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2,4-D crops: An unsustainable techno-fix for the failure of herbicide-tolerant GM crops

By **Antje Lorch**

Why old herbicides are returning

"Less herbicides, less toxic herbicides, protecting the environment and farm workers from impacts of agro-chemicals, stopping soil erosion." Those were the slogans to promote the first generation of genetically modified (GM) crops, engineered to be tolerant to herbicides. This envisioned golden future was all too brief, however, and is in fact already past. After the introduction of Monsanto's Roundup Ready crops – tolerant to the herbicide glyphosate – in the USA and a few other countries, weeds soon became resistant to glyphosate and have posed increasing problems to farmers. Instead of stepping back from herbicide-tolerant crops, the GM industry is now stepping up the development of new GM crops that are tolerant to multiple – and often older, more toxic – herbicides. Among them: GM crops engineered to be tolerant to 2,4-dichlorophenoxyacetic acid (2,4-D).

A short history of herbicide-tolerant GM crops

In their 2013 report "The rise of superweeds – and what to do about it", the Union of Concerned Scientists (USA) described in detail the main failings of herbicide-tolerant crops, in particular Roundup Ready crops.

> For several years, Monsanto's system did seem to work as intended. But after a temporary reduction, herbicide use on US farms has increased dramatically because of growing weed resistance to Roundup; given that other chemical agents also have to be employed, overall pesticide use is an estimated 404 million pounds greater than if Roundup Ready crops had not been planted (Benbrook 2012). Farmers' costs are rising, moreover, and the short-term benefit of reduced soil erosion is being reversed because farmers facing resistant weeds often find they need to till again (Price et al. 2011)…

Address: 131 Jalan Macalister, 10400 Penang, MALAYSIA **Tel**: 60-4-2266728/2266159 **Fax**: 60-4-2264505
E-mail: twn@twnetwork.org **Website**: www.twn.my

> At present, more than 15 years after farmers began growing Roundup Ready crops, the most widely grown US commodity crops are glyphosate-resistant, and farmers douse at least 150 million acres with the herbicide every year (USDA 2013; USDA ERS 2013). As a result of this heavy use, weeds showing resistance to glyphosate began appearing in fields more than a decade ago (Van Gessel 2001) – first as occasional interlopers but eventually as large infestations. (Gurian-Sherman & Mellon 2013:2)

These weeds are not just a menace, but a serious problem. Glyphosate-resistant Palmer pigweed (*Amaranthus palmeri*), for example, was first discovered on a farm in the USA in 2005. It can grow up to 2.5 metres tall and produce 600,000 seeds, and its woody stem can wreck farm equipment that tries to uproot it. Less then 10 years later, in 2013, it was found on 92% of all cotton and maize fields in the South-East of the USA (Fraser 2013 in Gurian-Sherman & Mellon 2013).

The development of weed resistance is clearly attributed to over-reliance on glyphosate and a reduction in the diversity of weed management practices adopted by farmers, following the widespread adoption of glyphosate-tolerant GM crops.

> There is broad agreement that the spread of these resistant plants has its roots in the widespread adoption of crops engineered to be resistant to glyphosate. (*Nature* Editorial 2014)

Herbicide-resistant weeds are the reason for new GM crops

The first herbicide-tolerant GM crops – with tolerance against glyphosate or glufosinate – were developed to change the use of herbicides. The new GM crops developed now are meant to fight the herbicide-resistant weeds that the first GM crops created.

Already in 2005, Monsanto advised farmers to apply three additional herbicides to its Roundup Ready cotton (Monsanto 2005) when resistant weeds were discovered. This has now resulted in GM crops tolerant to these and other herbicides.

A 2014 joint paper by German, Swiss and Austrian state environmental agencies on "Agronomic and environmental aspects of the cultivation of genetically modified herbicide-resistant plants" describes the fundamental problem with this approach.

