkey Farms	2	Yes

See slide 11 from presentation by MDARD

3. The US has no required withdrawal time for lasalocid

- Cattle: zero days before slaughter.
- Sheep: zero days before slaughter.
- Chicken and Partridges: zero days before slaughter.
- Rabbits: zero days before slaughter.
- Chukar up to 8 weeks: no withdrawal necessary.

http://www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=096-298

5. Lasalocid residues in poultry decrease as birds are fed clean feed during a withdrawal period (WP)

Table 1. Mean lasalocid residual concentrations (μg kg^{-1} ± SD) detected by LC-MS/MS in the edible tissues of broiler chickens throughout the 5 days of the WP.

	Day of WP						
Matrix	0	1	2	3	4	5	6
Heart	610.2 ± 15.7	129.1 ± 6.9	7.7 ± 1.8	171.8 ± 27.5	12.7 ± 0.5	14.3 ± 5.7	5.9 ± 1.6
Breast	58.3 ± 10.6	17.4 ± 3.7	4.6 ± 0.4	37.6 ± 13.4	11.5 ± 1.8	2.7 ± 0.1	0.3 ± 0.03
Thigh	217.6 ± 9.9	79.9 ± 6.3	30.4 ± 9.1	85.7 ± 2.2	25.2 ± 5.6	4.7 ± 0.2	1.1 ± 0.1
Kidney	346.1 ± 21.9	89.4 ± 4.9	2.2 ± 0.4	204.3 ± 23.2	111.9 ± 14.4	22.1 ± 4.8	1.9 ± 0.2
Liver	1112.7 ± 83.1	131.5 ± 10.1	47.9 ± 7.2	250.5 ± 15.7	182.3 ± 4.2	19.0 ± 5.7	7.7 ± 0.3
Gizzard	94.0 ± 31.6	10.8 ± 0.9	1.3 ± 0.2	89.4 ± 2.9	24.1 ± 4.9	4.3 ± 0.4	1.8 ± 0.1
Fat/skin	532.9 ± 29.7	93.1 ± 32.2	54.3 ± 2.4	160.9 ± 3.5	72.1 ± 4.0	17.4 ± 1.0	2.4 ± 0.1

http://www.researchgate.net/publication/221865584_Determination_of_lasalocid_residues_in_the_tissues_of_broiler_chickens_by_liquid_chromatography-tandem_mass_spectrometry

4. Maximum Residue Limits (MRLs) of Lasalocid in poultry vary by country

Tissue	**CVMP*** 5-day withdrawal	**Japan** 7-day withdrawal	**USA** 0-day withdrawal	**Australia** 0-day withdrawal
Muscle	20 ug/kg	10 ug/kg	Not established	50 ug/kg
Liver	100 ug/kg	10 ug/kg	400 ug/kg	700 ug/kg
Kidney	50 ug/kg	10 ug/kg	Not established	700 ug/kg
Skin/Fat	100 ug/kg	10 ug/kg	1200 ug/kg	1200 ug/kg
Eggs	150 ug/kg	10 ug/kg	-	50 ug/kg

CVMP – Committee for Medicinal Products for Veterinary Use, European Medicines Agency
ftp://ftp.fao.org/codex/meetings/ccrvdf/ccrvdf20/rv20_11_add1e.pdf

6. Ionophores such as monensin and lasalocid are widely used

"... more animals have been medicated with ionophores, such as monensin [and lasalocid], for control of disease than any other medicinal agents in the history of veterinary medicine."
http://ps.oxfordjournals.org/content/89/9/1788.long

7. Lasalocid has a low therapeutic index

Therapuetic Index (TI) compares the amount of a drug needed for a therapeutic effect to the amount that causes toxicity. A low therapeutic index means that the difference between the amount of drug needed to have an effect and the amount of drug that is toxic, is very small.

TABLE 1. Antimalarial activities and toxicities of various ionophore compounds[a]

