EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
**C2 - Management of scientific committees ; scientific co-operation and networks**

**SCIENTIFIC COMMITTEE ON PLANTS**

**SCP/2,4D/002-Final**
**21 May 2001**

# OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF 2,4 DICHLOROPHENOXY ACETIC ACID (2,4 D) IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET

(Opinion adopted by the Scientific Committee on Plants on 25 April 2001)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: B232 6/25.
Telephone: direct line (+32-2)295.77.05, switchboard 299.11.11. Fax: 295.73.32.

Internet: Michael.Walsh@cec.eu.int

## 1. TITLE

**OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF 2,4 DICHLOROPHENOXY ACETIC ACID (2,4 D) IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET**
(Opinion adopted by the Scientific Committee on Plants, 25 April 2001)

## 2. TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is requested to respond to the following question in the context of the Commission's work on the implementation of Council Directive 91/414/EEC concerning the placing of plant protection products on the market.

"Can the Committee comment on the adequate animal model to be used for the derivation of the ADI (Acceptable Daily Intake) and the AOEL (Acceptable Operator Exposure Level)?"

## 3. BACKGROUND

2,4 Dichlorophenoxy acetic acid, also known as 2,4-D, is one of the existing active substances (a.s.) in the context of Council Directive 91/414/EEC, which has been selected in the first review list published in Commission Regulation 3600/92.

A draft evaluation report (monograph) has been prepared by the Rapporteur Member State (RMS, Greece) on the basis of a common dossier presented by a task force of several notifiers (Rhône-Poulenc Agrochimie, now Aventis CropSciences, Agrolinz, Nufarm, AH Marks, DowElanco now Dow AgroSciences and Sanachem International)[1]. In order to prepare its opinion the Scientific Committee on Plants had access to this draft evaluation report and the recommendation of the ECCO[2] Peer Review Programme.

2,4-D is a systemic herbicide, member of the phenoxy acetic acid family. It is a widely used herbicide to control broad-leaved weeds in a wide range of graminea crops (cereals, sugar cane, pasture) as well as in non cultivated areas. The rate of use, in Europe, ranges from 0.42 to 3 kg a.s./ha.

## 4. OPINION

### 4.1 Question

**"Can the Committee comment on the adequate animal model to be used for the derivation of the ADI (Acceptable Daily Intake) and the AOEL (Acceptable Operator Exposure Level)?"**

**<u>Opinion of the Committee:</u>**

**Available data support the hypothesis that the dog has a reduced capacity of urinary excretion of weak organic acids such as 2,4-D (i.e. the effect is not compound specific). The**

[1] Other companies joined the 2,4-D Dossier Preparation Working Group as late notifiers (PBI Gordon, BASF), some of the early notifiers were acquired (Sanachem by Dow, Agrolinz by Nufarm) or sold their business (Aventis to Nufarm).
[2] European Commission Co-ordination.

**most likely mechanism is a reduced renal active excretion, but the tubular re-absorption may also play a role. The net result is a reduced ability of the dog to excrete 2,4-D when compared to other animal species and humans. This is consistent with the higher sensitivity of dogs as compared to rodents to the toxic effects of 2,4-D, although the difference between dog and other species is not large. On this basis, mice and rats appear to be the preferable species to be used for human risk assessment.**

**Scientific background on which the opinion is based:**

An evaluation of the extensive toxicological database of 2,4-D lead the RMS to conclude that it is not genotoxic or carcinogenic or teratogenic and does not cause toxicity to reproduction. 2,4-D has neurotoxic potential at high doses. 2,4-D has a low volume of distribution, is highly protein bound and is excreted mainly unchanged in the urine.

The target organ in all studied species is the kidney. With respect to kidney toxicity, the dog appears to be the most sensitive species. In fact the NOAEL[3] in dogs was 1 mg/kg bw in both a 13-week study and a 1-year study; whereas the NOAELs for mice and rats were about 15 mg/kg bw per day in 13-week studies and about 5 mg/kg bw per day in 2-year studies. Histopathological lesions of the kidney were observed, consistently accompanied in the dog by serum BUN (Blood Urea Nitrogen) and creatinine increases.

