Drug Residues

in Food

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drug residues

- politics not pharmacology
  - risk to consumers is practically zero
  - some people are allergic to penicillin
  - antibiotics make milk useless for cheese
  - residues are used as a non tariff trade barrier

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sources of residues

- drugs
- pesticides
- environmental contamination
- plant / fungal toxins

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positives 2004/5

- antibiotics – 1
- organochlorine – 1
- anthelmintincs – 3
- detectable but below MRL – 47

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positives 2002

- zeranol – 37 below MRL
- zearalenone – 163 below MRL
- aminoglycosides 1 below MRL
- carbadox – 1 above & 11 below MRL
- sulphonamides – 2 above MRL
- benzimidazoles – 1 above & 16 below MRL
- avermectins – 16 below MRL
- organochlorines – 391 below MRL
- heavy metals – 8 above & 116 below MRL
- brodifacoum – 14 above MRL

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chickens 2002 (300 birds)

- nicarbazin – 8 below MRL
- ionophores – 3 above & 9 below MRL
- heavy metals – 1 below MRL

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reducing residues

- drug / chemical registration
  - conditions applied to drug use
- witholding periods
  - vets
  - farmer education
- milk / meat testing at abattoir
  - large penalties for positive results

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withholding period

- = withdrawal time
- period which must elapse between last treatment and use as food to enable the drug to be eliminated

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acronyms

- NOEL – no observable effect level
- ADI – acceptable daily intake
- MRL – maxiumum residue limit
  - = tolerance level
  - = maximum permitted tolerance
  - = maximum permissible level (of residue)

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withholding times calculation

- 2x lab animal NOEL
- human ADI calculated using fudge factor (100 – 500)
- MRL calculated from ADI
- witholding period calculated from pharmacokinetics (+ fudge factor)

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NOELs

- toxic NOEL
- pharmacological NOEL
- microbiological NOEL
- tested on rodents + another species

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ADI

$$\frac{\text{NOEL (mg/kg/day) most sensitive animal}}{\text{fudge factor (100 - 1000)}} = \text{ADI}$$

assuming the average human weighs 60kg

total ADI = ADI x 60

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If the drug is used in people, a human NOEL may be available

This is only used to set the fudge factor

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MRLs

- calculated from ADI
- assuming intake of 500g meat +1.5L milk / day / 60kg for life

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MRLs

- some drugs do not have MRLs
  - idiosyncratic reactions
  - not enough information
  - considered safe in normal use
  - (carcinogens)
- default MRL 100μg/kg

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MRL info

- NZ – New Zealand (Maximum Residue Limits of Agricultural Compounds) Food Standard 2007
  - `http://www.nzfsa.govt.nz/policy-law/legislation/food-standards/nz-mrl-fs-2007-consolidation.pdf`
- EU – EMEA
  - `http://www.eudra.org/emea.html`
- WHO – Technical Report Series
- USA – FDA FOI summaries
  - `http://www.fda.gov/cvm/efoi/foidocs.html`
- Beware – MRLs are different in different countries!

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withholding times

- the time taken for tissue drug levels to fall below the MRL in nearly all animals
- different for different formulations of the same drug

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withholding time info

- NZ – IVS, (NZFSA website)
  - http://www.nzfsa.govt.nz/acvm/registers-lists/acvm-register/index.htm
- UK – NOAH
  - http://www.noahcompendium.co.uk/Compendium/Overview/
- UK, NZ, Australia
  - "The Veterinary Formulary"
- USA – FARAD
  - http://ace.orst.edu/info/farad/

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standard WHTs (days)

NZ

animal	meat	milk	eggs
ruminants	91	35	
pigs and horses	63		
birds	63		10
camelids	63		
rabbits and hares	63		

