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Rationale supporting zero-day preslaughter withdrawal of swine orally administered lincomycin.

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Introduction

As assay methodologies become more and more sensitive - capable of detecting a few parts per million or even a few parts per billion - it becomes more and more important that science determine the practical significance of minute residues of drugs in the human food supply. Since the concern over residues stems from a concern for human safety, it follows that the significance of a residue is its potential for causing human health problems. For most substances it can be shown that no-adverse-effect levels exist, that is, even though a substance is biologically active at "high" levels, it causes no adverse effect at "low" levels. This idea was expressed succinctly by Paracelsus almost 400 years ago : "The dose makes the poison".

Almost all substances that humans are routinely and more or less constantly exposed to, including food and water, are toxic at some "high" level, but are non-toxic or even necessary for survival at "low" levels. Obviously the determination that science must make about residues in the human food supply is not their presence or absence, but their significance, that is, whether the levels are above or below the no-adverse-effect level. For obvious reasons, humans are not usually in this testing. Science relies on a data accumulated from other species, typically mice, rats, dogs, guinea pigs, monkeys, etc. Conclusions are conservatively extrapolated to humans; safety factors of 100 or 1000 are commonly incorporated to assure that no-adverse-effect levels in non-human species do not over-estimate no-adverse-effect levels in humans. Science can thereby make a reasonable (though properly conservative) determination on the significance of residues of substances that enter the human food supply.

The attached information compares the residues from oral administration of lincomycin in swine with the no adverse effect levels established from tests in rats and dogs. The data support the conclusion that the residues in swine treated orally with lincomycin, even with no withdrawal period, are not a human health concern.

Metabolism data

Using radio-labeled drug (which allows for detection of minute amounts of the parent compound and its metabolites) "total C-14" tissue residues in parts per million (ppm) in swine tissues have been shown to be :

	Withdrawal time		
	4h	48h	96h
Liver	14.0	3.7	1.0
Kidney	10.1	2.5	1.15
Muscle	0.7	0.15	0.35
Fat	0.05	0.04	0.02

Reference for metabolism data : technical report 768-9760-81-001.

Toxicity data

Toxicity data support a no effect level (NEL) in rats of at least 100 mg/kg body weight. A brief summary of these data is provided below :

Synopsis of recent lab animal feeding studies

Study	Doses	No. animals per group	Comments
Rat teratology study	0, 10, 30, 100 mg/kg	24	NEL of 100 mg/kg
Three generation reproductive study in rats	0, 0.375, 0.75, 1.5 mg/kg premix grade and 1.5, 100 mg/kg USP grade	60M 60F	No effects seen at any doses tested
One year dog study	0, 0.375, 0.75, 1.5 mg/kg premix grade and 1.5 mg/kg USP grade	5M 5F	No effects seen at any doses tested
26 month oral rat study	0, 0.375, 0.75, 1.5 mg/kg premix grade and 1.5, 100 mg/kg USP grade	60M 60F	No toxic effects seen at any dose tested

Synopsis of early lab animal feeding studies

Species/route	Dosage mg/kg/day	Results and comments
Rat/oral	600, 1000 for 3 months	Non-toxic. Increased weight of intestinal tract in treated rats.
Dog/oral	400, 800 for 3 months	Increased SGPT in 4 of 4 at 800 mg/kg and 1 of 4 at 400 mg/kg after 1 month. Decreased back to normal within 3 weeks indicating adoptive tolerance.
Dog/oral	30, 100, 300 (1/3 dose, 3x/day) for 6 months	All dogs clinically normal; no-drug related changes.

Species/route	Dosage mg/kg/day	Results and comments
Rat/oral	30, 100, 300 for 1 year	No toxic effect; no clinical signs.

Synopsis of genotoxicity studies

Study	Conclusion
Lincomycin evaluation via Salmonella/Microsome test (AMES) assay	No evidence of bacterial mutagenicity
Lincomycin evaluation via DNA Damage/Alkaline elution assay	No indication of any DNA damaging or genotoxic potential for lincomycin
Lincomycin evaluation via micronucleus test	Lincomycin did not act as a clastogen or chromosomal mutagen
Lincomycin evaluation via V-79 mammalian cell mutation assay -- with and without S9 activation system	Lincomycin was not mutagenic with or without activation
Lincomycin evaluation via primary rat hepatocyte unscheduled DNA synthesis assay	Lincomycin was inactive in the primary rat hepatocyte UDS assay

Collectively these data provide no evidence of toxic effects of lincomycin when tested at concentrations of up to 100 mg/kg body weight.