Urinary elimination of organic acids results from the combination of filtration, secretion and reabsorption. 2,4-D, also a weak organic acid, is mainly excreted unchanged in the urine. In rodents, 2,4-D pharmacokinetics is non-linear but it is dose dependent. In fact, it shows saturation at high doses, which is consistent with an active, carrier-mediated secretion.

In a document prepared for the sponsor by Timchalk (1998) data obtained from the literature allowed the calculation of relevant pharmacokinetic parameters for 2,4-D in different species. Renal clearance, volume of distribution and plasma half-life of 2,4-D correlated with body weight for all species (including mouse, rat, pig, calf and human) with the exception of the dog which showed a lower than expected renal clearance and a longer than expected plasma half-life. The calculated renal clearance in dogs was about 1 order of magnitude lower than the values expected from allometric scaling (Bachmann *et al*, 1996) for the other species; this is consistent with acute toxicity data showing that the dog NOAEL is about 1 order of magnitude lower than rodent NOAELs. When comparing to the 2 year rodent study, the NOAELs are within the same order of magnitude. The same pharmacokinetic calculations made for 2,4,5-T (Timchalk, 1998; Hook *et al.*, 1976; Piper et *al.*, 1973), 1-aminocyclopropanecarboxylic acid (Cherkofsky, 1995) and 3,5,6-trichloro-2-pyridinyloxyacetic acid (triclopyr) (Timchalk and Nolan, 1997) yielded similar results. This difference between dog and other mammals is apparently not due to differences in the extent of plasma protein binding of 2,4-D.

It has been suggested that the species difference between dogs and other mammals in excretion of weak organic acids might be due to the lower capacity of the dog renal proximal tubules to actively secrete organic acids. For instance, it has been shown that in dogs triclopyr competes with phenolsulfonphthalein (a weak organic acid) for the active renal secretion mechanism because increased plasma concentrations of triclopyr reduce phenolsulfonphthalein excretion (Timchalk *et al*., 1997); likewise excretion of 2,4,5-T was reduced by administration of p-amino hippurate (Hook *et al*., 1976). This is also supported by *in vitro* data showing inhibition of 2,4-D and 2,4,5-T renal uptake by p-amino hippurate (Koschier and Berndt, 1976; Koschier *et al.*, 1978). However, it was also shown that 2,4,5-T binding to plasma proteins is stronger than that of p-amino hippurate (Hook

[3] No Observed Adverse Effect Level.

*et al.*, 1976). Organic acids can also be reabsorbed by the renal tubule, but the relevance of this phenomenon for the whole net excretion balance has not been clearly established.

In conclusion, available data support the hypothesis that the dog has a reduced capacity of urinary excretion of weak organic acids such as 2,4-D (i.e. the effect is not compound specific). The most likely mechanism is a reduced renal active excretion, but the tubular reabsorption may also play a role. The net result is a reduced ability of the dog to excrete 2,4-D when compared to other animal species and humans. This is consistent with the higher sensitivity of dogs as compared to rodents to the toxic effects of 2,4-D, although the difference between dog and other species is not large. On this basis, mice and rats appear to be the preferable species to be used for human risk assessment.

## 5. REFERENCES


Bachmann K, Pardoe D, White D. Scaling basic toxicokinetic parameters from rat to man, Environmental Health Perspectives, 1996, 104:400-407.

Cherkofsky SC. 1-Aminocyclopropanecarboxylic acid: mouse to man interspecies pharmacokinetic comparison and allometric relationships. Journal of Pharmacological Sciences 1995, 84:1231-1235.

Hook JB, Cardona R, Osborn JL, Bailie MD. The renal handling of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in the dog. Food and Cosmetic Toxicology 1976, 14:19-23.

