Innolytics, LLC
The Pigeon Control Company

The Secondary Toxicity of OvoControl® (nicarbazin) in Birds

The rationale for the absence of secondary toxicity of nicarbazin in birds is twofold,

1. The circulating and tissue concentrations of DNC in an OvoControl-treated bird are far too low to achieve the dose required for interference with egg hatchability in a secondary bird, and,

2. The bioavailability of DNC, the active component in nicarbazin, is extremely limited once absorbed by the animal consuming the OvoControl bait.

Chemistry and Absorption

Chemically, nicarbazin is an equimolar complex of 4,4′-dinitrocarbanilide ("DNC") and 2-hydroxy-4,6-dimethylpyrimidine ("HDP"). DNC is the biologically active component and, for effective absorption, must be complexed with HDP[1,2]. Due to its hydrophobic nature, DNC without HDP has very limited biological availability and will simply pass through birds unabsorbed.

Following digestion and absorption by the bird, DNC and HDP follow separate excretion pathways. DNC is unable to re-complex with HDP, and therefore, once digested, there is no potential for any secondary effect.

The metabolism of the compound has been well characterized in residue depletion studies with Carbon-14 labeled nicarbazin[3]. Both components are absorbed through the intestines into the blood. HDP is excreted rapidly, predominately through the kidneys and in urine, whereas DNC is excreted through the feces via the liver. No detectible residues of either component remain in any tissue after 7 days. DNC does accumulate in the egg and the accumulated egg DNC concentration is typically less than 5 ppm.

Mechanism and Action

The mechanism of nicarbazin requires that the bird ingest the bait at a sufficient rate to achieve a circulating blood concentration of DNC that can then be deposited into the yolk of the developing egg[4]. It requires 5-7 days to achieve this blood level for effective concentrations to be absorbed in the yolk. The egg requires 14 days to develop in the bird with emphasis on the last 5-7 days when the yolk is maximized, the albumin and shell are completed and the egg is laid[5]. Interference with egg hatchability can only occur if the target bird consumes an effective dose of bait during the development period[6].

While applied in 5000ppm concentration bait, tissue and egg concentrations of nicarbazin in the treated bird are well below the no-effect level ("NOEL") for any toxic effect in any bird.

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[1] Ott, W.H., S. Kuna, C.C. Porter, and A.C. Cuckler. 1956. **Biological studies on nicarbazin, a new anticoccidial agent.** Poultry Science 35:1355-1367.
[2] Burnett, T.J. Elanco Animal Health, 2010. "**Relative Bioavailability of DNC in Rats Administered Alone, Mixed with HDP and as Nicarbazin**. HVDRA Conference, Ghent, Belgium. June 1-4, 2010.
[3] World Health Organization (WHO), FAO Food and Nutrition Paper #41/11. **Residues of Some Veterinary Drugs in Animals and Foods** (1999).
[4] Reinoso, V. 2008. **Contraceptive Action of Nicarbazin in White Pekin Ducks** (Master's thesis). Retrieved from http://etda.libraries.psu.edu/theses/approved/WorldWideIndex/ETD-3193/index.html
[5] Jones, J.E., J. Solis, B.L. Hughes, D.J. Castadldo, and J.E. Toler. 1990. **Reproduction responses of broiler-breeders to anticoccidial agents**. Poultry Science. 69:27-36.
[6] Reinoso, V. P., R. Katani, and G. F. Barbato. 2007. **Nicarbazin reduces egg production and fertility in White Pekin ducks via reducing ZP3 in the perivitelline membrane**. Poultry Sci. 86 (Suppl. 1): 536.

72377 Magnesia Falls Dr., Rancho Mirage, CA 92270
Tel: 949.388.3671 – FAX: 760.282.3080 – email: erick.wolf@ovocontrol.com

Secondary Effects

The effect of nicarbazin on a domestic chicken, a goose surrogate and, a raptor such as an eagle, is provided for illustration purposes. The chicken is the most sensitive bird, absorbing nicarbazin at a rate in excess of all other birds tested. This has been demonstrated in comparative blood levels of DNC in the chicken, mallard duck and Canada goose with the chicken twice as sensitive as the other two species[7].

The DNC tissue concentrations in the chicken are well established and were published by WHO/FAO JECFA[8] within the human food safety evaluation. The quantities present in a 2 kg chicken after 49 days at 125ppm nicarbazin in the total diet are as follows,

Liver	14.4 to 21.0ppm
Kidney	2.8 to 5.4ppm
Muscle	1.4 to 2.2ppm
Skin/fat	1.6 to 3.0ppm

Assuming that the entire chicken or goose is consumed by an eagle with an average concentration of 5ppm, a total of 10,000ppm (2000gram x 5ppm) would be ingested. The quantity of nicarbazin required by a goose to inhibit hatchability is 25g X 5000ppm or 125,000ppm, each day.

Assuming an eagle weighs the same as a goose and eats a 2 kg chicken or goose, its intake would be 10x lower than that needed to produce an effect. The raptor would actually need to eat 10 geese per day, over 10 days (100 geese), during its own breeding season to have any possible effect. Furthermore, the example assumes that all DNC from the tissues is biologically available to the raptor, which is not the case.

Likewise, the consumption of OvoControl bait through undigested prey gut contents could also be considered a means of exposure. However, unlike a toxicant, the consumption of one pigeon with undigested bait does not constitute even a single dose for a raptor. OvoControl requires both an adequate dose and adequate duration to achieve a contraceptive effect.

For example, a 1500 gram Peregrine falcon requires 5x the dose of a 300 gram pigeon and would have to consume 5 pigeons/day. Furthermore, the dose must be provided daily, for a minimum of 5 days to achieve a contraceptive blood level. In other words, the falcon would have to consume the undigested OvoControl containing gut contents of 25 pigeons over 5 days to achieve the contraceptive blood level. This scenario is simply not realistic.

Bioavailability

Nicarbazin does not circulate in the blood or tissue as an intact molecule – only as DNC and HDP. It is well documented that the bioavailability of DNC without HDP is very limited[1]. The lack of DNC bioavailability from the tissues and eggs is the second of two reasons why secondary toxicity of nicarbazin is not possible.

Summary

The scientific rationale demonstrates that the potential impact of secondary toxicity to a raptor or any other animal is extraordinarily low, if not non-existent, and any amount absorbed would be well below the established no-effect levels.

[7] Yoder, C. A., L. A. Miller, and K. S. Bynum. **Comparison of Nicarbazin Absorption in Chickens, Mallards and Canada Geese.** National Wildlife Research Center, Fort Collins, CO. 2005 Poultry Science 84:1491-1494.

[8] United Nations World Health Organization (WHO), Food & Agriculture Organization (FAO), Joint Expert Committee on Food Additives (JECFA). **Evaluation of Certain Veterinary Drug Residues in Food (Nicarbazin).** Series 888, pp66-72. 2000.