Toxicokinetics (absorption, metabolism, distribution and elimination)

The information provided in Section 4.1 contained a number of errors. Syngenta have provided a re-write using track changes of the required corrections, although it is acknowledged this has no impact on classification and labelling endpoints.

4.1.1 Non-human information

Mammalian toxicity studies were conducted on cyproconazole (code-named SAN 619 F) and metabolite M36 (NOA405872), which was confirmed as being present in rat urine and faeces. The purity of cyproconazole both radiolabelled and non-radiolabelled was reported to be between 91 and 99.9%. All tests were conducted in accordance with GLP. A number of studies were performed prior to the guidelines and deviated slightly, however these deviations were not considered to affect the validity of the studies or the scientific outcomes.

Absorption

Cyproconazole (radiolabelled) was found to be rapidly and extensively ab~~d~~sorbed at the low dose (10 mg/kg) with maximal blood levels reached between ~~1.5~~3 – ~~7~~ 9 hours post dosing. Rats administered the high dose (130 mg/kg) displayed a slower but equally extensive ab~~d~~sorption, with maximal blood concentrations reached between ~~24–48~~13-24 hours. Based on bile duct cannulated ~~experiment~~ rats, cyproconazole had a total ~~bioavailability~~ oral absorption of > 86%. Repeated administration resulted in ~~an increased absorption with levels in the~~ blood concentrations reaching a ~~maximum~~ plateau after 8 days ~~despite further administration~~. ~~Based on the absorption studies provided there was no evidence of accumulation in any tissues of the rat.~~

Distribution

~~Cyproconazole was found to have a rapid and extensive volume of distribution as evidenced by maximal blood levels being reached between 1.5 and 7 hours and with most tissues having higher residue levels than found in the blood by 3 hours.~~ Cyproconazole was found to be predominately associated with the organs of elimination (kidney and~~,~~ liver ~~and pancreas~~) as well as ~~the spleen~~renal fat and adrenal glands. Following repeated administration a similar pattern of distribution was observed, with cyproconazole ~~accumulating~~ residues reaching steady state in all tissues up to 7 days after which point no further accumulation was observed despite further dosing. Upon cessation of treatment cyproconazole was rapidly eliminated from all tissues with half-lives in the range of 1 - 3 days and no signs of residue retention.

Metabolism

The metabolic profile of cyproconazole is based on the fate of [Phenyl-U-^{14}C] labelled SAN 619 F, with conclusions based on both single and multiple dosing. Cyproconazole was extensively metabolised, with a greater number of metabolites identified in the urine in comparison to the faeces. In the faeces, parent cyproconazole and the identified metabolite

NOA421152 ~~are~~ were the major components and accounted for 9.1~~5~~ – 11.5% and ~~2.2~~8.7 – 13.9% dose respectively (after single dosing at 10 mg/kg). The metabolite pattern was almost identical after high doses and after multiple dosing with slight quantitative differences. ~~Parent cyproconazole and~~ NOA42115~~2~~3 ~~were~~ was also ~~found in the urine but less than other metabolites~~the major urinary metabolite in female rats, however the metabolic profile in the urine was the same after single and multiple dosing. ~~As with multiple dosing, pre-treatment with a larger dose of cyproconazole was found to have no effect on the metabolism profile.~~ Further analysis of the metabolism profile revealed 35 metabolites of which 13~~3~~ were identified~~considered significant~~. ~~The metabolic pathway was elucidated based on the metabolite profile identified.~~

The predominant metabolic reactions of cyproconazole in the rat were:

a) oxidative elimination of the triazole ring,

b) hydroxylation of the carbon bearing the methyl group,

c) oxidation of the methyl group to the carbinol and further to the carboxylic acid and

d) reductive elimination of the carbon bearing the methyl group, yielding a benzyl alcohol which ~~is~~ was further oxidised to the corresponding ketone (Figure 1).

~~Based upon an observation that diastereoisomer A of cyproconazole was metabolised faster than diastereoisomer B, a customized study was done.~~ For both diastereoisomers, the route and rate of excretion were ~~in the same range~~similar. Diastereoisomer A was biotransformed more extensively than
diastereoisomer B; however, based upon metabolite profiles, the course of metabolism of the two diastereoisomers was shown to be similar.

There were no clear differences in metabolism in the rat, either between sexes, dosages or due to pre-treatment. Examination of species related differences revealed no difference in the metabolic pattern between rats and goats. *In vitro* investigation of metabolism ~~of~~using subcellular fractions of rat and mice livers revealed that those derived from mice ~~metabolised cyproconazole at a slower rate but~~ gave a similar spectra of metabolites ~~was observed with the exception of the metabolite M9~~compared to rats *in vivo*. ~~Pre-treatment was found to slightly alter the rate of metabolism but not the profile in either rat or mouse, but pre-treatment increased the rate of metabolism of cyproconazole to a greater extent in the mouse.~~

