A brief overview of the gaps in the federal EPA regulation of pesticides, and then the outcome of recent cancer risks identified for two common herbicides, glyphosate (Roundup) and 2,4-D. The focus will be on the regulation and human health risks from pesticides.

EPA OVERSIGHT OF PESTICIDES – a flawed system

Pesticides are regulated much more strictly than industrial chemicals under U.S. law, requiring a significant amount of safety data before being registered for use, and undergoing a registration review process every 15 years in case new data on potential harm has come to light. Nonetheless, there are weaknesses, loopholes, and flaws in all aspects of the process from legal requirements to implementation to enforcement and oversight.

Failure to test for known risks - Most legal limits for pesticides are based on “toxic ignorance”, not on safety. That is, toxicity studies required to register a pesticide do not include many disease endpoints such as immune system toxicity, endocrine or hormone system disruptions, learning deficits, or chronic diseases such as Parkinson’s Disease. Yet, all of these have been linked to pesticide exposure in the peer-reviewed scientific literature (see reviews here and here). Further, pesticides are only reviewed every fifteen years, leaving long lag times between science and regulations.

Register now, test later: The problem of conditional registrations - Pesticides are only allowed onto store shelves and for use in agriculture and into consumer products if they have been approved by the EPA. Unfortunately, investigations by NRDC and later confirmed by the Government Accountability Office pulled back the curtain on a deeply flawed system. This loophole, called a ‘conditional registration’ has allowed the majority of pesticides onto the market without a public and transparent process and in some cases, without a full set of toxicity tests. In fact, as many as 65 percent of more than 16,000 pesticides were first approved for the market using this loophole. (see NRDC comments on nanosilver here). Completion and review of these studies may occur years later, if at all, with little public oversight. EPA approved the bee-toxic neonicotinoid pesticides through this loophole without adequate bee toxicity tests, and also approved nanosilver and ‘nanosilva’ nanomaterials as antimicrobial pesticides through this loophole. NRDC won a lawsuit in 2013 challenging the approval of nanosilver, and filed a legal petition in 2014 to cancel the neonicotinoid pesticides.

The problem of inerts - An inert ingredient means any substance (or group of structurally similar substances if designated by the Agency), other than an active ingredient, which is intentionally included in a pesticide product. That means an ‘inert’ in a pesticide product could be toxic in other contexts. Moreover, inerts could raise the toxicity or exposure potential of a product formulation, intentionally. For example, inerts may serve as a solvent, allowing the pesticide's active ingredient to penetrate a plant's outer surface, making it a more effective pesticide but also more easily penetrate non-target plants and possibly also human skin. In some instances, inert ingredients are added to extend the
pesticide product's shelf-life or to protect the pesticide from degradation due to exposure to sunlight, which also makes it more persistent in the environment. Pesticide products can contain more than one inert ingredient, but current federal law only requires that the total percentage of inert ingredients be labeled on the pesticide product; it does not require that these ingredients be individually identified by name or percentage on the label.

An example of the problem of lack of regulatory oversight of inerts is the introduction of nanomaterials into pesticides. A US-based company is claiming to add nanomaterials as adjuvants to glyphosate, to help it work better against resistant weeds. Although researchers at Purdue University have tested them and found they don’t work, since they are inerts they are unregulated and even unreported to EPA. A report in Mother Jones (July 2015) by Tom Philpott found that the materials being mixed with glyphosate are carbon nanotubes, often compared with asbestos in toxicity.

The European Food Safety Agency (EFSA) inventory of food and agricultural applications of nanotechnology found several dozen products that used nano-encapsulation in pesticides as of 2012 (report here), in addition to many of food and food contact materials that are nano, mainly nanosilver (antimicrobial) and nano titanium dioxide (blocks UV rays).

**Industry science versus academic science** - The truth is that when new studies are published that indicate the need for more protective exposure limits, the pesticide labels are stuck in time. This is because the exposure limits are set based on the data supplied by the industry (the registrant). This restrictive and biased use of science is defended by industry claims that only the industry data is conducted according to pre-validated study designs required for the registration process and performed in Good Laboratory Practices (GLP)-certified labs. However, study designs are often very outdated and do not reflect the current science, most sensitive disease endpoints, or chronic disease outcomes. Moreover, GLP standards were imposed on industry labs during the 1970’s after flagrant violations and fraud were identified. GLP requirements are designed to set a baseline of cleanliness, animal care, and record-keeping; they are not associated with higher quality research, proper study design or correct statistical analysis. In contrast, academic research which has found pesticides to be harmful has been published in respected scientific journals and relies on the peer-review process and public accessibility to uphold scientific quality.

**Failure to promote reduced risk alternatives** - When registering pesticides, there is no requirement for EPA to consider reduced risk or non-toxic alternatives or lower use/exposure levels. While registrants have an incentive to approval the greatest potential uses of their product, EPA does not assess the availability of safer alternatives when considering product registration.