Compound	In vitro antimalarial activity (*P. falciparum* IC_{50} [ng/ml])	In vitro differential activity (mean)	LD_{50} (mg/kg) in mice		ED_{50} (mg/kg)		TI
			Acute	Subacute	*P. chabaudi*	*P. vinckei petteri*	
Carboxylic ionophores							
Class 1a							
Alborixin	0.6	57	<1 (i.p.)	ND[b]	ND	ND	
Lonomycin A	1.4	202	10 (i.p.)	2.5 (i.p.)	0.44 (i.p.)		5.7 (i.p.)
Nigericin	1	141	14.2 (i.p.)	ND	2.3 (i.p.)		6 (i.p.)[c]
						1.1 (i.p.)	4.5 (i.p.)
Narasin	1	402	4 (i.p.)	1.75 (i.p.)	0.42 (i.p.)	ND	4.2 (i.p.)
Monensin A	1.5	80	8.5 (i.p.)	>6 (i.p.)	4.1 (i.p.)	ND	2.1 (i.p.)[c]
			51 (p.o.)[d]	>30 (p.o.)	10.1 (p.o.)	ND	5 (p.o.)[c]
Monensin A methyl ether	6.5	73	30 (i.p.)	>17.5 (i.p.)	ND	2.5 (i.p.)	12 (i.p.)[c]
Class 2							
Lasalocid A	28	43	30 (i.p.)	13.3 (i.p.)	4 (i.p.)	ND	3.3 (i.p.)
5-Bromo lasalocid A	69	55	80 (i.p.)	30 (i.p.)	1.4 (i.p.)		22 (i.p.)
						2 (i.p.)	14 (i.p.)
			613 (p.o.)	230 (p.o.)	ND	11 (p.o.)	21 (p.o.)
Quasi-ionophore, gramicidin D	0.035	1,328	482 (i.p.)	>140 (i.p.)	ND	1.4 (i.p.)	344 (i.p.)[c]
			>1,000 (p.o.)		ND	>100 (p.o.)	

[a] Ionophores are classified by Pressman (23) as true ionophores (mobile carriers) and channel-forming quasi-ionophores. Carboxylic ionophores are subdivided into class 1a for ionophores specific to monovalent cations and class 2 for ionophores able to complex mono- and divalent cations (31). The in vitro IC_{50} against the intraerythrocytic stage of *P. falciparum* and differential activity between mammalian cells (U937 macrophages and Jurkat lymphoblasts) and *P. falciparum* were determined previously (12). Acute and subacute LD_{50}s were determined for mice (i.p., intraperitoneal administration; p.o., oral administration). ED_{50}s were determined by a 4-day suppressive test with *P. chabaudi*- or *P. vinckei-petteri* infected mice. The TI is the LD_{50}/ED_{50} ratio and is based on subacute toxicity.
[b] ND, not determined.
[c] TI is based on the acute LD_{50} and represents an upper limit of the TI. Drugs were dissolved in 10% (wt/vol) arabic gum in water unless indicated otherwise.
[d] Vehicle corresponds to 0.5% Tween 80.

http://aac.asm.org/content/41/3/523.long

There are incentives for farmers to use lasalocid because it is an antibiotic that is not approved for human use; this is because of recent efforts to ban the kinds that are approved for human use, from use in farm animals. This means that we are very likely to see an increase in the use of antibiotics like lasalocid in farm animals. Indeed, many producers who say they are "antibiotic free" mean only that they are free of the kinds of antibiotics that are also used for humans. They still use ionophores like lasalocid.

- Sensitivity to lasalocid varies greatly between animal types. Dogs and horses, for example, are much more sensitive than other animals. Human sensitivity is unknown.

- In cows, lasalocid is toxic at a lower dose for young animals than it is for older animals. If this is also true for humans, then children would be more sensitive than adults.

- Lasalocid is known to be present in the tissues of animals that consume the drug at certain levels, which drop when the animals are fed clean feed. Because of this, poultry in the EU is required to go through a 7-day withdrawal before sending the birds to market. The US has no withdrawal requirements.

- In general, the amount of lasalocid permitted in different animal tissues is much higher in the US than it is in the EU.

- In general, it doesn't really matter how much lasalocid is permitted in different animal tissues, because neither the Federal Govt nor the State Govt test for lasalocid.

- The permitted amount of lasalocid per tissue is determined by estimating the total amount that a person can tolerate per pound of body weight, estimating the amount of different food products that a person is likely to eat in a given day, and making sure that even in a worse case scenario the total amount of lasalocid consumed will be below the estimated limit. However, to my knowledge these estimates assume that the drug residues will only be found in the food types where it is permitted - poultry meat and beef. So if we also have widespread residues in eggs, pork, and milk, for example, the estimates of how much we are exposed to may be much higher than the models estimate.

- When animals eat lasalocid they grow fatter on less feed. If we have lasalocid and similar drugs in our diets, it seems reasonable to suspect that it is having the same effect on us.

- When young cows are fed lasalocid, it reduces the age at which they can bear their first calves. Again, consider the implications if the drug has the same effect on humans.