

Dichlorvos: carcinogenic for man? Position paper

by

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Abstract

Following the technique of the systematic review, an analysis has been performed of the available literature concerning the carcinogenic activity of the insecticide dichlorvos in animal and man. Using the IARC criteria, the review concluded that dichlorvos should be classified as a "possible carcinogen for man" – IARC class 2b. The analysis also led to the calculation of long term accepted exposure limits, below which the cancer risk is considered negligible. These accepted exposure limits are 4×10^{-4} mg/kg bw/day for the oral route (or ADI) and 0,01 mg/m³ via inhalation. This classification and these accepted exposure limits differ from those applied at the European level and discussions will, therefore, follow with all interested stakeholders. Strict application of these exposure limits might have an impact on the registrations of dichlorvos as an insecticide for agricultural and non-agricultural uses in Belgium.

Key-words

Dichlorvos, carcinogen, environmental, man, review.

1. Background

The HGR-CSH, in collaboration with the Committee on Pesticides (Ministry of Agriculture, Belgium), started a program of reviewing pesticides already on the market in Belgium. This program runs in parallel with the Belgian participation in the European Monograph Program, reviewing new and existing pesticides for agricultural use. The first review addressed the possible carcinogenic effects of dichlorvos and the final report has recently been approved by the HGR-CSH. That final report (1) – written in Dutch and French – describes in detail the methodology and criteria applied, and the data, and the consecutive steps of the risk-assessment process and gives a full literature list. It is available on request from the HGR-CSH. This position paper summarises the findings and conclusions of the report.

Dichlorvos, with a broad use in and outside agriculture, is a cholinesterase inhibitor primarily producing neurotoxicity. It also has been challenged as a potential immunotoxic, teratogenic, and carcinogenic agent. The review focused on the alleged carcinogenicity.

2. Hazard identification: classification with regard to man

The hazard identification has been performed on the basis of a systematic literature review. The data bases Medline, Toxline and Poltox have been consulted from 1981 up to today. All available studies were, as much as possible, identified and submitted to a qualitative evaluation using a priori defined criteria and, on this basis, categorised as having a low, moderate or high risk of bias. These criteria followed those developed by the International Agency for Research on Cancer (IARC, WHO). The findings concerning the different tumour types were then evaluated on the basis of predetermined decision and conclusion criteria.

In a first step the possible relationship between exposure to dichlorvos and development of cancer in the experimental animal was evaluated. All studies retrieved, except two, were judged to present a high risk of bias. Two studies from the US National Toxicology Program (USNTP) received the qualification "moderate risk of bias". On the basis of these two studies, it was accepted that dichlorvos produced leukaemia in the

rat and neoplastic lesions in the forestomach in the mouse. These effects appeared after long time administration of non toxic doses of dichlorvos. The mechanism is not known, but might imply the formation of a reactive metabolite. A genotoxic effect, demonstrated *in vitro*, was not confirmed in *in vivo* tests. Together with IARC, it was concluded that there is sufficient evidence that dichlorvos is carcinogenic in the experimental animal.

In a second step, a similar evaluation took place of epidemiological studies in man. Only three studies were identified mentioning a possible carcinogenic effect of dichlorvos – leukaemia in children and adults, and brain tumours in children. All three studies, however, presented a high risk of bias which led to the conclusion that there is insufficient evidence that dichlorvos is carcinogenic in man.

On the basis of sufficient evidence in the animal, and insufficient evidence in man, and in the absence of arguments that none of the experimental tumours can be extrapolated to man, dichlorvos should be classified as a **possible carcinogen for man** (IARC classification 2b).

The Belgian HGR-CSH proposes to classify dichlorvos as a class 3 carcinogen within the European classification system.

3. Dose-effect relationship and a proposed Accepted Exposure Level (AEL long term)

Because of lack of proven genotoxic activity *in vivo*, it seems acceptable to propose a long term accepted exposure level (AEL long term) with regard to cancer. Till now Belgium accepted the oral AEL long term, or accepted daily intake (ADI), of 4×10^{-3} mg/kg bw/day, determined by the Joint Meeting on Pesticide Residues (JMPR FAO/WHO), based on erythrocyte cholinesterase inhibition in man, and related to neurotoxicity. However, taking into account a possible carcinogenic effect, a margin of exposure of at least 1,000 is requested between the oral AEL long term – or ADI – and the oral lowest observed adverse effect level (LOAEL) for cancer in the animal. At first glance this seems to be the case with regard to the dose of 4 mg/kg bw/day producing leukaemia in the rat. A lower dose, however, has not been studied and 4 mg/kg cannot be accepted as a LOAEL. An assessment factor of 10,000 is, therefore, applied giving an AEL long term of 4×10^{-4} mg/kg bw/day – which

at the same time should become the ADI to be applied in Belgium. This is 10 times lower than the value of 4×10^{-3} mg/kg bw/day, which remains the AEL short term with regard to neurotoxicity.