Elimination

After oral doses, the major route of excretion was via the faeces (43 - 60% dose) and faecal excretion was higher in males than females. Urinary excretion accounted for 28 - 42% dose and

was higher in females than males. In bile duct cannulated rats, t~~T~~he major route of elimination ~~of cyproconazole~~was ~~in the rat was predominately~~ shown to be *via* the bile, accounting for approximately ~~75~~76% in males and ~~59~~60% in females. ~~Elimination *via* the urine occurred to a greater extent in females (26.8%) than males (9.5%), which accounted for the difference in elimination in the bile. Faecal elimination accounted for less than 5% of the administered dose. The majority of the test substance was eliminated *via* the urine and bile within the first 48 hours post administration irrespective of the route of administration. However some of the test substance may be reabsorbed from the bile and excreted *via* the urine.~~ Over ~~85~~84% of ~~cyproconazole~~ the dose was eliminated within 144 hours. Repeated administration had no significant effect upon the routes and rates of elimination compared to a single oral dose. The elimination from most tissues occurred rapidly, following monophasic kinetics. Biphasic elimination was observed for adrenals with a first phase half-life similar to the other tissues and a slower second phase. There was no sign of an unusual retention of cyproconazole-derived material in the rat after a single oral dose.

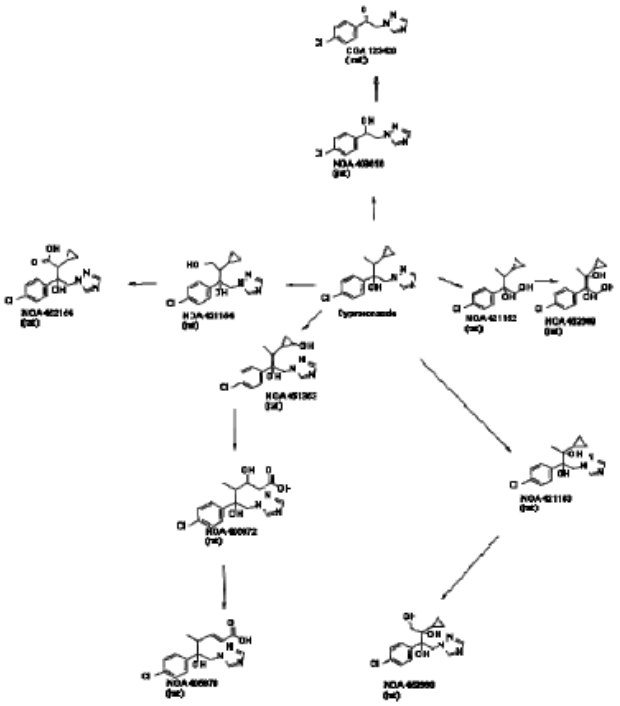


Figure 1. Summary diagram of the metabolic pathway in the rat.

Comment [A1]: Clearer figure attached at end of document

4.1.2 Human information

None available.

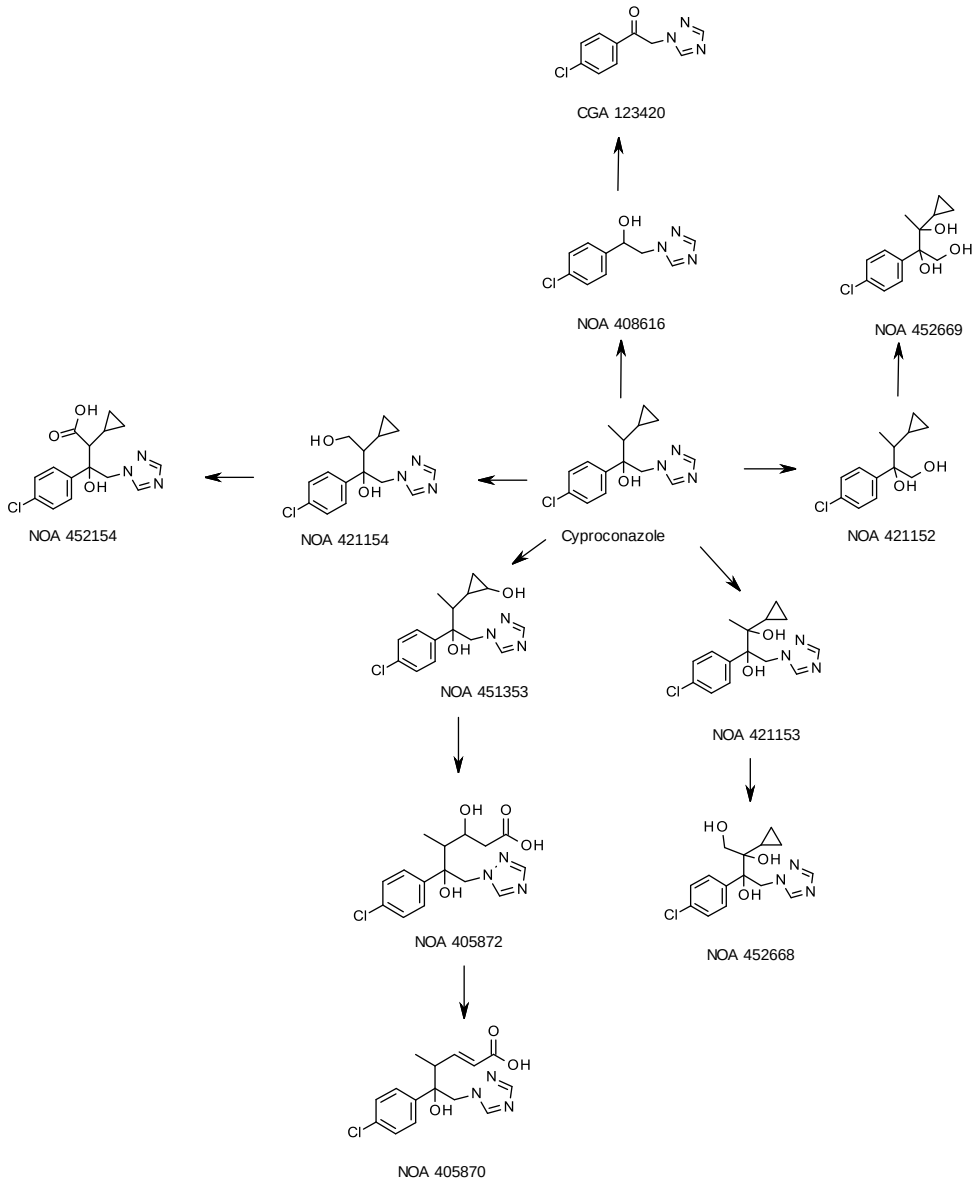
4.1.3 Summary and discussion on toxicokinetics

