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Review

Review of developmental toxicity of nitrophenolic herbicide dinoseb, 2-*sec*-butyl-4,6-dinitrophenol

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ABSTRACT

The present review paper summarizes the data available in the literature concerning prenatal exposure to dinoseb (2-*sec*-butyl-4,6-dinitrophenol; CAS No. 88-85-7), evaluating reported developmental toxicity in experimental animals. In particular, we have focused on the variable factors in the manifestation of the developmental toxicity of dinoseb. In this review, we showed that developmental toxicity of dinoseb was remarkably different between animal species used in experiments. Teratogenicity was detected in rats fed a diet containing dinoseb, in mice given dinoseb by gavage, intraperitoneally or subcutaneously, and in rabbits given dinoseb by gavage or dermally. Teratogenicity in rats given dinoseb by gavage was influenced by the dietary composition used in the experiments. We postulated that evaluation of the developmental toxicity after exposure by anticipated routes of human exposure would be important for risk assessment in humans.

Contents

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1. Introduction

Dinoseb, 2-*sec*-butyl-4,6-dinitrophenol (CAS No. 88-85-7), is used as a nitrophenolic herbicide in soybeans, vegetables, fruits, nuts, citrus and other field crops for the selective control of grass and broadleaf weeds. It is also used as an insecticide in grapes and as a seed crop drying agent [1]. Dinoseb is a high volume chemical with production or importation exceeding 1000 tonnes per year in Organisation for Economic Co-operation and Development (OECD) member countries and widely used [2,3]. The volume of dinoseb imported into Japan is estimated to be 110 tonnes from April 2005 to March 2006 [4].

Dinoseb is a dark reddish-brown solid or dark orange viscous liquid, depending on the temperature (melting point 32–42 °C) [5]. Dinoseb is well absorbed from the gastrointestinal tract by the oral route in mice and can pass through the placenta into the fetus of mice [6]. A dermal study showed that in 6 h young and adult female rats absorbed about 44% of the dose, while at 120 h 75.9% was absorbed in young and 92.5% in adults [7]. Dinoseb shows relatively strong acute toxicity with the oral LD_{50} of 5–50 mg/kg in female rats [8], the intraperitoneal LD_{50} of 14.1–22.5 mg/kg in mice [9] and the dermal LD_{50} of 40 mg/kg in rabbits [9]. The inhalation LC_{50} is 33–290 mg/m^3 for 4-h exposure in rats [9]. The basic mechanism of toxicity is thought to be stimulation of oxidative metabolism in cell mitochondria by the uncoupling of oxidative phosphorylation [10]. Toxicity of dinoseb is enhanced by physical activity and high ambient temperature such as in an outdoor agricultural environment [10,11]. Early symptoms of dinoseb exposure include hyperthermia, sweating, headache and confusion. Severe exposure may result in restlessness, seizures, coma and death [10–12].

Exposure to dinoseb may occur by direct contact, ingestion and inhalation for users and producers, but potential indirect exposure to dinoseb via the environment is also anticipated. Dinoseb is not strongly adsorbed on most agricultural soils. Microbial breakdown of dinoseb is demonstrated on soils, but dinoseb persists for about 2–4 weeks after application. Dinoseb was reported to be detected in water supplies in Canada and the US [13]. The US FDA examined 70 food items in 1985 and 1986 for dinoseb residues. Although no residues were detected in most of crops treated with dinoseb, a positive result was obtained in one cotton meal sample [13].

Dinoseb has an interesting history as a developmental toxicant. Dinoseb was approved for sale in the US in 1948 [1] and was one of the chemicals permitted on the market on the basis of safety tests conducted by Industrial Bio-Test Laboratory, a concern later found to have submitted many flawed and even fraudulent reports on its procedures and results [14]. In a later study, dinoseb showed teratogenicity in mice when administrated intraperitoneally, but not by gavage administration [15]. In a subsequent study, gavage dosing of dinoseb induced both maternal toxicity and developmental toxicity without teratogenic effects, but dietary administered dinoseb was reported to be teratogenic in rats [16]. In an unpublished study conducted in rabbits, neural malformations without maternal toxicity were observed after dermal application of dinoseb [13,17]. Dinoseb as a pesticide was banned in the US in 1986 and the EU in 1991, based on the potential risk of birth defects and other adverse health effects in humans [1,18].

