Can We Combine Data From Avian Reproduction Studies On Different Test Species To Improve Risk Assessments?

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The problem

- Under Regulation (EC) No. 1107/2009, an avian reproduction study is required.
- Studies are often available on two species, such as mallard duck (*Anas platyrhynchos*) and bobwhite quail (*Colinus virginianus*).
- For risk assessment, the guidance of EFSA (2009) states the lowest endpoint from available studies should be used → Additional high quality data does not contribute to reduction of uncertainty in the risk assessment!
- Dose rates may be widely spaced →NOAEL may be lower than true effect threshold which is poorly defined.

Can the studies on different avian test species be *combined* to improve endpoints?

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Mallard duck and bobwhite quail – can they be considered equivalent for risk assessment purposes?

Example

Compound X is a real acaricide with three avian reproduction studies. There is one apparently anomalous result: Study 2 NOAEL 2.1 mg a.s./kg bw/day.

Study 1: Bobwhite quail, 1999 EPA/FIFRA guideline 71-4			Study 2: Mallard duck, 1999 EPA/FIFRA guideline 71-4			Study 3: Mallard duck, 1999 FIFRA, ASTM and OECD guidelines		
Dietary concentration (ppm)	Daily dose (mg as/kg bw/day)	Effect	Dietary concentration (ppm)	Daily dose (mg as/kg bw/day)	Effect	Dietary concentration (ppm)	Daily dose (mg as/kg bw/day)	Effect
250 ppm	23.8 **NOAEL**	No	120 ppm	12.7	Yes	120 ppm	16.9 (♂) **NOAEL** 18.3 (♀)	No
125 ppm	11.8	No	65 ppm	7.5*	Yes	65 ppm	Not reported	No
40 ppm	3.7	No	20 ppm	2.1 (♂) **EU NOAEL** 2.3 (♀)	No	-	-	-
NOAEL = 23.8 mg a.s./kg bw/d			NOAEL = 2.1 mg a.s./kg bw/d (♂endpoint)			NOAEL = 16.9 mg a.s./kg bw/d (♂endpoint)		

Simultaneous studies in same test facility.
EU agreed NOAEL 2.1 mg a.s./kg bw/day from apparently anomalous Study 2

Study 3 indicates that Study 2 is anomalous – no effect at 120 ppm

Combined studies 1 & 2			
Study 1 Bobwhite	Study 2 Mallard	Daily dose (mg as/kg bw/day)	Effect
250 ppm	-	23.8	No
125 ppm	-	11.8	No
-	120 ppm	12.7	Yes
-	65 ppm	7.5[a]	Yes
40 ppm	-	3.7[b]	No
-	20 ppm	2.1[c]	No

[a] Current LOAEL;
[b] **Proposed NOAEL preserves existing LOAEL;**
[c] Existing EU agreed NOAEL
Wide spacing between 20 and 65 ppm in Study 2!

What does the EFSA (2009) guidance say?

Section 2.4: Incorporation of additional toxicity information

"It can be assumed that as Annexes II stipulates reproductive data on one species of bird and mammal, then an appropriate level of protection is provided by applying an uncertainty factor or assessment factor of 5 to the appropriate toxicity endpoint for a single species". ***Data on either species is treated the same in risk assessment – does this mean the species can be considered equivalent for risk assessment purposes?***

Section 2.4.3 How to deal with more than one reproduction study on the same species highlights the following requirements:

Section 2.4.3. EFSA, (2009)	Compound X example
Similar protocol or guideline must be used	✓ Both conducted to same protocol
Key endpoints must be assessed in all studies	✓ Same endpoints assessed
The two studies must have have similar dose responses	✓ Proposed NOAEL is below existing LOAEL, which is preserved
The same species must be used	✓ Test species considered *equivalent* because a study with only one of either species is required to fulfil the protection goal

Proposal

For Compound X, and other active ingredients with similar available data, it is proposed to combine the existing studies. In this example, the bobwhite quail and mallard duck studies (Studies 1 & 2) are combined to derive an alternative, slightly higher **NOAEL of 3.7 mg a.s./kg bw/day**. This is based on high quality regulatory studies conducted to GLP and standard test guidelines. The proposed NOAEL of preserves and respects the existing LOAEL and takes account of all available data.

• Only one study with either species is needed to achieve the protection goal, therefore the test species are treated as equivalent by EC Regulation 1107/2009 • Test designs are extremely similar between species • The same TER trigger is applied to risk assessments with each species • Test concentrations can be widely spaced - true effect threshold may be uncertain, especially if only one of multiple available studies used. Combining studies may provide a more precise measure of effect threshold.

European Food Safety Authority; Guidance Document on Risk Assessment for Birds & Mammals on request from EFSA. EFSA Journal 2009; 7(12):1438. doi:10.2903/j.efsa.2009.1438. Available online: www.efsa.europa.eu