UK

animal	meat	milk	eggs
mammals	28	7	
birds	28		7
fish	500°days		

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calculating WHTs

- use pharmacokinetic data
- if you double the dose
  - add one half life

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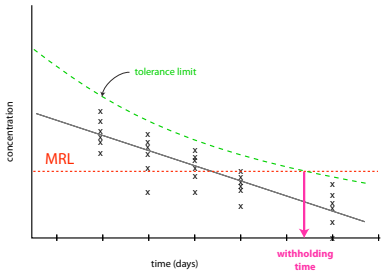

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role of the vet

- make sure farmers know the importance of withholding periods
- follow the instructions on the label
- any deviation from label dose – increase the withholding periods
  - illegal for some drugs
- inject at the recommended site – cranial neck
- make sure treated animals are identified
- leave a written record of all treatments and withholding periods

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residue testing

- milk – dairy companies
- meat – NZFSA (farm and slaughterhouse)
- both – importing countries at point of entry
- both – NZFSA (at shops)

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residue testing

- results published by NZFSA in "Surveillance"
- published results necessary for EU and US exports
- results sent to all importers

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residue testing

- random monitoring
  - gives an overall view of what is going on
- surveillance sampling
  - of farmers who may cause a problem
- surveys to identify potential problems
  - used to assess if testing is necessary

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penalties

- condemnations
- suspect listing
  - increased costs
- blacklisting by processors
- prosecution

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penalties

- apply to the farmer
- farmer then sues vet!
- $15,000 fine for failing to give farmer info

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residue detection overseas

- consignment rejected
- NZ exports credibility reduced
- increased costs
- market access restricted
- consumer reaction

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NZ legislation

- ACVM Act (1997)
- Food Act (1981)
  - NZ (MRLs of Ag Compounds) Food Standard 2007
  - Food Regs (1984/262)
- Meat Act (1981)
  - Meat Regs (1996/199)
- Animal Products Act (1999)
- ANZFSA ?

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overseas

- WHO Codex alimentarius
- Europe EMEA
- US FDA
- NZ must meet international standards

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“banned” drugs in NZ

- chloramphenicol
- β agonists
- stilbenes
- thyreostatics

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sort of banned in NZ

- chloramphenicol
- colchicine
- chloroform
- nitrofurans
- nitroimidazoles
- chlorpromazine
- dapsone
- phenylbutazone
- dipyrone
- arsenilic acid
- nadrolone

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banned drugs in EU

- chloramphenicol
- chlorpromazine
- dapsone
- dimetridazole
- furazolidone
- nitrofurans
- ronidazole

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banned drugs in USA

- chloramphenicol
- clenbuterol
- stilboestrol
- nitroimidazoles
- nitrofurans
- fluoroquinolones *
- glycopeptides
- sulphonamides *

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bobby calves

- where do residues come from?

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bobby calves

- residues come from
  - cow *in utero*
  - cow's milk
  - calf treatment
  - cross contamination of milk

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bobby calves

- cow (usually dry cow mastitis tubes)
  - meat withholding period (~28d)
  - treatment to calving time (~28 – 49d)
  - milk withholding period (~8 milkings)
- calf
  - milk suitable for bobby calves for (7d)

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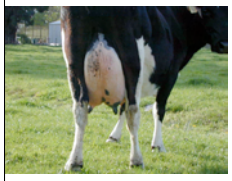
cow with mastitis



- farmer has given intramammary penicillin this morning
- cow now worse
- you decide to give im penicillin
- withholding time?

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withholding times

- label procaine penicillin injection – 48hours
- label procaine penicillin intramammary - 108hours
- combined WHT?

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withholding times

- label procaine penicillin injection – 48 hours
- label procaine penicillin intramammary - 108 hours
- combined WHT?
- benzylpenicillin $t_{1/2}$ < 1 hour
- milk : plasma 0.2

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residues

- NZ's export trade relies on residue free products
- follow the instructions on the label or be prepared to justify yourself in court
- always make sure that the farmer knows the withholding time
- know your pharmacokinetics!

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