> Since 1999, a number of weed species have become more troublesome first in the US Cotton Belt, later also in soy and maize growing regions, e.g. the abundance of glyphosate resistant horseweed (*Conyza canadensis*), which is well-adapted to no-till systems, increased tremendously (Heap 2008, 2012). Tank mixtures (Clarity [dicamba] or Kixor [saflufenacil] and glyphosate), autumn burndown herbicides such as Valour [imazethapyr plus pendimethalin], or the additional use of pre-emergence herbicides (e.g. 2,4-D, Clarity) were recommended against horseweed (Freudling 2004, Deterling 2003, Waggoner et al. 2011).
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> However, weeds resistant to herbicides other than glyphosate infest millions of hectares already. Of the 393 listed herbicide resistant weed populations 127 are resistant to ALS inhibitors, 42 to ACCase inhibitors, and 30 to synthetic auxins such as 2,4-D (Heap 2012).
>
> Quite a few of them exhibit multiple resistance, e.g. including to glyphosate. For this reason, stacking of herbicide resistance traits in transgenic crops is unlikely to reduce selection pressure on weeds and to lower herbicide amounts applied. (Tappeser et al. 2014:19)

A detailed and continuously updated list of weed resistance is available at the website weedscience.org. At the time of writing, this list contains more than 240 cases of weed resistance to glyphosate. It also lists 28 instances of weed resistance to 2,4-D in 11 countries, among which are the USA, Canada, Australia and Malaysia. Some of these weeds are resistant to several herbicides. Already in 2010, wild radish (*Raphanus raphanistrum*) was discovered in Australia with resistance to eight different herbicides, including 2,4-D and glyphosate (weedscience.org).

While the GM industry is developing multi-herbicide-tolerant GM crops – supposedly to give farmers an advantage over herbicide-resistant weeds – many of the weeds are already resistant to many of the herbicides that will be used with them.

What is 2,4-D?

2,4-dichlorophenoxyacetic acid (2,4-D) is a synthetic plant hormone (auxin) that is used as an active ingredient in widely used systemic herbicides against broadleaf weeds. Plants absorb it through their leaves, from where it spreads through the plant tissue to other, unsprayed parts. It leads to uncontrolled and unsustainable growth, stem curl-over, leaf withering, and death of the plant. Commercial herbicides use 2,4-D as an active ingredient in different forms (amine salts or esters). Because 2,4-D affects broadleaf plants but not other plants, it is currently used in the cultivation of annual and perennial cereal crops, sugar cane, pasture, industrial areas and lawns, home gardens and golf courses (African Centre for Biosafety et al. 2012).

The Union of Concerned Scientists concluded that 2,4-D herbicides "are also highly prone to drifting on the wind and to volatilizing – dispersing into the air after application – so that they may settle far from where they are sprayed. And they are highly toxic to broadleaf plants – which include many of the most common fruit and vegetable crops" (Gurian-Sherman & Mellon 2013:4).

Current use with GM crops

2,4-D and other older herbicides are already now used as additional chemicals to fight herbicide-tolerant weeds, but their application is restricted due to their damaging effects on broadleaf crops.

> In parts of the growing areas for oilseed rape, soybean and cotton, it has become necessary to add 2,4-D and/or other herbicides to glyphosate or glufosinate based weed control programs (Benbrook 2009). This so called "double knockdown" approach has also been advocated as a tool to address development of weed resistance (Weersink et al. 2005). With the advent of stacked herbicide resistance traits in transgenic crops (APHIS 2012), "old" herbicides such as 2,4-D, dicamba, ACCase- and ALS-inhibitors are coming back. (Tappeser et al. 2014:39)

Effects on human health

2,4-D is part of a "chemical class known as phenoxy herbicides, which studies have associated with increased rates of certain diseases, including non-Hodgkin's lymphoma, among farmers and farm workers (Blair and Zahm 1995)" (Gurian-Sherman & Mellon 2013). Studies linking 2,4-D with non-Hodgkin's lymphoma have been published as early as 1981 (Hardell et al. 1981), while "other herbicides of its class have been independently associated with deadly immune system cancers, Parkinson's disease, endocrine disruption, and reproductive problems" (Center for Food Safety 2014).

Effects on human health and on the environment have led to a total ban on 2,4-D in Norway, Sweden and Denmark, and partial bans on its use in other countries including Canada and South Africa.

In June 2015, the World Health Organization's International Agency for Research on Cancer (IARC) announced that it would classify 2,4-D as "possibly carcinogenic to humans", based on *inadequate evidence* in humans and *limited evidence* in experimental animals (IARC 2015a). The IARC conclusion is based on a scientific article (Loomis et al. 2015) in which a group of 26 experts was asked to assess the carcinogenicity of several herbicides. While the IARC did not place 2,4-D in a higher category of a "probable" human carcinogen, a "substantial minority" of the IARC working group (which also included members of the industry-sponsored 2,4-D working group) considered there to be *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in animals, criteria that would have placed it in the higher category if the working group had agreed on this (Loomis et al. 2015).

