Increased Cancer Burden Among Pesticide Applicators and Others Due to Pesticide Exposure

We agree with the introduction to the article by Alavanja et al that research should identify pesticides that are potential human carcinogens and that policies should be in place to reduce human exposure to them.[1] However, we respectfully disagree that currently registered pesticides have resulted in excess cancer risk to those who are highly exposed. The review of cancer burden by Alavanja et al concludes that "pesticides do cause cancer."[1] However, the authors' description of their analysis indicates that the review is not particularly exhaustive in either depth or scope. They assert that uses need to be curtailed absent clear evidence of harm and in the face of clear value and societal benefits. However, it should be emphasized that uses for 20 of the pesticides discussed in Table 5 in their article have in fact been "curtailed" and are no longer registered by the US Environmental Protection Agency (EPA). As representatives of manufacturers of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), we would like to provide additional information to the review by Alavanja et al, because it applies to a currently registered pesticide for which exhaustive laboratory, animal, and human research has not supported evidence that it causes cancer.

EPA Assessments

The EPA and other regulatory agencies conduct an exhaustive series of risk assessments to evaluate the human health and environmental impacts of a pesticide prior to its registration. The EPA subsequently requires and evaluates new data periodically. The general standard for pesticide registration is that there are no unreasonable adverse effects to humans or the environment when the pesticide is used according to label directions. The regulatory standard with respect to the safety of pesticide residues in food is reasonable certainty of no harm, taking into account the aggregate of dietary exposure and other exposures for which there is reliable information. Hazard characterizations and risk assessments conducted by the EPA thoroughly evaluate the potential health effects of the product that may occur from different types of exposure to users of the product (applicators and handlers) or to bystanders. The EPA evaluates various sensitive subpopulations to these exposures as a normal process. For example, toxicology testing includes a wide array of doses, routes of exposure, durations of exposure, and critical life stages including development and reproduction, as well as bodily metabolism and excretion. The EPA integrates their analyses to compare toxicity with environmental exposure concentrations and then uses this information to make their "no unreasonable adverse effects" determination. The aggregate of dietary and incidental exposures are also considered to make a finding of reasonable certainty of no harm in comparison with potentially sensitive subpopulations, in addition to the general population.

The EPA's current Registration Review program functionally continues the reevaluation process conducted under reregistration by requiring currently registered products to be reassessed to update older studies or to illuminate new areas of science. Additional studies are required from time to time, such as the Endocrine Disruptor Screening Program assay test orders. It is widely recognized that the EPA is a leading world authority on pesticide toxicology, exposure, and epidemiology.

The EPA's final risk management decision integrates the law, the data, and the experienced judgments of many experts into registration of protective label directions and precautions.

Comments

The review by Alavanja et al[1] suggests that pesticide applicators are at an increased risk of cancer. However, a recent study by Koutros et al of more than 50,000 pesticide applicators and their spouses in Iowa and North Carolina reported a 7% to 18% deficit of cancer.[2] These investigators observed that this finding was consistent with previous observations among farmers. Another comprehensive review of cancer among pesticide manufacturers and applicators by Burns concluded that "there is little indication of increased cancer risk among pesticide manufacturers or sprayers."[3] With respect to 2,4-D, the review by Alavanja et al highlights that 2,4-D is the most commonly used herbicide in both the home and garden market (Table 2 in their article) and the commercial market (Table 3 in their article).[1] However, exposure studies have detected little more than trace levels of 2,4-D in the urine of the general population[4] and the children of applicators.[5] Evaluations of these and other exposure studies have concluded that actual exposures are well below the conservative assumptions made by policy makers for the registration process.[6]

As noted above, the review by Alavanja et al selectively provides examples of studies showing links between a pesticide and a cancer.[1] The single National Cancer Institute (NCI) epidemiological study from Kansas that was selected as evidence of an association between 2,4-D and non-Hodgkin lymphoma in Table 5 in the article by Alavanja et al[1] did not even evaluate 2,4-D per se, but only asked participants about herbicides.[7] Furthermore, De Roos et al concluded, "[t]his analysis of the pooled data found no association with having ever used 2,4-D," referring to the NCI's studies in Kansas and Nebraska.[8] Although some

studies have reported an association between a cancer and the use of 2,4-D, independent investigations with more robust methods did not validate these findings.[9]