Koschier FJ; Girard PR; Hong SK. Transport of 2,4-dichlorophenoxyacetate by rat renal cortical slices. Toxicology and Applied Pharmacology. 1978 45: 883-94

Koschier FJ; Berndt WO. In vitro uptake of organic ions by renal cortical tissue of rats treated acutely with 2,4,5-trichlorophenoxyacetic acid. Toxicology and Applied Pharmacology. 1976, 35:355-64

Piper WN, Rose JQ, Leng ML, Gehring PJ. The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to rats and dogs. Toxicology and Applied Toxicology, 1973, 26:339-351.

Timchalk C. Relevance of dog toxicity data for evaluation of human health risk from exposure to 2,4-dichlorophenoxy acid (2,4-D) and related organic acids. Unpublished report dated 23/06/1998 and submitted to the SCP by NuFarm GmbH 28/07/2000.

Timchalk C, Finco DR, Quast JF. Evaluation of renal function in rhesus monkey and comparison to beagle dogs following oral administration of the organic acid triclopyr (3,5,6-trichloro-2-pyridinyloxyacetic acid). Fundamental and Applied Toxicology, 1997, 36:47-53.

Timchalk C, Nolan RJ. Pharmacokinetics of triclopyr (3,5,6-trichloro-2-pyridinyloxyacetic acid) in Beagle dogs and Rhesus monkey: perspective on the reduced capacity of dogs to excrete this organic acid relative to the rat, monkey, and human. Toxicology and Applied Pharmacology, 1997, 144:268-678.

## 6. DOCUMENTS MADE AVAILABLE TO THE COMMITTEE

1. Evaluation of 2,4-Dichlorophonoxy acetic acid (2,4-D) in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (Doc. SCP/2,4D/001) submitted by DG Health and Consumer Protection, 11.05.2000.

2. Evaluation of 2,4-Dichlorophonoxy acetic acid (2,4-D) in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Summary of intended uses (Doc. SCP/2,4D/004) submitted DG Health and Consumer Protection, 13 June 2000.

3. Evaluation of 2,4-Dichlorophonoxy acetic acid (2,4-D) in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Addendum to the monograph Annex B 2. Physical and chemical properties (Doc. SCP/2,4D/005) submitted DG Health and Consumer Protection, 19 June 2000.

4. 2,4-D EU Working group's position on AOEL and ADI setting (Doc. SCP/2,4D/006) submitted by the 2,4-D Dossier preparation Working Group, 28 July 2000.

5. 2,4-D Independant pathology peer review of kidney tissues from rats and mice assigned to multiple (8) studies to evaluation the subchronic toxicity of 2,4-Dichlorophonoxy acetic acid (Doc. SCP/2,4D/007) submitted by the 2,4-D Dossier preparation Working Group, 28 July 2000.

6. 2,4-D Relevance of dog toxicity data for evaluation of human health risk from exposure to 2,4-Dichlorophonoxy acetic acid and related organic acids, C. Timchalk (Doc. SCP/2,4D/008) submitted by the 2,4-D Dossier preparation Working Group, 28 July 2000).

7. 2,4-D Allometric theory and its application in pharmacology/toxicology inter-species comparisons and risk assessment, C. Timchalk (Doc. SCP/2,4D/009) submitted by the 2,4-D Dossier preparation Working Group, 28 July 2000.

8. 2,4-D Response document to the monograph (Doc. SCP/2,4D/010) submitted by the 2,4-D Dossier preparation Working Group, 28 July 2000.

9. 2,4-D Clarification regarding implied effects on white blood cell count in the two subchronic studies in mice (Doc. SCP/2,4D/011) submitted by the 2,4-D Dossier preparation Working Group, 28 July 2000.

## 7 ACKNOWLEDGEMENTS

The Committee wishes to acknowledge the contributions of the working group that prepared the initial draft opinion.

Toxicology: Prof. Maroni (Chairman) and Committee members: Dr. Delcour-Firquet, Prof. Leszkowicz, Dr. Meyer, Dr Moretto, Prof. Petzinger, Prof. Savolainen, Prof. Silva Fernandes, Dr. Speijers, invited experts Dr. Fait and Dr. McGregor.