Overview of the toxic effects of 2,4-D

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Introduction

2,4-D (2,4-dichlorophenoxyacetic acid) is a common herbicide used around the home and garden, on golf courses, ball fields, parks, in agriculture and forestry. Agricultural uses include pasture land, wheat, corn, soybeans, barley, rice, oats, and sugar cane. In Canada, there are currently 205 registered products containing 2,4-D.[1]

Despite industry efforts claiming the safety of this chemical, there is a large body of evidence indicating major health effects, from cancer to immunosuppression, reproductive damage to neurotoxicity. Environmental contamination, particularly in wetlands has also been demonstrated, in direction infringement of the *Fisheries Act* R.S., c. F-14, s. 36.

This paper aims to provide an overview of the scientific body of evidence demonstrating the toxic effects of 2,4-D.

Health Effects

In mammals, 2,4-D disrupts energy production (Zychlinkski & Zolnierowicz, 1990), depleting the body of its primary energy molecule, ATP (adenosine triphosphate) (Palmiera et al., 1994). 2,4-D has been shown to cause cellular mutations which can lead to cancer. This mutagen contains dioxins, a group of chemicals known to be hazardous to human health and to the environment (Littorin, 1994).

Numerous epidemiological studies have linked 2,4-D to non-Hodgkin's lymphoma (NHL) among farmers (Zahm, 1997; Fontana et al, 1998, Zahm & Blair, 1992, Morrison et al. 1992). Multi-center studies in Canada and in Sweden of members of the general public found a 30-50% higher odds of 2,4-D exposure among people with NHL(McDuffie et al. 2001, Hardell & Eriksson, 1999, Sterling & Arundel, 1986).

The teratogenic, neurotoxic, immunosuppressive, cytotoxic and hepatoxic effects of 2,4-D have been well documented (Blakely et al., 1989; Sulik et al, 1998; Barnekow et al., 2000; Rosso et al., 2000; Venkov et al., 2000; Charles et al., 2001; Madrigal-Bujadar et al., 2001; Osaki et al., 2001; Tuschl & Schwab, 2003).

Other researchers publishing in the open scientific literature have reported oxidant effects of 2,4-D, indicating the potential for cytotoxicity or genotoxicity. For example, Bukowska (2003) reported that treatment of human erythrocytes in vitro with 2,4-D at
250 and 500 ppm resulted in decreased levels of reduced glutathione, decreased activity of superoxide dismutase, and increased levels of glutathione peroxidase.56 These significant changes in antioxidant enzyme activities and evidence of oxidative stress indicate that 2,4-D should be taken seriously as a cytotoxic and potentially genotoxic agent.

[1] PMRA, Electronic Labels: Search and Evaluation (ELSE). http://eddenet.pmra-arla.gc.ca/4.0/4.01.asp. Accessed January 13, 2005.

2,4-D causes significant suppression of thyroid hormone levels in ewes dosed with this chemical (Rawlings et al., 1998). Similar findings have been reported in rodents, with suppression of thyroid hormone levels, increases in thyroid gland weight, and decreases in weight of the ovaries and testes (Charles et al., 1996). The increases in thyroid gland weight are consistent with the suppression of thyroid hormones, since the gland generally hypertrophies in an attempt to compensate for insufficient circulating levels of thyroid hormones. Thyroid hormone is known to play a critical role in the development of the brain. Slight thyroid suppression has been shown to adversely affect neurological development in the fetus, resulting in lasting effects on child learning and behavior (Haddow et al., 1999).

2,4-D causes slight decreases in testosterone release and significant increases in estrogen release from testicular cells (Liu et al., 1996). In rodents, this chemical also increases levels of the hormones progesterone and prolactin, and causes abnormalities in the estrus cycle (Duffard et al., 1995). Male farm sprayers exposed to 2,4-D had lower sperm counts and more spermatic abnormalities compared to men who were not exposed to this chemical (Lerda & Rizzi, 1991). In Minnesota, higher rates of birth defects have been observed in areas of the state with the highest use of 2,4-D and other herbicides of the same class. This increase in birth defects was most pronounced among infants who were conceived in the spring, the time of greatest herbicide use (Garry et al, 1996).