Residue data

Five residue studies have been conducted using non-radio labeled lincomycin. The microbiological assay used in these studies detects the bioactive portion of the residues. The bioactive residue is less than the total C-14 residue except where pigs were dosed at about 20 times the highest recommended dose. Results are presented below :

Reference	Tissue	Drug concentration	Withdrawal period (days)	No./group	Highest conc. of lincomycin seen
524-9660-038	Muscle	110 g/t	0	3	< 0.1 ppm
"	"	"	1	3	< 0.1 ppm
"	"	"	2	3	< 0.1 ppm

Reference	Tissue	Drug concentration	Withdrawal period (days)	No./group	Highest conc. of lincomycin seen
524-9660-038	Liver	110 g/t	0	3	0.17 ppm
"	"	"	1	3	< 0.1 ppm
"	"	"	2	3	< 0.1 ppm
"	Kidney	"	0	3	0.56 ppm
"	"	"	1	3	< 0.1 ppm
"	"	"	2	3	< 0.1 ppm
524-9660-004	Muscle	2930 g/t	0	6	1.75 ppm
"	"	"	3	4	< 0.1 ppm
"	"	"	6	4	< 0.1 ppm
"	"	"	9	4	< 0.1 ppm
"	Liver	"	0	6	7.00 ppm
"	"	"	3	4	< 0.1 ppm
"	"	"	6	4	< 0.1 ppm
"	"	"	9	4	< 0.1 ppm
"	Kidney	"	0		24 ppm
"	"	"	3	4	0.12 ppm
"	"	"	6	4	< 0.1 ppm
"	"	"	9	4	< 0.1 ppm
524-9760-008	Liver	4400 g/t	0	4	5.5 ppm
"	"	"	3	4	0.3 ppm
"	"	"	6	4	0.15 ppm
"	"	"	9	4	0.13 ppm
"	Liver	5500 g/t	0	4	11.7 ppm
"	"	"	3	4	0.43 ppm
"	"	"	6	4	0.32 ppm
"	"	"	9	4	0.36 ppm
"	Kidney	4400 g/t	0	4	16.5 ppm
"	"	"	3	4	0.38 ppm
"	"	"	6	4	0.26 ppm
"	"	"	9	4	0.20 ppm

Reference	Tissue	Drug concentration	Withdrawal period (days)	No./group	Highest conc. of lincomycin seen
524-9760-008	Kidney	5500 g/t	0	4	28.4 ppm
"	"	"	3	4	1.41 ppm
"	"	"	6	4	0.99 ppm
"	"	"	9	4	1.11 ppm
524-9660-005	Muscle	1100 g/t	0	4	0.88 ppm
"	"	"	4	4	< 0.1 ppm
"	"	"	5	4	< 0.1 ppm
"	"	"	6	4	< 0.1 ppm
"	Liver	"	0	4	3.1 ppm
"	"	"	4	4	< 0.1 ppm
"	"	"	5	4	< 0.1 ppm
"	"	"	6	4	< 0.1 ppm
"	Kidney	"	0	4	6.0 ppm
"	"	"	4	4	< 0.1 ppm
"	"	"	5	4	< 0.1 ppm
"	"	"	6	4	< 0.1 ppm
524-9660-006	Muscle	110 g/t	0	4	< 0.1 ppm
"	"	"	3	4	< 0.1 ppm
"	"	"	4	4	< 0.1 ppm
"	"	"	5	4	< 0.1 ppm
"	Liver	"	0	4	0.19 ppm
"	"	"	3	4	< 0.1 ppm
"	"	"	4	4	< 0.1 ppm
"	"	"	5	4	< 0.1 ppm
"	Kidney	"	0	4	0.57 ppm
"	"	"	3	4	< 0.1 ppm
"	"	"	4	4	< 0.1 ppm
"	"	"	5	4	< 0.1 ppm

Conclusion

Comparison of observed residues with toxicity data demonstrates that residues, even at zero (4-hour) withdrawal, are thousands of times smaller than levels that have been shown to be no-adverse-effect levels. Zero-day withdrawal does not cause a human health concern.

References

Upjohn intern report 524-9660-004
Tissue residue in pigs fed a supplement containing 2860 mg of lincomycin per kilogram
A.R. Barbiers, M.J. DeGeeter, L.J. Smith, C.C. Ruppel

Upjohn intern report 524-9660-005
Tissue residue in swine fed supplement-type diets containing 1100 mg of lincomycin per kilogram
M.J. DeGeeter, A.R. Barbiers, L.J. Smith, C.C. Ruppel

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Tissue residue in swine fed diets containing 110 mg of lincomycin per kilogram
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Upjohn intern report 524-9760-008
Lincomycin residue study in pigs fed supplements containing 4000 or 5000 grams per ton lincomycin
A.R. Barbiers et. al.

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Upjohn intern report 524-9660-038
Lincomycin residue in tissue of swine after withdrawal of lincomycin from diets for one or two days.
for one or two days
M.J. DeGeeter, A.R. Barbiers