**Failure to regulate to reduce over-use** - The amount of pesticide residue that is legally allowed on our food, called a ‘tolerance’ is set based on how much pesticide a person can ‘safely’ consume and still meet the EPA standard of ‘reasonable certainty of no harm’, considering aggregate (from other uses of the same pesticide) and cumulative (uses of other pesticides in the same mode of action family) exposures. This may be much higher than a pesticide needs to be to have its desired pesticidal effect. It is likely that pesticides most could be used in far less amounts and still be effective. Unfortunately, this is not in the interests of the companies that manufacture and sell the pesticide, and negotiate the registration with EPA.

**Illegal uses** - All of the above limitations in pesticide regulations presume legal use of pesticides. However, we know that illegal uses take place routinely, albeit not always intentionally; for example, the
use of old stores of pesticides that have since been banned, or the use of pesticides according to last year’s practices even though current labels have been updated to reflect that application rates have been lowered or buffer zones have been increased. Many stores and small outlets sell pesticides that have been banned, or maybe that have never been legal in the US, for residential uses including folk remedies and other off-label illegal applications. These uses of pesticides can be dangerous, and even deadly.

**GLYPHOSATE – cancer risks**

The International Agency for Research on Cancer (IARC) - the cancer evaluation arm of the World Health Organization - convened a meeting of 17 scientific experts from 11 countries to assess whether certain pesticides, including glyphosate, caused cancer in humans (Meeting 112, March 2015). The outcome of that meeting is that glyphosate "probably" causes cancer in people (IARC Group 2A). This is particularly alarming for a chemical that is used in over 750 herbicide products and applied to fields in the US at over 250 million pounds annually (USGS 2012 data). The IARC review underscores the need for the Environmental Protection Agency (EPA) to examine and act on all we've learned about glyphosate's dangers in the two decades since it was last approved for use. IARC's decision is based on three lines of evidence:

"**Sufficient**" evidence of cancer in mice and rats that were fed glyphosate over a several years (see reports by EPA 1991 and the WHO 2004)

The IARC Working Group reviewed ten laboratory studies on rodents, five on mice and five on rats, culled from the public literature and reports of the EPA (1991) and the WHO (2004). One mouse study reported a positive trend for heamangiosarcoma (WHO report) and another mouse study reported a rare tumor called a renal tubular carcinoma (EPA study) associated with glyphosate in long-term feeding studies. In both cases, effects were stronger in the males than females. The IARC Working Group of experts also reviewed five studies in rats: two reported significant increases in pancreatic islet-cell adenomas in male rats (EPA report); two studies did not find significant cancer increases; one study did not last long enough to draw any conclusions about cancer risks. The Working Group determined that there was a statistically significant trend in the occurrence (incidence) of haemangiosarcoma in the male mice, but not the female mice. In accordance with the pre-specified procedures and criteria of IARC, the Working Group concluded that the studies provided evidence of carcinogenicity in experimental animals.

"**Strong**" evidence from mechanistic or cellular studies that explain how glyphosate may cause cancer.

The IARC experts also reviewed cellular studies and determined that there was "strong" evidence from mechanistic studies showing that glyphosate caused damage to the cell's genetic information (genotoxicity), which can lead to abnormal cell function and ultimately a cancerous cell. Studies also showed that glyphosate also caused oxidative stress in cells, which can lead to cellular damage and elevate the risk of a cell becoming cancerous. This mechanistic evidence - both genotoxicity and oxidative stress - provides a plausible explanation for how glyphosate may cause cancer, and therefore supports the evidence from the animal studies.

"**Limited**" evidence from epidemiologic studies of people, particularly pesticide applicators and farmworkers.
The IARC experts found that the evidence from epidemiologic studies provided some evidence of cancer, in particular elevated risk of non-Hodgkin lymphoma, but it was "limited" because the studies were either weakly positive or did not find a cancer risk at all.

Taken together, these three lines of evidence support the classification of glyphosate as a Group 2A chemical that "probably" causes cancer in exposed people, according to the pre-specified procedures and criteria of IARC. The IARC Working Group of experts made an independent assessment of existing studies, including those sponsored by Monsanto, the glyphosate manufacturer. Monsanto representatives attended the 8-day meeting as observers and given the opportunity to speak, but did not vote on the classification of glyphosate or other pesticides being reviewed by the Working Group experts.

The details of the IARC decision are reported in the Lancet Oncology in summary, with the full length Monograph expected by early 2016. A meta-analysis of all the relevant epidemiologic studies was conducted by IARC staff scientists in 2014 that reported an overall lack of data, particularly in low- and middle-income regions of the world where the health of agriculture workers is poorly documented, if at all.

2,4-D

Cancer risks

This past June 2015, 2,4-D was classified by IARC as possibly carcinogenic to humans (Group 2B), based on inadequate evidence in humans and limited evidence in experimental animals. There is strong evidence that 2,4-D induces oxidative stress, a mechanism that can operate in humans, and moderate evidence that 2,4-D causes immunosuppression, based on in vivo and in vitro studies. However, epidemiological studies did not find strong or consistent increases in risk of NHL or other cancers in relation to 2,4-D exposure.