Furthermore, as the task of the group was to assess each herbicide individually, all population-based studies in which workers manufacturing and applying pesticides were exposed to mixed herbicides were excluded as "uninformative". This is despite the fact that the application of several herbicides over a period or at the same time is a reality, as is the exposure of farmers, farm workers and their families to it.

Enlist Duo: Pre-mixed 2,4-D and glyphosate

In the cultivation of 2,4-D-resistant GM crops, 2,4-D will *not* be used on its own. Most 2,4-D-resistant crops are so-called stacked GM crops that are resistant to (at the time of writing) up to four herbicides.

In October 2014, just a month after the approval of Enlist 2,4-D-tolerant maize and soybeans, the US Environmental Protection Agency (EPA) approved Enlist Duo – a blend of 2,4-D and glyphosate – despite the concerns raised by US environmental groups (Center for Food Safety 2014).

In 2015, the IARC classified glyphosate as "probably carcinogenic to humans" (IARC 2015b, Guyton et al. 2015). In the evaluation, glyphosate was also found in the blood and urine of farm workers, indicating that it can be absorbed in the body.

The effects of 2,4-D used in the cultivation of multi-herbicide-tolerant crops will therefore come on top of the effects of glyphosate and/or other herbicides that farmers, farm workers, their families and others living in agricultural areas already experience.

In November 2015, the EPA announced that it would revoke its approval of Enlist Duo, after determining that the combination of chemicals is likely significantly more harmful for the environment than initially believed. The EPA said that it had initially concluded, based on information from the developer Dow AgroSciences, that the two herbicides in Enlist Duo were not synergistic, meaning the toxicity of the two chemicals combined was not greater than expected based on the properties of the individual chemicals. However, new information the EPA received, regarding potential synergistic effects between the two herbicides on non-target plants, prompted the move to nullify the approval. The information was contained in a Dow patent application for Enlist Duo, which stated that the two chemicals would have "synergistic herbicidal weed control" properties.

Agent Orange and dioxin contamination

2,4-D has a long, and deadly, history. It was discovered in the 1940s and was soon developed further as a chemical warfare agent, but without being used as such during the Second World War. Between 1961 and 1971, it was used as one of the two components of Agent Orange – the biological warfare agent that till today has major impacts on human health and a lasting environmental legacy.

> Although the main health effects of Agent Orange were blamed on the other component of the mixture (2,4,5-T) and dioxin contamination, the data indicates that 2,4-D has significant health risks of its own. It remains unclear whether continuing low-level contamination of 2,4-D with dioxins or dioxin-like compounds plays a role. (African Centre for Biosafety et al. 2012)

GRAIN (2014) concluded that "some of today's 2,4-D preparations are likewise contaminated with dioxins due to the way they are manufactured" and "commercial 2,4-D formulations contain highly toxic adjuvants (other chemicals which enhance the herbicide's effectiveness)." In 2013, journalists in Australia reported that they found elevated dioxin levels in a generic 2,4-D product (Cohen 2013).

This also highlights another problem with herbicide-tolerant GM crops: every herbicide consists of its active ingredient (for example, glyphosate or 2,4-D) and a range of other substances that are needed to turn the active substance into a commercial product. In risk assessments, often only the isolated active ingredient is tested, not the commercial product (for example, Roundup) that will later be used in the field. Effects of these so-called inactive substances are thus not taken into account.

Herbicides causing antibiotic resistance

In March 2015, a study revealed that the application of commercially available herbicides containing 2,4-D, glyphosate or dicamba as active substances caused resistance to several antibiotics in the two tested bacteria *E. coli* and *Salmonella* (Kurenbach et al. 2015). These antibiotics are used in human medicine.

The herbicides in these applications were not lethal to the bacteria, and the resulting antibiotic resistance is a reaction of the bacteria to the threat posed by the herbicides. Risk assessments usually only assess for lethal effects such as the killing of soil microflora, but they generally do not assess for sub-lethal effects.