We previously reported the results of a combined repeated dose toxicity study with reproduction/developmental toxicity screening test, in which Crj:CD(SD)IGS rats were dosed with dinoseb by gavage at 0, 0.78, 2.33 or 7.0 mg/kg bw/day. At the highest dose, the numbers of dams that delivered their pups and of dams with live pups at delivery were reduced, with only one dam delivering live pups at this dose. Developmental toxicity of dinoseb was not completely elucidated in our previous study because this screening test used a relatively small number of animals and investigated a limited number of endpoints. Only an external examination was performed in live newborns. No increased incidences of pups with malformations were noted [19]. Although our study provided limited information on the teratogenicity of dinoseb, our findings supported the results of a study of Giavini et al. [16] that gavage dosing of dinoseb was not teratogenic in rats. However, the same authors also showed that dietary administered dinoseb produced fetal malformations in rats [16]. These results indicate that the manifestation of developmental toxicity by dinoseb depends on the mode of administration in rats. However, these relationships are much more complicated than originally thought, and the composition of the diet has been shown to influence the ability of dinoseb to induce microphthalmia in pups [20].

Developmentally toxic effects of chemicals are influenced by the susceptibility of animal species and strains, the developmental stages of offspring and administration doses [21,22]. Teratogenicity is governed by dose–effect relations, but there are many variable factors such as the duration of chemical treatment [23], frequency of dosing [24], routes or modes of administration [25–28], the vehicle/suspending agent [29] or a combination of chemicals [30]. Dinoseb is one of the chemicals which show different developmental toxicity according to these variable factors. The present review paper summarizes the data available in the literature concerning prenatal exposure to dinoseb, evaluating reported developmental toxicity in experimental animals with particular focus on the variable factors in the manifestation of the developmental toxicity of dinoseb.

2. Developmental toxicity of dinoseb

The relationship between maternal toxicity and developmental toxicity has been expressed in several ways in an attempt to clarify the toxicity [31,32], however the relevance of these expressions has not been established. This paper focuses on the developmental toxicity of dinoseb, but both maternal and fetal toxicities are summarized to show their relationship with respect to dinoseb. It should be noted that the term dinoseb has been used in the literature to refer to several related chemicals based on 2-*sec*-butyl-4,6-dinitrophenol (CAS: 88-85-7). In this paper, dinoseb refers to the parent molecule only.

2.1. Developmental toxicity in rats

Table 1 shows the results of developmental toxicity studies of dinoseb in rats. There are oral (gavage and diet) and i.p. administration studies. The data were reviewed by routes of administration, in order of the most likely route of human intake. Only statistically significant effects are summarized unless noted otherwise.

2.1.1. Gavage studies in rats

In our previous study, male Crj:CD(SD)IGS rats were dosed dinoseb by gavage for a total of 42 days beginning 14 days before mating and females were dosed for a total of 44–48 days beginning 14 days before mating to day 6 of lactation at 0 (vehicle corn oil), 0.78, 2.33 or 7.0 mg/kg bw/day [19]. As for the developmental parameters, no changes attributable to the chemical were noted in the 0.78 and 2.33 mg/kg bw/day dose groups. Eight of twelve females died and two animals were moribund during late pregnancy at 7.0 mg/kg bw/day. Developmental toxicity of dinoseb was not completely estimated because only one dam with live pups was obtained at the highest dose and newborn rats were examined only externally. No increased incidence of pups with an external malformation was noted in the dinoseb-treated groups.

In teratology studies in rats, skeletal variation, delayed ossification and/or decreased fetal body weight was commonly observed