Non-cancer risks (Excerpts from blog by Dr. Kristi Pullen, September 2014) –

In addition to cancer, 2,4-D has been associated with a number of negative health outcomes including decreased fertility, higher rates of birth defects, and other signs of endocrine disruption – especially through heightened impacts on the thyroid system. Thyroid hormones play an essential role in the maintenance of body temperature, metabolism, cell differentiation (helping cells know what type of tissue or organ to turn into), and fetal and postnatal brain development.

At the molecular level, new scientific tools developed by EPA, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and other government partners (Tox21) have shown that 2,4-D can prevent the thyroid receptor from binding to thyroid hormones (a process that can impact the proper functioning of the thyroid). Studies in zebrafish (an important animal model for developmental, reproductive, and neurological health impacts) have shown that 2,4-D can decrease thyroid hormone levels. Even EPA’s own health assessment of 2,4-D demonstrated that it can impair thyroid functioning in rats and dogs (see NRDC comments at pages 20-25 for more specific details), although EPA disregarded these effects. Finally, epidemiologic studies in people have shown that farm workers exposed to 2,4-D are at increased risk of developing hypothyroidism (an underactive thyroid) compared to farm workers that were not exposed to 2,4-D.
Exposure

2,4-D has been detected in domestic finished (tap water) ground and surface waters (see pages 41 through 45 of this EPA report for more details), indicating that U.S. populations could be exposed to 2,4-D through their drinking water. Infants could be exposed to 2,4-D via both breast milk and formula. Studies in pregnant rats have demonstrated that 2,4-D can be transferred through maternal milk to pups (see page 10), acting as a source of exposure for the developing pup. 2,4-D has also been shown, in rodent studies, to alter the nutritional content of maternal milk by decreasing the levels of important fats. Additionally, infant formula prepared with 2,4-D contaminated drinking water could lead to early childhood exposures.

Human populations can also be exposed to 2,4-D via inhalation or ingestion (by placing hands contaminated with 2,4-D directly into our mouths or onto the food we are about to eat) of 2,4-D particles in air and dust. Pesticides can be breathed in when the particles enter the air and travel far from their source via processes known as spray drift and volatilization. Spray drift is the movement of pesticide droplets in the air, typically as a function of the pesticide application. Volatilization is when a liquid or solid form of the pesticide converts into a gas form, allowing it to travel long distances. 2,4-D can travel by both spray drift and volatilization to contaminate distant sites including homes, school yards, gardens, and nearby crops that are not genetically modified to withstand the herbicide.

ENLIST DUO (Excerpted from blog by Dr. Kristi Pullen, October 2014)

Enlist Duo™ is the chemical combination of two herbicides: 2,4-D and glyphosate (the active ingredient in “Roundup®”). Intended for use with corn and soy that have been genetically modified to be resistant to both herbicides, Enlist Duo™ is the chemical industry solution to our herbicide resistance problem. Enlist Duo™ should not have been approved for a host of reasons, including some that are directly relevant to human health, like:

- Multiple streams of evidence (including molecular, animal, and epidemiologic studies) demonstrating adverse impacts of 2,4-D on the thyroid;
- High potential for infants, children, and women of child-bearing age to be exposed to Enlist Duo™ via air, food, and water;
- The complete absence of information on how the combination of 2,4-D and glyphosate will impact human and ecological health (including habitats for the iconic Monarch butterfly); and
- EPA’s hopelessly out-of-date health risk assessment for glyphosate (the last EPA human health risk assessment for glyphosate was completed over 21 years ago).

NRDC LITIGATION challenging Enlist Duo

Citing the devastating impact on monarchs, in 2014 NRDC filed an emergency petition with EPA to restrict glyphosate, which has soared ten-fold in use since biotech giant Monsanto’s introduction of glyphosate-resistant “Roundup Ready” crops in the 1990s. These crops have been widely adopted and as a result, farmers can drench their fields with the weed killer, in the process destroying vast amounts of native milkweed, the only food that monarch larvae can eat. The heavy use over the years has resulted in the rise of glyphosate-resistant “super weeds” (not including milkweed, however). Chemical maker Dow AgroSciences responded by developing new corn and soybeans resistant to both glyphosate and 2,4-D called Enlist Duo, approved by EPA in late 2014 in six states (Illinois, Indiana, Iowa, Ohio, South Dakota and Wisconsin). The Agriculture Department predicts Enlist Duo could result in as much as a six-fold increase in the use of 2,4-D. NRDC filed a lawsuit challenging the approval of Enlist Duo (see Dr.
Sylvia Fallon’s blog October 2014), but EPA went ahead and expanded its approval to an additional nine states (Arkansas, Kansas, Louisiana, Minnesota, Missouri, Mississippi, Nebraska, Oklahoma and North Dakota, so EPA filed a legal challenge against that too (see Dr. Sylvia Fallon’s blog April 2015).