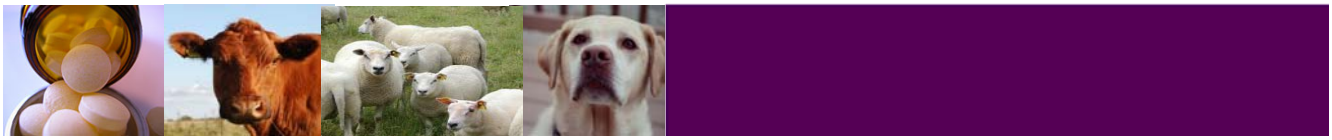
# Human Safety Assessment of Ractopamine Conducted by Health Canada

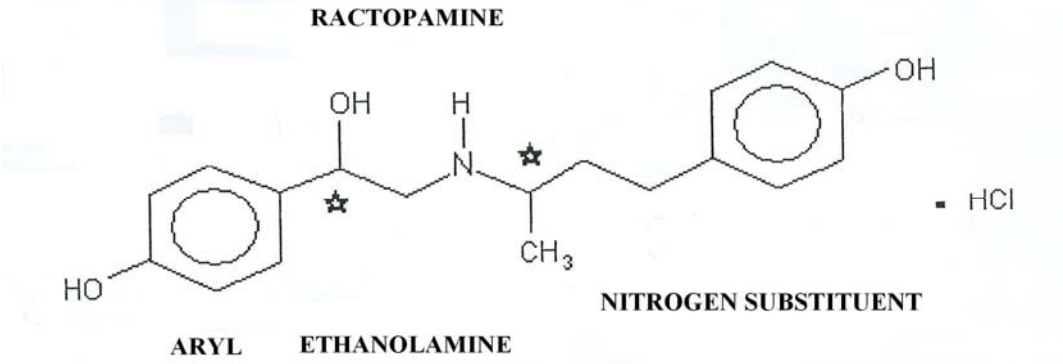
Human Safety Division
Veterinary Drugs Directorate
Health Canada
Ottawa, Canada


## Ractopamine

- A beta-adrenergic agonist
- Indications
  - For increased carcass leanness, increased dressing percent
  - For improved rate of weight gain and feed efficiency
- Two products approved in Canada
  - Paylean Premix - for use in swine and turkeys
  - Optaflexx Premix - for use in cattle



# Chemical Structure of Ractopamine Hydrochloride




# Paylean® for Pigs

Recommended for continuous feeding to finishing pigs at

5 – 10 mg/kg of feed to

- Increased carcass leanness and increased dressing percent
- For improved rate of weight gain and feed efficiency
- Zero-day (8-12 hrs.) withdrawal period

# Optaflexx® for Cattle

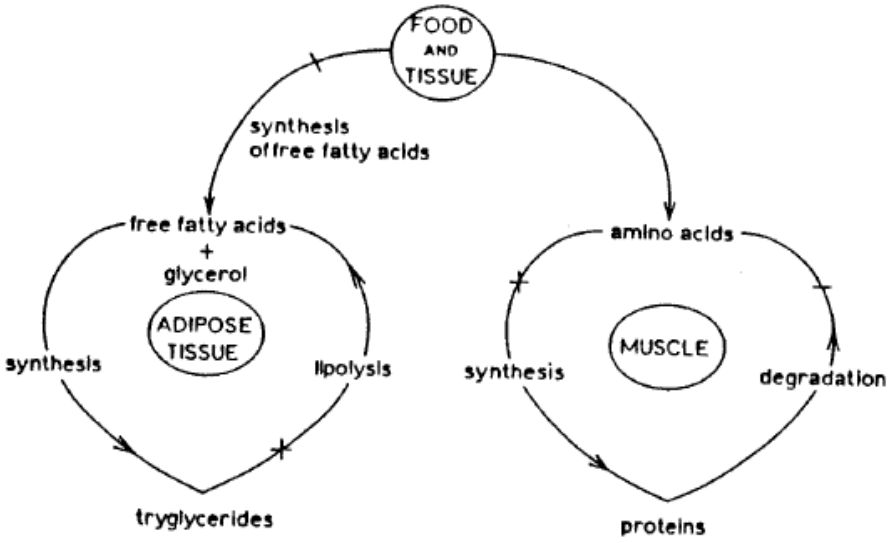
- Recommended for continuous feeding to finishing cattle at 10 – 30 mg/kg feed for approximately the last 28 – 42 days prior to slaughter
  - To increase the rate of weight gain,
  - Improve feed efficiency and
  - Increase carcass leanness
  - Zero-day (8-12 hrs) withdrawal period