Several published reviews of 2,4-D and cancer have concluded that 2,4-D does not cause cancer in animals or humans.[9-11] In addition, it is important to understand that the International Agency of Research on Cancer has never made 2,4-D a priority to evaluate. Their 1987 classification of phenoxy herbicides concluded there was "inadequate" data to classify 2,4-D for carcinogenicity in animals or for genetic activity in short-term tests.[12]

Mechanisms of Toxicity

With little exception, we agree with the authors' assertion that pesticides "have diverse chemical structures and exhibit a variety of biological modes of action in both target and nontarget organisms."[1] However, this statement is perplexing when considered alongside their later conclusion that, "Cancer risk does not seem to be limited to one functional class of pesticides…or to one chemical class…"[1] The acknowledged diversity of chemical compounds and modes of action represented in pesticides appear more likely to support the position that pesticides are not all somehow alike in posing a cancer risk. From a toxicological point of view, the answer seems to result from overinterpretation of nascent molecular toxicology data that include exposures that are unrepresentative of actual human exposures. Currently used pesticides have been tested in more ways than virtually any other set of substances. A large array of species, exposures, doses, and life stages are included such that we have an excellent understanding of what is and is not biologically plausible for these compounds. Hypothesizing alternative mechanisms of cancer causation for these well-studied compounds relying on a minimal number of exploratory molecular studies appears blatantly speculative in comparison with the rich animal toxicology database. For example, 2,4-D has been evaluated in multiple lifetime animal bioassays that have demonstrated that the herbicide is not a carcinogen. Other studies regarding genetic toxicology and toxicokinetics are also contraindications for carcinogenicity. Reaching for new pathways to toxicity needs to seriously consider the substantial mass of current understanding and justify a departure from well-established principles.

Societal Value

Crop protection products provide significant, measurable benefits to society. The CropLife Foundation states that crop protection technology, which includes all pesticides, herbicides, insecticides, and fungicides, as well as biotechnology products, helps to control the thousands of weed species, harmful insects, and numerous plant diseases that afflict crops. Without these important crop protection and pest control technologies, US food production would decline, many fruits and vegetables would be in short supply, and the price of food would rise.[13]

There are other positive aspects of crop protection and public health pesticides that are often taken for granted. The responsible and safe use of pesticides provides human health benefits by controlling household pests such as termites, roaches, ants, rats, and mosquitoes, which carry and can transmit deadly diseases. Herbicides are used to control vegetation that clogs waterways or threatens to obstruct highway, utility, and railroad rights of way, thus providing for safe transportation. Maintaining electrical right of way ensures that critical power flow continues to be available for medical care, computer networks, refrigeration of our food supply, and countless other public safety applications.

Conclusions

2,4-D herbicide plays a valuable role in protecting and enhancing lawns, gardens, public parks, playing fields, lakes, and ponds for public enjoyment. The National Agricultural Pesticide Impact Assessment Program[14] conducted a biological and economic assessment of the uses of 2,4-D and phenoxy herbicides in the United States. They found that "The phenoxy herbicides have greatly aided humankind by increasing worldwide food production and reducing the drudgery of weed management while generating an outstanding record of human and environmental safety." The study concluded that the general public would be impacted with "net societal losses from not using phenoxy herbicides of $2.559 billion annually."

The regulatory guidelines identify the risks posed by pesticide use and weigh these against the benefits from such use. Indeed, Kushi et al appreciated the clear benefits, stating that, "overwhelming scientific evidence supports the overall health benefits and cancer-protective effects of eating a diet rich in fruits and vegetables." With regard to the miniscule risk of pesticide residue on the produce, the study states, "At present there is no evidence that residues of pesticides and herbicides at the low doses found in foods increase the risk of cancer."[15]

Recently published reports from the American Cancer Society demonstrate that the death rate from cancer in the United States has fallen 20% from its peak in 1991. The American Cancer Society estimates that 60% to 70% of cancer deaths in 2012 will be related to overweight or obesity, physical inactivity, poor nutrition, and smoking.[15] Eating fruits and vegetables is a clear benefit to human health. Ensuring an abundant supply at reasonable cost will extend the availability to those most in need.

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