2,4-D also interferes with the neurotransmitters serotonin and dopamine. In young organisms, exposure to 2,4-D results in delays in brain development and abnormal behavior patterns, including apathy, decreased social interactions, repetitive movements, tremor, and immobility (Evangelista de Duffard et al, 1995). Females are more severely affected than males. Rodent studies have revealed a region-specific neurotoxic effect on the basal ganglia of the brain, resulting in an array of effects on critical neurotransmitters and adverse effects on behavior (Bortolozzi et al., 2001).

A peer-reviewed, developmental neurotoxicity study demonstrated severe neurotoxicity in young rats exposed to 2,4-D from postnatal days 12 to 25 at doses of 70 mg/kg/day. These pups showed decreases in GM1 level, diminution in myelin deposition and alterations in all behavioral tests at all doses (Rosso et al, 2000). This herbicide specifically appears to impair normal deposition of myelin in the developing brain (Duffard et al., 1996). The neurotoxic and anti thyroid effects of 2,4-D make it highly likely that fetuses, infants, and children will be more susceptible to long-term adverse health effects from exposure to this chemical although they may appear normal at birth.

Young animals can also be exposed to 2,4-D through maternal milk. Recent research has revealed that 2,4-D is excreted in breast milk, thereby resulting in potentially significant exposures to the nursling. The researchers detected 2,4-D residues in stomach content, blood, brain and kidney of 4-day-old neonates fed by 2,4-D exposed mothers (Sturtz et al., 2000). When maternal exposures stopped, the chemical continued to be excreted in maternal milk for a week. Thus, postnatal exposures to this chemical during the critical period for development of the infant brain are of serious scientific concern.

Agricultural Workers

Workers applying chlorinated phenoxy herbicides frequently have nervous system disorders, are exposed to a higher risk of soft tissue sarcoma, and show symptoms of hormonal and internal organ irregularities. (Kogevinas, 1995; National Research Council of Canada, 1983). A study of farmers in Alberta, Saskatchewan and Manitoba linked use of 2,4-D to an increased incidence of prostate cancer (Morrison et al, 1993). An Italian study by Miligi et al (2003) showed that an associated between NHL and 2,4-D in women. Hardell & Eriksson (1999) also demonstrated the link between exposure of 2,4-D and NHL. Their research identified a latency period between exposure and diagnosis of NHL, which could be a reason why there is conflicting research on the issue.

The risk to farm workers is pronounced because of the use of sunscreen. Agricultural workers are encouraged to wear sunscreen to protect their skin from UV-related skin cancer. However, studies have shown that the use of sunscreen increases the rates of penetration of 2,4-D. This has also been shown for the insect repellant DEET (Windheuser et al, 1982). One study demonstrated 14% palmar absorption of 2,4-D after skin application of DEET (Moody et al., 1992). Studies have also shown that most commercial sunscreen formulations enhance the penetration of 2,4-D through hairless mouse skin. One such study found that sunscreens increase penetration of 2,4-D by over 60 percent, from an average penetration of 54.9% to 86.9% (Pont et al., 2004). Another study found more than a doubling in absorption from an average penetration of 39.1% for the no sunscreen control to 81.0% for mice pre-treated with Neutrogena Oil Free Sunscreen (Brand et al., 2002). These results in the mouse appear also to be relevant to humans (Pont et al., 2004). In addition to penetration enhancement due to commonly-applied topical products, one study in rodents has demonstrated a 2.2-fold enhancement in dermal absorption after regular ethanol consumption over a 6 to 8 week period (Brand et al., 2004).

This scenario was not examined by the USEPA in its evaluation of 2,4-D. However, it is a reality of agricultural workers and must be examined. It is important to note that the reevaluation document produced by the USEPA also did not use any form of occlusion over the applied 2,4-D. Therefore the effect of 2,4-D that soaks clothing, or is subsequently covered by clothing or gloves would not be adequately assessed. Existing research on other chemicals indicates that occlusion is known to significantly enhance skin absorption of dermally-applied materials (Riviere et al., 2003). As much of the reevaluation process is harmonized between countries, this could be the case in the PMRA's evaluation as well, and it is crucial that these issues are not overlooked.