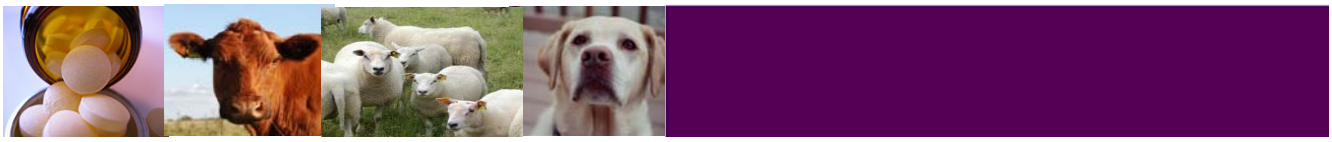
# Paylean® for Turkeys

Recommended for continuous feeding to heavy finishing tom and hen turkeys at the rate of 5 to 9 mg/kg of feed (90% dry matter basis) ractopamine HCl to

- Increased rate of weight gain and improved feed efficiency in heavy finishing tom turkeys when fed for the last 14 days prior to slaughter
- Increased rate of weight gain and improved feed efficiency in heavy finishing hen turkeys when fed for the last 7 to 14 days prior to slaughter.
- Zero-day ( 6 hrs) withdrawal period

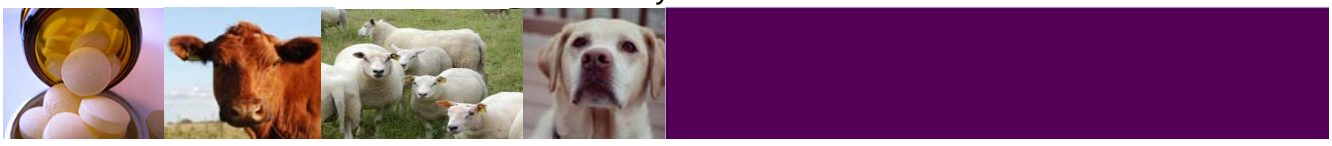
# Mode of Action of Beta Agonists as Partitioning Agents



# Toxicity Data Submitted by the Manufacturer

a. 90-day study in rats and dogs
b. 90-day study in Rhesus monkey
c. 1-year study in Beagle dog
d. 2- year carcinogenicity study in rats
e. carcinogenicity study mice
f. 2-generation reproduction study with teratology
g. Special cardiovascular studies
h. Genotoxicity studies
   - *In vitro* Bacterial Gene Mutation Assay
     *S. typhimurium* and *E. Coli*, reverse mutation assay.
   - *In vitro* Mammalian Gene Mutation
     Chromosomal Aberration, Sister Chromatid Exchange, and Micronucleus Assay
     *In vivo Mammalian Bone Marrow Cytogenetic Test*
     *Unscheduled DNA Synthesis*



# Toxicology Studies (cont.)

## Special cardiovascular studies

- Hemodynamic effects of IV administration in anesthetised dogs
- Hemodynamic effects of IV administration in anesthetised monkeys
- Hemodynamic effects of IV administration in conscious and anesthetised monkeys
- Acute cardiovascular toxicity study administered orally in the conscious instrumented beagle
- Effect of sub-chronic administration on heart rate and electrocardiographic waveforms in conscious Rhesus Monkeys
- Cardiovascular activity and safety in humans: determination of a no effect dose

# IV Infusion Study in Dogs

- 2 male/2 female dogs were infused with Ractopamine at a rate of 35µg/kg.bw for 10 minutes.
- Heart rate increased approximately 65% during the 10 minutes infusion and remained elevated at least up to 50 % throughout the 30 minutes of monitoring period.
- Systemic effects included tachycardia and peripheral vasodilatation and a drop in mean arterial pressure.

