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# Uterine adenocarcinoma in the rat induced by afidopyropen. An analysis of the lesion's induction, progression and its relevance to humans

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ABSTRACT

Afidopyropen is a novel insecticide that acts as a TRPV channel modulator in chordotonal organs of target insects. In two carcinogenicity studies with Fischer rats, an increased incidence of uterine adenocarcinomas was observed at 1000 and 3000 ppm. This finding prompted an investigation of the mechanism of the tumor formation as well as the relevance of this mechanism to humans. The mechanistic work took parallel paths: one path investigated the pharmacokinetic properties of the test substance at the doses where the tumors were found; while the second path examined the key mechanistic events that culminated in uterine adenocarcinomas. The results of the investigation indicated that the tumors only occurred at doses where excretion of test substance was saturated – indicating that homeostatic biological and/or physiological processes were overwhelmed. At the doses where these processes were overwhelmed, the test substance acted through a mechanism of dopamine agonism, triggering a cascade key events that resulted in uterine adenocarcinomas. An analysis of these mechanisms observed in rat showed that they are both quantitatively (pharmacokinetic mechanism) and qualitatively (dopamine agonism mechanism) not relevant to humans. Therefore the uterine adenocarcinomas observed in the rat associated with high doses of Afidopyropen are not expected to pose a carcinogenic risk to humans.

## 1. Introduction

Afidopyropen (CAS # 915972-17-7; Fig. 1; also known as Inscalis™) is a novel insecticide that acts as a TRPV channel modulator in the chordotonal organs of target insects (Kandasamy et al., 2017). The safety of the insecticide was evaluated through a battery of acute, subchronic and chronic toxicology studies, including carcinogenicity studies in rats and mice. In carcinogenicity studies with Fischer 344 (F344) rats, an increased incidence of uterine adenocarcinoma was observed at 1000 and 3000 ppm after two years of dietary administration of Afidopyropen. These lesions were not observed in an 18-month carcinogenicity feeding study with the CD-1 mouse. No other statistically significant increases in neoplastic lesions were reported in the rat or mouse carcinogenicity studies.

The finding of uterine adenocarcinomas in the rat prompted several obvious avenues of inquiry: 1) Was there evidence of mutagenic activity? 2) Were there direct estrogenic effects (an alteration of the critical estradiol:progesterone ratio)? and 3) Was there evidence of precursor lesions that could progress to uterine adenocarcinomas?

All of these obvious avenues of tumor formation were investigated, and none were consistent with the effects observed with Afidopyropen. Examination of the data showed that Afidopyropen was not genotoxic; did not induce estrogenic activity with *in vitro* assays or *in vivo* studies; and did not lead to precursor lesions in shorter duration studies that could culminate in uterine adenocarcinomas.

Without obvious, direct effects leading to uterine adenocarcinomas in the rat, we took parallel paths to investigate the lesions. In the first path, we conducted an investigation of the pharmacokinetic properties of the test substance at the doses where the tumors occurred. In certain cases, pharmacokinetics can indicate that effects at particular doses are not quantitatively relevant to humans. In the second path, we examined the key mechanistic events that led to uterine adenocarcinomas.

### 1.1. Toxicokinetic investigation

Had the pharmacokinetic data been available prior to the initiation of the cancer studies, this would have guided the selection of appropriate doses. Nevertheless, because the tumors in rats were only observed at high doses, we reasoned that tumors may have only occurred at doses exhibiting nonlinear pharmacokinetics (PK). PK data can reveal

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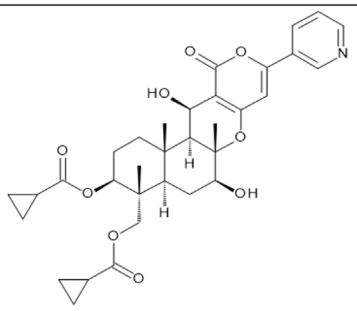
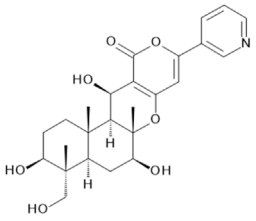
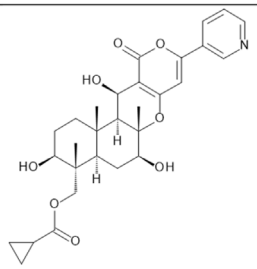
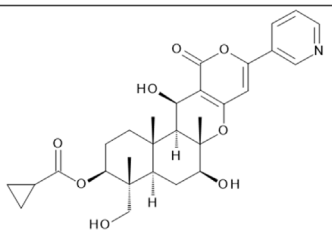
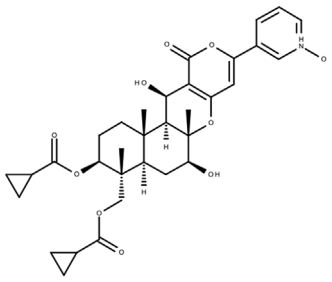
| Compound | Structure |
|---|---|
| **Afidopyropen (parent)** |  |
| **M440I001 (rat metabolite)** |  |
| **M440I002 (rat metabolite)** |  |
| **M440I003 (rat metabolite)** |  |
| **M440I017 (rat metabolite)** |  |

**Fig. 1.** Chemical structures of Afidopyropen and metabolites.

whether the kinetics for serum Afidopyropen levels are linear (constant elimination rate) over the entire range of test doses, or non-linear due to saturation of metabolic clearance and/or detoxification processes.

Adverse effects (regardless of mode of action) at non-linear PK doses are quantitatively not relevant to humans – particularly when the human exposure is expected to be well below the non-linear PK dose (Conolly et al., 1999; EPA, 2005; Barton et al., 2006; OECD, 2012a, 2012b). Use of PK data to identify an appropriate top dose in animal