This initial study does not clarify which substance in the herbicides caused the bacteria to develop antibiotic resistance, whether it is the so-called "active" substances such as 2,4-D or glyphosate, or any of the "inactive" substances (see above). This is a relevant research question, but in the field its outcome will not make a difference. For now, these *are* the herbicides that are available to farmers to apply to 2,4-D-resistant GM crops.

Farmers, farm workers and others living in rural areas can be affected by an increase in antibiotic-resistant bacteria – potentially compromising medical therapy – at a time when antibiotic resistance is already a major public health problem.

2,4-D-tolerant GM crops

Dow AgroSciences has developed 2,4-D-tolerant GM maize and soybeans, which were approved for cultivation in Canada and the USA in 2014. Both are marketed under the brand name Enlist. Canada and the USA also approved Enlist Duo, a herbicide mix containing 2,4-D and glyphosate. The US EPA announced in November 2015 that it would seek the revocation of its approval of Enlist Duo, although Dow harbours hopes that the situation can be speedily resolved. A handful of other countries have given approval for these GM crops for import as food and feed, or for processing.

GM maize

Dow AgroSciences's DAS-40278-9 Enlist maize is resistant to 2,4-D and to herbicides with aryloxyphenoxypropionate (AOPP) acetyl coenzyme A carboxylase (ACCase) inhibitors.

By crossing this GM maize with a Roundup Ready maize NK603 from Monsanto, a stacked GM maize DAS-40278-9 x MON-00603-6 was created that is tolerant to three herbicides: glyphosate, 2,4-D and AOPP.

Enlist Duo, a herbicide mix that contains both the active ingredients glyphosate and 2,4-D, could be used on this GM maize (see above).

In the next stage, two multi-stacked GM maize varieties were created:

- GM maize MON-89034-3 x DAS-01507-1 x MON-00603-6 x DAS-40278-9 is tolerant to four herbicides and produces three toxins against lepidoptera (butterflies and moths). 2,4-D-resistant maize was crossed with Monsanto's glyphosate-resistant NK603, Dow's Herculex I maize TC1507 (tolerant to glufosinate, producing Bt toxin Cry1F) and Monsanto's YieldGard VT Pro maize MON89034 (producing two Bt toxins Cry2Ab2 and Cry1A.105).
- MON-89034-3 x DAS-01507-1 x MON-88017-3 x DAS-59122-7 x DAS-40278-9 has a tolerance to 2,4-D, AOPP, glyphosate and two glufosinates, and produces six Bt toxins against butterflies, moths and beetles. 2,4-D-resistant maize was crossed with Herculex I maize TC1507 and YieldGard VT Pro maize – producing the Bt toxins Cry1F, Cry2Ab2, Cry1A.105 and conferring tolerance to glufosinate – as well as Monsanto's YieldGard VT Rootworm/RR2 maize MON88017 (glyphosate tolerance and Bt toxin Cry3Bb1) and

Dow's Herculex RW Rootworm Protection maize (glufosinate tolerance and Bt toxins Cry34Ab1 and Cry35Ab1).

GM soybeans

Dow AgroSciences's Enlist soybean DAS-68416-4 is tolerant to both 2,4-D and glufosinate herbicides. Similar to 2,4-D-tolerant Enlist maize, this soybean was crossed with one of Monsanto's glyphosate-tolerant soybeans, the Roundup Ready2Yield variety MON89788-1. The resulting DAS-68416-4 x MON-89788-1 is therefore tolerant to three herbicides and the herbicide mix Enlist Duo can be applied to it.

Scenarios

There is no specific experience with 2,4-D-tolerant GM crops yet, or with multi-herbicide-tolerant GM crops that include 2,4-D. But past experience with 2,4-D and experience with using multiple herbicides on other crops are sufficiently available.

Estimates for US agriculture exist for damage done to non-target plants, both in absolute figures and in comparison to the most widely used herbicide in the USA, glyphosate.