# Toxicology Studies: NOELs

| Study type | Species | Doses (mg/kg/d) | NOEL (mg/kg/d) |
|---|---|---|---|
| 90-d oral | Mouse | 25, 175, 1250 | 25 |
| 90-d oral | Rat | 1.3, 14, 155 | 1.3 |
| 2 gen reprod | Rat | 0.15, 1.4, 15, 160 | 15 |
| Acute oral | Dog | 0.002, 0.05, 0.125 | 0.002 |
| Cardiovascular | | | |
| 14-d oral | Dog | 0.05, 0.15, 1.5 | 0.05 |
| 1-yr oral | Dog | 0.112, 0.224, 5.68 | NE |
| 90-d gavage | Monkey | 0.125 | 0.125 |
| 6-wk gavage | Monkey | 0.25, 0.5, 4.0 | 0.25 |
| 1-yr oral | Monkey | 0.125, 0.5, 4.0 | 0.125 |
| 2-yr oral | Mouse | 35, 175, 1085 | 320 |
| IV Infusion | Human | $2 \times 10^{-5}$-$1.2 \times 10^{-4}$ | 0.014 |

# Study Used by Canada for the Establishment of a tADI

- The hemodynamic effects of butopamine, the active RR Isomer of Ractopamine, were studied in 8 patients with moderate to severe heart failure following an IV infusion.
- Successive infusions of 0.02, 0.04, 0.06, 0.08, 0.10 and 0.12 µg/kg/minute were given for an hour.
- The parameters tested were heart rate, systemic and pulmonary blood pressure, cardiac output and stroke volume.

## Study Used by Canada for the Establishment of a tADI (Cont.)

NOEL = (1002 µg/day) / 70 kg (mean weight of volunteers)

= 14 µg/kg bw/day

ADI = (14 µg/kg bw/day)/safety factor of 10

= 1.4 µg/kg bw/day

## Study Used by US CVM for the Establishment of a tADI

Based on 1 year oral study in rhesus monkey

NOEL = 0.125 mg/kg bw/day

ADI = (0.125 mg/kg bw/day)/safety factor of 100

= 1.25 µg/kg bw/day

## Study Used by JECFA for the Establishment of a tADI

- Six healthy male volunteers (mean bw = 75.5 kg) were orally given dosages of 0, 5, 10, 15, 25 and 40 mg of Ractopamine with a washout period of 48 hours between doses.
- At doses of 15, 25 and 40 mg sensations of increased heart rate were reported for 2, 3 and 4 volunteer and sensations of heart pounding in 1, 3 and 1 volunteer respectively.
- At a dose of 5 mg, there was apparently no cardiovascular adverse response and at 10 mg only minor effects were reported.