In case of severe, irreversible effects, whether or not a threshold applies, the United States Environmental Protection Agency (USEPA) calculates, on the basis of a linearized multistage model, a virtual safe dose (VSD*), representing the exposure level that would produce 1 excess cancer case on 1×10^6 persons exposed. For dichlorvos the VSD* has been estimated as 3.7×10^{-6} mg/kg bw/day. The AEL long term proposed here is 100 times higher than this VSD*, an order of difference which is not exceptional between the American and European approaches. Moreover, it remains impossible to determine which accepted exposure level most correctly reflects the real risk.

Although the USEPA estimates quite high the carcinogenic potency of oral administered dichlorvos, it finds the carcinogenic potency of inhaled dichlorvos negligible. In the absence of explicitly published arguments, the HGR-CSH prefers a straightforward approach and also proposes a long term inhalation AEL with regard to cancer. Therefore a factor of 10 – the same factor as for the oral accepted exposures – is applied to the short term inhalation AEL – with regard to cholinesterase inhibition and neurotoxicity – of 0.1 mg/m^3 . This gives a long term inhalation AEL of 0.01 mg/m^3 .

4. Exposure, risk and risk management

Dichlorvos residues are negative in the total Belgian diet. Assuming that real concentrations attain half of the determination limits, a daily ingestion of 2.9×10^{-4} mg/kg bw/day can be calculated, which remains below the AEL long term with regard to cancer. Nevertheless, this would not be the case if dichlorvos would be applied in all registered uses and up to accepted residue levels, the exposure would then be 6.1×10^{-3} mg/kg bw/day. Measures to limit the actually registered uses should therefore be taken. Air concentrations of dichlorvos, during the application of no-pest-strips at home and in the workplace (1 strip for 30-40 m³), vary between 0.05 and 0.1 mg/m^3 during the first weeks and decline towards 0.01 mg/m^3 at 3-4 months. This lies above the inhalation long term AEL with regard to cancer for people residing continuously, for a long time in these environments. The actual registrations should, therefore, be evaluated case by case before further authorisations should be delivered.

The Belgian HGR-CSH is aware that other countries came to different points of view. The Netherlands do not take carcinogenicity into account and only rely on cholinesterase inhibition, and neurotoxicity, to perform risk assessments. The USEPA proposes very stringent limitations of accepted uses of dichlorvos in agriculture and food industry, on the basis of its oral carcinogenic potential, and in the environment, on the basis of its neurotoxic effects after inhalation. Till now, the European authorities do not classify dichlorvos as a possible carcinogen and apply the short term AEL's mentioned above also for long term exposures. Since Belgium eventually should follow the European classification, discussions will have to take place with all interested stakeholders.

Samenvatting

Op basis van techniek van de systematische review, werd er een literatuuranalyse doorgevoerd naar de carcinogene werking van het insecticide dichloorvos bij het proefdier en bij de mens. Toepassen van de criteria van IARC op de resultaten van deze review, leidt tot een classificatie van dichloorvos als „mogelijk carcinogeen bij de mens” – IARC klas 2b. Op basis van de uitgevoerde analyse werden eveneens aanvaarde blootstellingsgrenzen berekend – voor lange termijn, repetitieve blootstelling – beneden dewelke het risico op ontwikkelen van kanker als verwaarloosbaar wordt geacht. Deze bedragen 4×10^{-4} mg/kg lg/dag voor de orale weg (of een ADI) en $0,01$ mg/m³ bij blootstelling via de ademhaling. Deze classificatie en aanvaarde blootstellingsgrenzen verschillen van deze die op Europees niveau worden gehanteerd. Dit brengt mee dat een discussie zal gestart worden met alle geïnteresseerde partijen. Behoud van deze blootstellingsgrenzen kan een impact hebben op de huidige registraties van dichloorvos voor gebruik binnen en buiten de landbouw in België.

Résumé

Une analyse de la littérature, portant sur l'effet cancérigène du dichlorvos chez l'animal et chez l'homme, a été réalisée à l'aide de la technique de la revue systématique. En appliquant les critères de l'IARC, la revue a permis de conclure que le dichlorvos devrait être classé comme «cancérigène possible pour l'homme» – IARC classe 2b. Sur base de cette analyse, des niveaux d'exposition acceptables – en cas d'exposition répétée à long terme – ont été calculés. Ils s'élèvent à 4×10^{-4} mg/kg pc/jour pour la voie orale (ou DJA) et à $0,01$ mg/m³ pour la voie inhalatoire. Cette classification ainsi que les niveaux d'exposition acceptables sont différents de ceux appliqués par l'Europe et des discussions devaient suivre avec toutes les parties concernées. Le maintien de ces propositions pourrait avoir un impact sur les enregistrements du dichlorvos pour usage agricole et non-agricole en Belgique.

Reference

1. VAN MAELE-FABRY G, WILLEMS J L. Dichloorvos: carcinogeen voor de mens? Een risico-analyse op basis van een systematisch literatuuroverzicht. Rapport n° 6953. Hoge Gezondheidsraad, Ministerie van Sociale Zaken, Volksgezondheid en Leefmilieu, en Erkenningscomité voor Gewasbestrijdingsmiddelen, Ministerie van Middenstand en Landbouw, Brussel, België, oktober 1997.