WITHHOLDING TIMES

do it yourself
WHY?

- one off discretionary use
- routine off label use of registered drug
- routine (off label) use of unregistered drug
ACRONYMS

➤ MRL
  ➤ maximum residue level
  ➤ = MPL, ESI, threshold, tolerance

➤ ADI
  ➤ acceptable daily intake

➤ WHT / WHP
  ➤ withholding time / period
MRLS

different for every country

NZ - Maximum Residue Levels for Agricultural Compounds

http://www.foodsafety.govt.nz/elibrary/industry/register-list-mrl-agricultural-compounds.htm

Aus - Agricultural and Veterinary Chemicals Code Instrument No. 4 (MRL Standard) 2012


Codex Alimentarius


EMA

### Schedule 1: Maximum Residue Levels for Agricultural Compounds

<table>
<thead>
<tr>
<th>Compound Common Name</th>
<th>CAS#</th>
<th>Residue to which the maximum residue level applies</th>
<th>Food</th>
<th>Maximum Residue Level (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abamectin</td>
<td>71751-42-2</td>
<td>Sum of: avermectin B1a avermectin B1b (Z)-8,9 avermectin B1a (Z)-8,9 avermectin B1b</td>
<td>Avocados&lt;br&gt;Cattle fat&lt;br&gt;Cattle liver&lt;br&gt;Cattle meat&lt;br&gt;Kiwifruit&lt;br&gt;Pome fruits&lt;br&gt;Sheep fat&lt;br&gt;Sheep kidney&lt;br&gt;Sheep liver&lt;br&gt;Sheep meat&lt;br&gt;Strawberries&lt;br&gt;Tomatoes</td>
<td>0.02(<em>)&lt;br&gt;0.02&lt;br&gt;0.015&lt;br&gt;0.01&lt;br&gt;0.02(</em>)&lt;br&gt;0.02(<em>)&lt;br&gt;0.05&lt;br&gt;0.02&lt;br&gt;0.025&lt;br&gt;0.02&lt;br&gt;0.02(</em>)&lt;br&gt;0.1</td>
</tr>
<tr>
<td>Acephate</td>
<td>30560-19-1</td>
<td>Acephate</td>
<td>Brassica vegetables&lt;br&gt;Citrus fruits&lt;br&gt;Fruiting vegetables&lt;br&gt;Leafy vegetables&lt;br&gt;Potatoes&lt;br&gt;Tamarillos</td>
<td>2&lt;br&gt;5&lt;br&gt;1&lt;br&gt;6&lt;br&gt;0.5&lt;br&gt;0.5</td>
</tr>
<tr>
<td>Acibenzolar-s-methyl</td>
<td>135158-54-2</td>
<td>Sum of Acibenzolar-s-methyl and Acibenzolar acid (CGA210007) Expressed as: Acibenzolar-s-methyl</td>
<td>Kiwifruit</td>
<td>0.02(*)</td>
</tr>
<tr>
<td>Albendazole</td>
<td>54965-21-8</td>
<td>Sum of: Albendazole&lt;br&gt;Albendazole sulphoxide&lt;br&gt;Albendazole sulphone&lt;br&gt;Albendazole sulphone amine Expressed as: Albendazole sulphone amine</td>
<td>Edible offal of sheep&lt;br&gt;Sheep meat</td>
<td>3&lt;br&gt;0.2</td>
</tr>
</tbody>
</table>

**NOTE:** (*) indicates that the maximum residue level has been set at or about the limit of analytical quantification
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>FOOD</th>
<th>MRL (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD 0560</td>
<td>Adzuki bean (dry)</td>
<td>T*0.002</td>
</tr>
<tr>
<td>TN 0660</td>
<td>Almonds</td>
<td>*0.01</td>
</tr>
<tr>
<td>FP 0226</td>
<td>Apple</td>
<td>0.01</td>
</tr>
<tr>
<td>FI 0326</td>
<td>Avocado</td>
<td>T0.06</td>
</tr>
<tr>
<td>FI 0326</td>
<td>Beetroot leaves</td>
<td>0.5</td>
</tr>
<tr>
<td>FB 0264</td>
<td>Blackberries</td>
<td>T0.1</td>
</tr>
<tr>
<td>FB 0020</td>
<td>Blueberries</td>
<td>T*0.02</td>
</tr>
<tr>
<td>VA 0035</td>
<td>Bulb vegetables</td>
<td>T0.05</td>
</tr>
<tr>
<td>VB 0041</td>
<td>Cauliflowers, Head</td>
<td>T0.05</td>
</tr>
<tr>
<td>MO 0812</td>
<td>Cattle, Edible offal of</td>
<td>0.1</td>
</tr>
<tr>
<td>MF 0812</td>
<td>Cattle fat</td>
<td>0.1</td>
</tr>
<tr>
<td>MM 0812</td>
<td>Cattle meat</td>
<td>0.005</td>
</tr>
<tr>
<td>ML 0812</td>
<td>Cattle milk</td>
<td>0.02</td>
</tr>
<tr>
<td>VS 0624</td>
<td>Celery</td>
<td>T0.35</td>
</tr>
<tr>
<td>FC 0001</td>
<td>Citrus fruits</td>
<td>0.01</td>
</tr>
<tr>
<td>SO 0697</td>
<td>Peanut</td>
<td>T*0.002</td>
</tr>
<tr>
<td></td>
<td>Peppers, Chili, other cultivars</td>
<td>T0.1</td>
</tr>
<tr>
<td>MO 1284</td>
<td>Pig kidney</td>
<td>0.01</td>
</tr>
<tr>
<td>MO 1285</td>
<td>Pig liver</td>
<td>0.02</td>
</tr>
<tr>
<td>MM 0818</td>
<td>Pig meat [in the fat]</td>
<td>0.02</td>
</tr>
<tr>
<td>FI 0353</td>
<td>Pineapple</td>
<td>T*0.002</td>
</tr>
</tbody>
</table>
WITHHOLDING TIME

time from last treatment to slaughter to allow [drug] to fall below the MRL

- all pigs?
- most pigs?
- individual variation?