Children living in agricultural communities are heavily exposed to pesticides, whether or not they work in the fields (Lu et al., 2000; Fenske, 1997). Farm children come in contact with pesticides through residues from their parents' clothing, dust tracked into their homes, contaminated soil in areas where they play, food eaten directly from the fields, drift from aerial spraying, contaminated well water, and breast milk. Furthermore, farm children often accompany their parents to work in the fields, raising their pesticide exposures even higher.

Household Use

Perhaps the most documented effect of household use of 2,4-D is its association of exposure with cancer in canines. Particularly the study by Hayes et al (1991) has implicated 2,4-D with an odds ratio of 1.32 linking malignant lymphoma and 2,4-D exposure. This study was reviewed by a number of industry sponsored initiatives, and the authors of the original study released their response in 1995 which demonstrated that their scientific methods were sound and that the study had indeed demonstrated this increased risk of malignant lymphoma.

These risks are elevated when one discovers that homeowners using 2,4-D are likely to track the pesticide into their home where it is expected to persist for up to one year (Nishioka et al. 1999). This persistence is seen after a single turf application at a concentration of approximately 0.5µg/g (Nishioka, 1996).

Surrounding and in the home is also where most exposure to children will occur. The levels of exposure to small children are pronounced for dermal exposure and have not been studied for dermal penetration of 2,4-D. We do know that the skin surface area of an infant per unit of body weight is double that of an adult and that all studies which have investigated dermal exposures to pesticides in children have found that this is a major route of exposure. Also, hands moist with saliva collect about 100 times more pesticide residue than dry hands, and children's hands are much more likely to be moist. A study of rats perinatal exposure of 2,4-D did not express effects of exposure until adulthood (Garcia et al., 2001). This demonstrates the insidious nature of the compound, and the enormous threat it poses to children.

Given that the "PMRA considers the unique biological characteristics and exposure patterns of children in its risk assessments," we trust that the studies such as those by Nishioka et al. (1996, 1999) and that of Lu et al., (2000) and Fenske (2003) will be included in the assessment process.

Environmental Effects

2,4-D is a moderately persistent chemical with a half-life between 20 and 200 days. Unfortunately, the herbicide does not affect target weeds alone. It can cause low growth rates, reproductive problems, changes in appearance or behaviour, or death in non-target species.

Due to the widespread use of 2,4-D on agricultural land, the environmental effects of this use are emerging in scientific studies. Donald et al. (1999) found agricultural pesticides in wetlands, and 2,4-D was the most commonly detected pesticide. Although its concentrations in wetlands exceeded the guidelines in less than 1% of the wetlands, these guidelines are created in isolation, not accounting for the synergistic effects of pesticides. For example, Forsyth et al. (1997) found synergistic effects of picloram and 2,4-D on macrophytes. The chemical will also be carried by run-off into the local river systems. This has been demonstrated here in Ottawa, where a city report on pesticide monitoring of local tributaries showed that 60% of all samples contaminated with phenoxy herbicides. Due to the numerous acceptable uses of 2,4-D, it is likely that the majority of watersheds in rural and urban Canada are contaminated.

Wildlife

2,4-D has been shown to have negative impacts on a number of groups of animals. In birds, 2,4-D exposure reduced hatching success and caused birth defects (Duffard et al., 1981). It is also indirectly affects birds by destroying their habitat and food source. The toxicity of 2,4-D to fish is variable, with the ester form of 2,4-D expressing greater toxicity than other forms. 2,4-D has also been demonstrated to bio-accumulate in fish (Wang et al., 1994). A product of the breakdown process of 2,4-D is 2,4-dicholorophenol. This chemical is extremely toxic to earthworms, 15 times more toxic than 2,4-D itself (Roberts & Dorough, 1984). Beneficial insects have reduced fecundity when exposed to 2,4-D.

The use of 2,4-D has had drastic affects for both agricultural and wildlife animals including, the deaths of cattle and horses grazing of treated plants, and the destruction of plant food sources of moose, gopher and voles.

Conclusion

Given the effects outlined above, Sierra Club of Canada insists that use of this chemical discontinued. Perhaps the most promising outcoming of this proposed action would be a decline in cancer, which we have seen in Sweden after the banning of phenoxy herbicides (Hardell and Eriksson, 2003). Cancer prevention could start with this step.

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