> USDA's [US Department of Agriculture] own analysis admits that approval of 2,4-D-resistant corn and soybeans will lead to an unprecedented 2 to 7 fold increase in agricultural use of 2,4-D by 2020, from 26 million to as much as 176 million lbs. per year. Even at current use levels, 2,4-D drift is responsible for more episodes of crop injury than any other herbicide. (Center for Food Safety 2014)

> Benbrook (2012a) expects that if corn and soybean resistant to several of these herbicides plus glyphosate and/or glufosinate are deregulated in the US, there will be growing reliance on older, higher-risk herbicides to manage glyphosate-resistant weeds. He estimates 2,4-D use on corn would increase by 2019 over 30 fold from 2010 levels. However, 2,4-D is 75 times and dicamba 400 times more toxic to broadleaf plants than glyphosate (Mortensen et al. 2012). The potential for non-target drift damage would increase significantly (Johnson et al. 2012). (Tappeser et al. 2014:40)

Already in its 2013 report, the Union of Concerned Scientists argued that GM crops resistant to multiple herbicides can lead to even faster development of herbicide resistance in weeds because many weeds are already resistant to glyphosate and/or other herbicides.

> In such a situation, the weeds would have to develop resistance to only the one additional herbicide to escape control. Moreover, weeds can develop resistance to multiple herbicides through single genes that detoxify multiple types of chemicals (Mortensen et al. 2012; Powles and Yu 2010). So it is not surprising that several weed species that include populations of glyphosate-resistant weeds are already showing resistance to at least one other herbicide (International Survey of Herbicide Resistant Weeds 2013), including several of the herbicides slated to be used with the next generation of engineered crops. And if weeds that possess resistance to different herbicides happen to mate, the resulting progeny will be multiple-herbicide-resistant weeds – resistant to all of the herbicides that the parent plants could survive.

> Rather than delaying resistance, the use of multiple herbicides would lead to the quicker evolution of weeds that have multiple resistances. Such weeds could be a nightmare scenario for farmers who rely primarily on herbicides, given that no fundamentally new types are in development that might be ready in the foreseeable future. (Gurian-Sherman & Mellon 2013:6)

Furthermore, the impacts of herbicide-tolerant crops have been devastating to the health of people living in close proximity to GM glyphosate-tolerant soybean plantations in South America, particularly in Argentina, where their use is widespread (African Centre for Biosafety et al. 2012). These health problems will very likely increase with the adoption of crops resistant to 2,4-D, as 2,4-D is a much more toxic herbicide.

Conclusions: What needs to be done

The first conclusion is an obvious one: The technology package of using herbicide-tolerant GM crops in no-till cropping systems has been an abject failure. It is now generally accepted that herbicide-resistant weeds have become a major problem, yet during the first decade of growing GM crops, the corporations developing these crops routinely denied the existence of such weeds. Roundup Ready crops have quite simply betrayed the promise that their use would result in reduced application of herbicides.

More specifically, this situation constitutes conclusive proof of the total failure of what has been far and away the most commercially successful genetically engineered trait: glyphosate resistance (GRAIN 2014).

2,4-D crops were not developed because 2,4-D is a herbicide of choice. It was simply picked off the shelf to deal with the mess left behind by Roundup Ready (glyphosate-tolerant) GM crops. It is a techno-fix – and a very bad one.

What needs to be done: *Reject* 2,4-D crops instead of approving them. *Assess* them for what they are and how they are used: in conjunction with a herbicide that should be banned instead of being used in an agricultural model that has proven to be a failure. *Understand* who is promoting it and why: those who already failed and who see it as the only way to keep their failed product selling for a bit longer. *Think* about what lies ahead: more herbicide-resistant weeds and, as a consequence, more herbicide use with devastating impacts on health, the environment, etc. *Use* agricultural practices such as crop rotation and weed control without herbicides.

Antje Lorch is a scientific consultant for several environmental NGOs on issues of GM crops and agriculture. She has been a civil society representative at most meetings of the Conference of the Parties (COP) to the Convention on Biological Diversity (CBD) and Meeting of the Parties (MOP) to the Cartagena Protocol on Biosafety since 2002. She has also been NGO representative at the Biosafety Clearing House (BCH) Informal Advisory Committee of the Cartagena Protocol on Biosafety since 2012. She was formerly Editor of *Biotechnology and Development Monitor* (1999-2002) and has served as Editor of the CBD Alliance newsletter *ECO* at most COPs and MOPs since 2009. She is a member of the Federation of German Scientists (VDW), European Network of Scientists for Social and Environmental Responsibility (ENSSER), Ecoropa and the Gen-ethic Network (Germany).

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