- every country different
- different for different formulations of the same drug
GENERAL APPROACHES

- read the WHT on the bottle
- apply a default WHT (NZ, UK)
  - a long time! NZ - pig meat - 63 days
  - UK - meat >28 days
- apply a standardised WHT (NZ)
  - only some drugs - oral oxytetracycline in pigs - 10 days
- use overseas WHT
- if you have data
  - simple approach
  - statistical approach
OVERSEAS WITHHOLDING TIMES

**FARAD**

[www.farad.org](http://www.farad.org)

**EMA**


**NOAH**

[www.noahcompendium.co.uk/pages/-312863/home/withdrawal-periods-312944](http://www.noahcompendium.co.uk/pages/-312863/home/withdrawal-periods-312944)
Welcome to FARAD

FARAD is a congressionally-mandated risk-management program that is supported by the USDA. The primary mission of FARAD is to provide science-based expert advice to help mitigate unsafe chemical residues (drugs, pesticides, biotoxins, etc.) in products derived from food animals. The program is maintained by a consortium of universities, including University of California-Davis, University of Florida, Kansas State University and North Carolina State University.

Until proven safe, the FDA's Center for Veterinary Medicine is taking legal action to remove this product from the marketplace.
FINDING DATA

- literature search
- not always useful
- Pubmed
- CAB Abstracts
  - [https://www.cabdirect.org](https://www.cabdirect.org)
Detection of rifilnur and oxytetracycline in oral fluids of swine with a per-surface competitive ELISA test after intramuscular injection.
Maisberg A, Karriker L, Zimmerman J, Irwin C, Coetzee J.
PMID: 21900003
Similar articles

Penetration of oxytetracycline into the nasal secretion and relationship between nasal secretion and plasma oxytetracycline concentrations after oral and intramuscular administration in healthy pigs.
Bimazule M, Cambier C, Baert K, Vanbelie S, Chap P, Gustin P.
PMID: 21365609
Similar articles

Determination of oxytetracycline in biological matrix.
Kowalski C, Pomorska M, Lebkowska B, Sławik T.
PMID: 17357697
Similar articles

Verification of compliance with organic meat production standards by detection of permitted and nonpermitted uses of veterinary medicines (tetracycline antibiotics).
Kelly M, Tarbin JA, Ashwin H, Sharman M.
PMID: 16478283
Fig. 1. Mean plasma oxytetracycline concentrations in pigs after intramuscular administration of two formulations of oxytetracycline at a dose of 30 mg/kg.

SIMPLE APPROACH TO WHT CALCULATION

- residues in all tissues in all animals have fallen below MRL

- add safety factor
  - 10 - 30%
  - $1 - 3 \times t_{1/2}$
TISSUE CONCENTRATIONS

log concentration

time
STATISTICAL APPROACHES

- linear regression of tissue concentration in terminal elimination phase
  - ACVM method (NZ)
  - FDA method (USA)
  - EMA method (UK & EU)

- population based pharmacokinetic modelling

- physiologically based pharmacokinetic modelling
  - not generally accepted yet
2 COMPARTMENT MODEL

drug in

central compartment

k₁₂

k₂₁

blood sample

drug out

peripheral compartment
log concentration

regression line

MRL

withholding time?
PROBLEMS?

- limit of quantification / detection
- number of points
- injection sites
- sick animals
  - intake of oral drugs
  - disposition
Analytical methodology

Oxytetracycline concentration was determined using a microbiological method. The test organism used was *Bacillus cereus* and the limit of quantification was 0.1 μg/mL. Each assay was performed in triplicate. The range of standards prepared with control plasma and used for calibration was 0.1–1 μg/mL.
PROBLEMS?

- limit of quantification / detection
- GLP
- number of points
- sick animals
  - intake of oral drugs
  - disposition
- injection sites
INJECTION SITES

➤ for slow release formulations, concentration likely to be higher than tissues

➤ NZ & FDA <10x MRL - ignore

➤ EMA must be <MRL

➤ Aus - ?
SICK ANIMALS

➤ pharmacokinetic studies always done in healthy animals

➤ young / old / dehydrated pigs different
PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING

- requires lots of data
  - blood flow etc
- requires fancy software
- way of the future???
FIGURE 7.3  Schematic diagram of a representative PBPK model designed for food residue avoidance. Tissue blocks represent common edible tissues. Arrows represent mass transfer via blood flow or elimination.

CONCLUSIONS

- avoid giving drugs
  - zero withholding time!
- decide on degree of certainty required
- check data available
  - usually not enough!
- choose appropriate method
- err on the side of caution!
  - longer rather than shorter