NOEL = (5 mg/day) / 75 kg = 67 µg/kg bw/day

ADI = (67µg/kg bw/day)/safety factor of 50

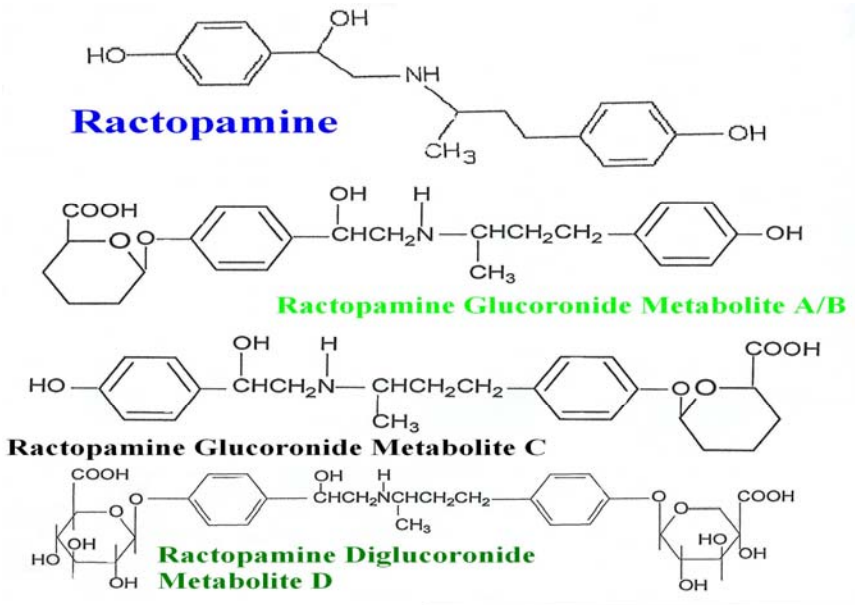
= 1.34 µg/kg bw/day ≈ 0-1 µg/kg bw/day

## Metabolism and Residue Chemistry Assessment of Ractopamine

# Phamacokinetics of Ractopamine

- Ractopamine metabolises solely by conjugation and has relatively short half-life.
- Absorption is rapid from gastrointestinal tract, with a fraction of at least 45 % for cattle and more than 85% for swine.
- Tissue distribution of ractopamine is extensive and occurs rapidly
- Total residue reaches the steady-state level 4 days after initiation of feeding
- Non-extractable residues also reach the steady-state level after 4 days and represent 26-29% and 15-16% of total residue in liver and kidney
- Residues relatively persist in liver and kidney but deplete fast from muscle and fat
- Low lipophilicity ( very low level residue found in fat tissue)
- The metabolic fate of ractopamine HCl is similar in the target species (pigs and cattle), laboratory animals and humans

# Ractopamine and its Metabolites




## Comaprative Metabolism of Ractopamine

The mean amount in ppm of ractopamine HCl and its metabolites (calculated as ractopamine HCl) in kidney and liver tissues of cattle, dogs and rats

| | Liver | | | Kidney | | |
|---|---|---|---|---|---|---|
| | Cattle | Dog | Rat | Cattle | Dog | Rat |
| Ractopamine HCl | 0.08 | 0.59 | 0.40 | 0.05 | 0.50 | 0.33 |
| Metabolite A | 0.02 | 0.46 | 0.17 | 0.02 | 0.18 | 0.52 |
| Metabolite B | 0.02 | 0.77 | 0.15 | 0.02 | 0.27 | 0.57 |
| Metabolite C | 0.24 | 1.76 | 0.10 | 0.25 | 0.63 | 0.08 |
| Metabolite D | 0.13 | 0.71 | 0.17 | 0.03 | 0.15 | 0.10 |

Dogs and rats used in the toxicological studies were exposed to the same metabolites as those found in the edible tissues of cattle.

## Comaprative Metabolism of Ractopamine

The mean amount in ppm of ractopamine HCl and its metabolites (calculated as ractopamine HCl) in kidney and liver tissues of pig, dogs and rats

| | Liver | | | Kidney | | |
|---|---|---|---|---|---|---|
| | Pig | Dog | Rat | Pig | Dog | Rat |
| Ractopamine HCl | 0.12 | 0.59 | 0.40 | 0.10 | 0.50 | 0.33 |
| Metabolite A | 0.03 | 0.46 | 0.17 | 0.05 | 0.18 | 0.52 |
| Metabolite B | 0.04 | 0.77 | 0.15 | 0.06 | 0.27 | 0.57 |
| Metabolite C | 0.02 | 1.76 | 0.10 | 0.09 | 0.63 | 0.08 |

Dogs and rats used in the toxicological studies were exposed to the same metabolites as those found in the edible tissues of pig.

## Comaprative Metabolism of Ractopamine

Ractopamine HCl and its Metabolites as Mean Percent and ppm[1] of the Total $^{14}C$ Residues in Liver Tissues from Animals Dosed with $^{14}C$ Ractopamine HCl.

| | Turkey | | Dog | | Rat | |
|---|---|---|---|---|---|---|
| | % | ppm | % | ppm | % | ppm |
| Ractopamine HCl | 39.0[2] | 0.220[2] | 8.4 | 0.589 | 31.6 | 0.397 |
| Metabolite A | 13.9 | 0.090 | 6.4 | 0.458 | 12.0 | 0.171 |
| Metabolite B | 16.3 | 0.104 | 10.7 | 0.768 | 10.6 | 0.150 |
| Metabolite C | 3.3 | 0.020 | 23.9 | 1.756 | 7.0 | 0.098 |
| Metabolite D | 1.0 | 0.006 | 9.8 | 0.712 | 11.8 | 0.166 |

[1]Calculated as ractopamine HCl :

| | |
|---|---|
| Turkeys | 895 dpm/µg |
| Dogs | 1108 dpm/µg |
| Rats | 1086 dpm/µg |

[2]Mean of data from turkeys 502M, 519M, 522F, and 530F from Experiment T4V739101.