Cyproconazole was found to be rapidly and extensively ~~adsorbed~~ absorbed ~~with a total bioavailability of~~via the oral route ~~-~~(>86%). ~~Absorption was similar for the low~~The rate of oral absorption was more rapid at the low dose level (blood C_{max} ~~1.5 – 7~~3 - 9 hours after 10 mg/kg) ~~and high doses~~than the high dose level (blood C_{max} ~~24 – 48~~13 - 24 hours at 130 mg/kg). ~~Cyproconazole~~ Radioactivity was rapidly distributed and ~~and had an extensive volume of distribution following either single or repeated administration. R~~residues were predominately associated with the organs of elimination (kidney and~~y,~~ liver ~~and pancreas~~) as well as the ~~spleen~~ renal fat and adrenal glands following oral doses. ~~Based on the absorption studies provided, there was no evidence of accumulation in any tissues of the rat.~~ Following repeated administration a similar pattern of distribution was observed, with cyproconazole residues reaching steady state in all tissues up to 7 days after which point no further accumulation was observed despite further dosing. Upon cessation of treatment cyproconazole was rapidly eliminated from all tissues with half-lives in the range of 1 - 3 days and no signs of residue retention.

Cyproconazole ~~is~~ was extensively metabolised, with a greater number of metabolites identified in the urine compared to the faeces. In the faeces parent cyproconazole and the identified metabolite NOA421152 ~~are~~ were the major components. The metabolite pattern was almost identical after low, high and multiple dosing with slight quantitative differences. ~~Pre-treatment with a larger dose of cyproconazole was also found to have no effect on the metabolism profile.~~ Further analysis of the metabolism profile revealed 35 metabolites of which 13 were ~~considered significant~~identified. Based on the metabolite profile the predominant metabolism reactions in the rat were a) oxidative elimination of the triazole ring, b) hydroxylation of the carbon bearing the methyl group, c) oxidation of the methyl group to the carbinol and further to the carboxylic acid and d) reductive elimination of the carbon bearing the methyl group, yielding a benzyl alcohol which ~~is~~ was further oxidised to the corresponding ketone (Figure 1).

~~There were no clear differences in metabolism either between sexes, species (rat and goat) dosages or due to pre-treatment for the rat.~~ After oral doses, the major route of excretion was via the faeces (43 - 60% dose) and faecal excretion was higher in males than females. Urinary excretion accounted for 28 - 42% dose and was higher in females than males. In bile duct cannulated rats, the ~~M~~major route of elimination ~~of cyproconazole in the rat~~ was the bile, accounting for approximately 75% in males and 59% in females. ~~Elimination via the urine occurred to a greater extent in females (26.8%) than males (9.5%). Faecal elimination accounted for less than 5% of the administered dose. The majority of the test substance was eliminated via the urine and bile within the first 48 hours post administration irrespective of the route of administration. However some of the test substance may be reabsorbed from the bile and~~

~~excreted via the urine.~~ Over 84~~5~~% of ~~cyproconazole~~ the dose was eliminated within 144 hours. Repeated administration had no significant effect upon the routes and rates of elimination compared to a single oral dose. The elimination from most tissues occurred rapidly, following monophasic kinetics.


CGA 123420
NOA 408616
NOA 452669
NOA 452154
NOA 421154
Cyproconazole
NOA 421152
NOA 451353
NOA 421153
NOA 405872
NOA 452668
NOA 405870