**PESTICIDE RESIDUES IN FOOD - 1982**

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 **EVALUATIONS 1982**

 Data and recommendations of the joint meeting

 of the FAO Panel of Experts on Pesticide Residues

 in Food and the Environment and the

 WHO Expert Group on Pesticide Residues

 Rome, 23 November - 2 December 1982

 Food and Agriculture Organization of the United Nations

 Rome 1983

 CHLORDANE

 

 Explanation

 Chlordane was evaluated in the Joint Meetings of 1963, 1965,

 1967, 1969, 1970, 1972, 1974 and 1977 (FAO/WHO, 1964, 1965, 1968,

 1970, 1971, 1973, 1975 and 1978)1/. Several acute oral studies and a

 90-day subchronic feeding study in rats, of Industrial Bio-Test

 Laboratories (IBT) origin, have been identified, which have not been

 validated. However, the no-effect level(s) (NEL) and ADI were not

 taken from the results of these data.

 Additional data pertaining to metabolism, absorption,

 distribution and excretion have been made available and are reviewed

 in this addendum.

 EVALUATION FOR ACCEPTABLE DAILY INTAKE

 BIOCHEMICAL ASPECTS

 Absorption, Distribution and Excretion

 More than 90% of single oral doses of high purity chlordane

 (98% + of a 3:1 mixture of cis- and trans-chlordane), cis-chlordane

 and trans-chlordane were eliminated from rats in the excreta within

 7 days after treatment, with faeces being the major route of

 elimination for both sexes. Single oral doses of oxychlordane resulted

 in only 21% of the administered dose appearing in rat excreta after 7

 days, demonstrating a greater potential for this metabolite of

 chlordane to accumulate in animals than the cis- and trans-chlordane

 isomers. Continuous feeding of cis- and trans-chlordane separately in

 the diet of rats for 14 days demonstrated preferential elimination of

 the cis-isomer. After 14 days of treatment, 75% of the total cis- and

 65% for the trans-chlordane were eliminated which indicates that in

 long-term exposures the trans-isomer would contribute a relatively

 greater amount to the body burden of the exposed animal than would the

 cis-isomer (Barnett and Dorough 1974).

 1/ See Annex 2 for WHO and FAO documentation.

 In a separate study, administration of cis-chlordane or trans-

 chlordane in single oral doses to rats via stomach intubation resulted

 in 86% of the total cis- and 66% of the total trans-chlordane being

 eliminated within 7 days after treatment. Furthermore, the rate of

 excretion of cis-chlordane (59% in 24 h) was more rapid than that of

 trans-chlordane (27%) (Tashiro and Matsumura 1977). There were no

 apparent sex differences with respect to the rate of dissipation, nor

 did males and females differ in the nature and relative concentrations

 of metabolites (Barnett and Dorough 1974).

 Biotransformation

 The metabolism of chlordane, per se, in rats resulted in the

 formation of dichlorochlordene via dehydrogenation followed by

 epoxidation to oxychlordane and subsequent hydroxylation. There was

 also direct hydroxylation of both the cis and trans-isomers to

 1-exo-hydroxydihydrochlordene with excretion in the faeces and urine

 as the glucuronide (Tashiro and Matsumara 1977).

 The level of residues in tissues of rats was generally low,

 except in fat. Metabolism of trans-chlordane resulted in higher tissue

 residues than cis-chlordane, primarily because of the formation of

 1,2-dichlorochlordane, which was favoured for the trans-isomer, thus

 leading to higher levels of oxychlordane. Feeding female rats high

 purity chlordane at levels up to 25 ppm for 56 days resulted in

 chlordane-14C equivalent in the fat at levels 3-4 times that in the

 diet. These levels did not plateau at the end of the treatment period.

 However, after 4 weeks removal from the diet, tissue levels were

 reduced by 60%. The levels of residues in tissues (other than fat)

 after 56 days of treatment were as follows (as the fraction of the

 administered dose): liver (1/8) > kidney (1/10) > brain (1/25)

 > muscle (1/50). Oxychlordane was the major component of all tissues

 and, after removing chlordane from the diet, contributed most of the

 14C residue in tissues (Barnett and Dorough 1974; Tashiro and

 Matsumura 1977; Street and Blau 1972).

 The metabolic intermediates of cis- and trans-chlordane, as well

 as oxychlordane, were further converted to two major metabolites,

 1-exo-hydroxy-2-chlorochlordene and 1-exo-hydroxy-2-chloro-2,3

 epoxychlordene. These latter metabolites were not readily degraded

 further in rats and may accumulate as terminal residues in the animal.

 Neither appeared to be more toxic than the cis- or trans-isomers, but

 this has not been verified in mammals (Tashiro and Matsumura 1977).