## Ractopamine-Total Residue Studies

- In swine, total residue studies were carried out at 20 to 30 ppm ( at dose levels 2 to 3 times higher than the maximum recommended dose (10 ppm).
- In cattle, total residue studies were carried out at 30-45 ppm which were 1-1.5 X of the maximum recommended dose (30 ppm).
- In turkeys, total residue studies were carried out at 13-20 ppm which were 1.5-2.0 of the maximum recommended dose (9 ppm)

# Consumption Factors Used

| | Cattle | Swine | Turkey |
|---|---|---|---|
| Edible Tissues | | Amount (gms/day) | |
| Muscle | 500 | 500 | 500 |
| Liver | 250 | 167 | 167 |
| Kidney | 167 | 125 | 100 |
| Fat | 125 | 125* | 250* |

* Skin/fat in natural proportion

# Safe Concentrations (TRLs) for Ractopamine in Cattle, Swine and Turkeys

ADI = 1.4 µg/kg bw/day

Safe Concentration (TRL) = ADI X 60 X 2 X CF (consumption factor).

| Edible Tissues | Cattle | Swine* (ppm) | Turkeys* |
|---|---|---|---|
| Muscle | 0.15 | 0.15 | 0.15 |
| Liver | 0.3 | 0.45 | 0.45 |
| Kidney | 0.45 | 0.6 | 0.75 |
| Fat | 0.6 | 0.6 | 0.3 |

* Skin/fat

# Residue Studies

Based on the radio-labelled studies:

Ratio of marker residue/total residue (MR/TRR):

| | Swine | Cattle | Turkeys |
|---|---|---|---|
| Muscle | 25%* | ---- | 21.35 |
| Liver** | 27.2% | 13.2% | 41.6 |
| Kidney | 23.4% | 22.5% | ---- |
| Fat | ---- | ---- | ---- |

*A conservative estimate
** Target tissue

# Maximum Residue Limits (MRL) in ppm

| | Swine | Cattle | Turkeys |
|---|---|---|---|
| Edible Tissues | | MRLs | |
| Muscle | 0.04 | 0.01* | 0.03 |
| Liver | 0.12 | 0.04 | 0.2 |
| Kidney | 0.14 | 0.10 | ---- |
| Fat | ---- | ---- | ---- |

* Based on twice of LOQ = 2 X 0.005 ppm = 0.01 ppm

# Analytical Methodology

Swine: A multi-residue β-agonist screening and confirmatory method including ractopamine with LOQ of 0.0005 ppm.

Cattle: A β-agonist screening method including ractopamine with LOQ of 0.0005 ppm, where positive indicated, it is subjected to a confirmation method for ractopamine with LOD of 0.0005 ppm, LOQ of 0.002 ppm.

Turkey: A β-agonist screening and confirmatory method including ractopamine with LOQ of 0.001 ppm.

# Comparison of MRLs (ppm) established in cattle and swine edible tissues in Canada, US FDA and Codex

| | Canada* | US FDA** | Codex* |
|---|---|---|---|
| **Cattle** | | | |
| Muscle | 0.01 | 0.03 | 0.01 |
| Liver | 0.04 | 0.09 | 0.04 |
| Kidney | 0.1 | ---- | 0.09 |
| Fat | ---- | ---- | 0.01 |
| **Swine** | | | |
| Muscle | 0.04 | 0.05 | 0.01 |
| Liver | 0.12 | 0.15 | 0.04 |
| Kidney | 0.14 | ---- | 0.09 |
| Fat | ---- | ---- | 0.01 |

*MRLs expressed as ractopamine free base
** MRLs expressed as ractopamine hydrochloride

## Comparison of MRLs (ppm) established in turkeys edible tissues in Canada, US FDA and Codex

| | Canada* | US FDA* | Codex |
|---|---|---|---|
| **Turkeys** | | | |
| Muscle | 0.03 | 0.1 | ---- |
| Liver | 0.2 | 0.45 | ---- |
| Kidney | ---- | ---- | ---- |
| Skin/Fat | ---- | ---- | ---- |

*MRLs expressed as ractopamine free base

## Summary

*Based on the assessment of available toxicological and residue data, Health Canada has concluded that the residues in edible tissues of cattle, swine and turkeys resulting from the use of the ractopamine products, according to the label directions, are considered to be safe and would not pose any adverse health effects in humans.*