Opportunities to Reduce Animal Use in the Carcinogenicity Evaluation of New Drugs

A 5-minute case study in counting animals
Counting the animals used:

- Suggests opportunities to reduce animal use
- Estimates the potential for reductions (low-hanging fruit)
- Measures progress toward replacement
<table>
<thead>
<tr>
<th>Species</th>
<th>Number</th>
<th>Dosage</th>
<th>Number per Study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>31,258</td>
<td>52 x 104 wk</td>
<td>601.1 rats/study</td>
<td>400?</td>
</tr>
<tr>
<td>Mice</td>
<td>24,504</td>
<td>33 x 104 wk</td>
<td>742.5 mice/study</td>
<td>400?</td>
</tr>
<tr>
<td>rasH2</td>
<td>9,579</td>
<td>24 x 26 wk</td>
<td>399.1 rasH2/study</td>
<td>210?</td>
</tr>
</tbody>
</table>

65,341 animals  109 studies

“...it is suggested that for each sex there should initially be at least 50 animals per treated group, and one control group of the same number for each sex dosed with the vehicle by the same route.” EMA/CPMP/SWP/2877/00
Total Number of Animals Used per Control and Dose Group in Main and Satellite Studies

- **104-week rats**:
  - Main Carcinogenicity Control: 8438
  - Main Carcinogenicity Dose: 19088
  - Toxicokinetics Control: 656
  - Toxicokinetics Dose: 2384
  - Other Satellite Control: 392
  - Other Satellite Dose: 120

- **104-week mice**:
  - Main Carcinogenicity Control: 5938
  - Main Carcinogenicity Dose: 12302
  - Toxicokinetics Control: 938
  - Toxicokinetics Dose: 4666
  - Other Satellite Control: 210
  - Other Satellite Dose: 270

- **26-week rasH2 mice**:
  - Main Carcinogenicity Control: 2290
  - Main Carcinogenicity Dose: 3111
  - Toxicokinetics Control: 3700
  - Toxicokinetics Dose: 30
  - Other Satellite Control: 30
  - Other Satellite Dose: 30

Legend:
- Main Carcinogenicity Control
- Main Carcinogenicity Dose
- Toxicokinetics Control
- Toxicokinetics Dose
- Other Satellite Control
- Other Satellite Dose
- Sentinels
“…it is suggested that for each sex there should initially be at least 50 animals per treated group, and one control group of the same number for each sex dosed with the vehicle by the same route.” EMA/CPMP/SWP/2877/00

“There are two categories of studies with dual control groups. The first category usually consists of studies using an untreated control group and a vehicle control group… The second category includes studies that use two identical control groups…” FDA, 2001. Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.
31,258 rats  52 x 104 wk  601.1 rats/study
24,504 mice  33 x 104 wk  742.5 mice/study
9,579 rasH2  24 x 26 wk    399.1 rasH2/study
65,341 animals  109 studies
Average Number of Animals Used per Control and Dose Group in Main and Toxicokinetics Studies

- Microsampling can reduce pain and distress in animals and improve animal welfare (refinement).
Microsample blood to eliminate TK satellite: 12,203 animals
Replace 33 long-term studies in mice: 11,332 mice
Waive 15 studies in rats based on chronic toxicity: 8,410 rats
Use single negative control groups: 4,482 animals