 Rat and human in vitro liver preparations displayed almost

 identical degradation abilities for trans-chlordane, but not for

 trans-nonachlor, which accumulated in humans but not in rats. Trans-

 nonachlor is a major constituent (7%) of technical chlordane. Both

 single oral dosing (0.05 µ Ci) and four-week dietary administration

 (100 ppm) of trans-nonachlor to rats have demonstrated the overall

 metabolic pattern and rate of excretion to be the same as for trans-

 chlordane. The fact that trans-nonachlor was not metabolized

 efficiently by human liver cells may be due to the inability to form

 trans-chlordane, which represents a significant difference from the

 rat (Tashiro and Matsumura 1978).

 A proposed metabolic pathway for chlordane in mammalian species

 is shown in Figure 1.

 TOXICOLOGICAL STUDIES

 Long-Term Study

 Rat

 The data submitted to the 1982 Meeting for evaluation of long-

 term effects were not sufficient in many critical areas of data

 content and were, therefore, inadequate for inclusion in this

 monograph.

 COMMENTS

 The ADI and long-term studies considered in support of the ADI

 were evaluated by the JMPR in 1967 and 1977 (FAO/WHO 1968 and 1978).

 Additional data on metabolism have been received.

 Significant differences in the metabolism of chlordane between

 rats and humans have been identified. Specifically, trans-nonachlor, a

 major constituent of technical chlordane, is poorly metabolized in

 humans. The Meeting was concerned about the accumulation of trans-

 nonachlor in humans. However, this concern was partly alleviated by

 the information that only very low levels (0.1 ppm on milk fat basis)

 appear to have been found in human milk samples.

 The Meeting was informed that studies pertaining to chlordane

 toxicology were in progress at the Research Institute for Animal

 Science in Biochemistry and Toxicology in Japan. The Meeting hopes

 that this data will eventually be made available to it.

 Pending receipt of a study on oxychlordane of at least 90 days

 duration in the rat, the Meeting assigned a temporary ADI to

 chlordane.

 TOXICOLOGICAL EVALUATION

 Level Causing no Toxicological Effect

 Rat: 5 mg/kg in the diet, equivalent to 0.25 mg/kg bw

 Dog: 3 mg/kg in the diet, equivalent to 0.075 mg/kg bw

 

 Estimate of Temporary Acceptable Daily Intake in Man

 0 - 0.001 mg/kg bw

 FURTHER WORK OR INFORMATION

 Required (by 1984)

 A study of at least 90 days' duration in rats using oxychlordane.

 Desirable

 1. Submission of the ongoing studies in Japan.

 2. Submission of monitoring data pertinent to the oxychlordane and

 trans-nonachlor levels found in humans.

 REFERENCES

 Barnett, J.R. and Dorough, H.W. Metabolism of chlordane in rats, J.

 1974 Agric. Food Chem. 22:612-619.

 Street, J.C. and Blau, S.E. Oxychlordane: accumulation in rat

 1972 adipose tissue on feeding chlordane isomers of technical

 chlordane. J. Agric. Food Chem. 20:395-397.

 Tashiro, S. and Matsumura, F. Metabolic routes of cis- and trans-

 1977 chlordane in rats. J. Agric. Food Chem. 25:872-880.

 1978 Metabolic routes of trans-nonachlor and related chlordane

 components in rat and man. Arch. Environm. Contam. Toxicol.

 7:113-127.

 See Also:

 [Toxicological Abbreviations](http://www.inchem.org/documents/eintro/eintro/abreviat.htm)

 [Chlordane (EHC 34, 1984)](http://www.inchem.org/documents/ehc/ehc/ehc34.htm)

 [Chlordane (HSG 13, 1988)](http://www.inchem.org/documents/hsg/hsg/hsg013.htm)

 [Chlordane (PDS)](http://www.inchem.org/documents/pds/pds/pest36_e.htm)

 [Chlordane (PIM 574)](http://www.inchem.org/documents/pims/chemical/pim574.htm)

 [Chlordane (FAO Meeting Report PL/1965/10/1)](http://www.inchem.org/documents/jmpr/jmpmono/v065pr09.htm)

 [Chlordane (FAO/PL:1967/M/11/1)](http://www.inchem.org/documents/jmpr/jmpmono/v067pr06.htm)

 [Chlordane (FAO/PL:1969/M/17/1)](http://www.inchem.org/documents/jmpr/jmpmono/v069pr07.htm)

 [Chlordane (AGP:1970/M/12/1)](http://www.inchem.org/documents/jmpr/jmpmono/v070pr03.htm)

 [Chlordane (WHO Pesticide Residues Series 2)](http://www.inchem.org/documents/jmpr/jmpmono/v072pr06.htm)

 [Chlordane (WHO Pesticide Residues Series 4)](http://www.inchem.org/documents/jmpr/jmpmono/v074pr09.htm)

 [Chlordane (Pesticide residues in food: 1977 evaluations)](http://www.inchem.org/documents/jmpr/jmpmono/v077pr13.htm)

 [Chlordane (Pesticide residues in food: 1984 evaluations)](http://www.inchem.org/documents/jmpr/jmpmono/v84pr12.htm)

 [Chlordane (Pesticide residues in food: 1986 evaluations Part II Toxicology)](http://www.inchem.org/documents/jmpr/jmpmono/v86pr03.htm)