An Evaluation of Traditional Threshold Theories: Failure to Adequately Protect Human Populations from Pesticide Exposure

Kelly Baglia

The scientific discipline of toxicology is based heavily on the theory of thresholds, or that toxic chemicals can be regulated to specific levels in order to prevent human populations from experiencing adverse effects. However, I contend that, in light of recent research, this threshold concept is inadequate for pesticide regulation and thus new tools and models are needed to determine safe exposure levels. For the sake of industrial economics and politics, human health is being knowingly compromised—with the grave potential to impact generations and perpetuate injustice.

In the realm of Environmental and Occupational Safety, a crucial concept for toxicology is that of thresholds. In essence, the theory is that certain toxic chemicals are needed in society but should be regulated to a specific level of exposure at which the most sensitive humans show no significant adverse effects. Thus, through experimentation with rats, this threshold, known as the No Observable Adverse Effect Level (NOAEL), is traditionally determined for each individual chemical. Public health policies are dependent upon these levels in order to ideally regulate the concentration, dosage, and exposure of all toxic chemicals in use (SC). Until very recently, the threshold theory went nearly unchallenged as it was developed and used by the Environmental Protection Agency, the Food & Drug Administration, and the U.S. Department of Agriculture, along with many other authoritative toxicology regulators around the world (SQ). However, new scientific studies on endocrine disrupting chemicals (EDCs) used in pesticides have begun a debate over the legitimacy of this theory. EDCs were found to be able to mimic hormones in the body, and any presence of these chemicals, even at extremely low concentrations, exceeds the threshold of the natural endogenous hormones (Crews and Gore 2014). In other words, any exposure to EDCs, regardless of the amount, can interfere with biological developmental changes in humans and wildlife, suggesting that a safe threshold for these chemicals does not exist (Bergman et al. 2013). Further studies on EDCs have also suggested there are many additional factors that can influence the degree of adversity to exposure, which cannot be accurately accounted for when calculating thresholds (Grandjean and Ozonoff 2013) (DC).

This is particularly concerning because the majority of humans are exposed to pesticides regularly, but arguably even more so because it calls into question the reliability of the threshold concept as a whole. If the idea of setting a safe threshold is erroneous for any chemical and there can be significant adverse effects to individuals caused by very minimal exposure below the set "safe levels", this necessitates new tools, theories, and regulations to determine safe amounts, as well as serious reconsideration of the use of these chemicals (Olden

et al. 2014) (C/B). NOAEL and all affiliate threshold concepts need to be immediately reevaluated in light of the following concerns that make the theory unsafe and inadequate for pesticide regulation (C): 1. Thresholds are unable to account for the complex mechanisms by which pesticide exposure can cause diverse biochemical effects; 2. The mixture of many chemicals in pesticides can react with each other, making it impossible to calculate a safe threshold for the whole; 3. Toxicology threshold assessments only test exposure as a single event and are unable to account for chemical pesticide body burden across an entire lifetime or even generations; and 4. Individual differences between people, especially levels of stress, make the concept of one threshold across an entire population invalid.

First, the mechanisms by which pesticide exposure causes diverse biochemical effects are not well understood as they interact with a plethora of biological functions, even at doses well below recommendations, and thus threshold values are unable to account for all such pathways and risks. Depending on the chemical, new studies are finding that the processes by which exposure damages the body are extremely elaborate and can have both short-term and long-term effects. Currently, disruption of the endocrine system, metabolic system alternation through oxidative stress, and epigenetic changes to gene expression are recognized as poorly understood mechanisms by which very low exposure to pesticides can cause significant health problems. Still, research is undergoing as many more pathways remain unidentified (Mrema et al. 2013, Mesenage et al. 2015). Over 105 separate chemicals used in pesticides are acknowledged as disrupters of biological functions at low doses and are correlated in numerous studies with hormone-dependent cancer risks, most significantly breast and prostate cancers, as well as being linked to endometriosis, infertility, neurodegenerative disorders, and immunotoxicity (Mnif et al. 2011, Multigner et al. 2010, Parron et al. 2011, Mrema et al. 2013). However, despite such strong correlations, the data is still considered largely inconclusive because of a lack of understanding of exactly *how* these changes are occurring. And without a comprehensive understanding of these pathways, it is impossible to accurately identify and predict values at which chemicals can be considered safe (WARRANT).

In a recent study done by Somayyeh Karami-Mohajeri and Mohammad Abdollahi, various pesticides were biochemically examined and tested for their direct influence on bodily processes and functions. Organochlorines (OC), organophosphates (OP), and carbamates (CB), three common chemicals used to make pesticides, were demonstrated to each use various intricate mechanisms, some the same and some different, through which they cause adverse effects. Karami-Mohajeri and Abdollahi indicated that "OP and CB show this effect through inhibition of AChE or affecting target organs directly. OC mostly affect lipid metabolism in the adipose tissues and change glucose pathway in other cells… all OP, CB and OC induce cellular oxidative stress via affecting mitochondrial function and therefore disrupt neuronal and hormonal status of the body" (Karami-Mohajeri and Abdollahi 2011). They conclude that much more work is needed in this area in order to reduce the toxic effects of these three chemicals on humans, as the effects are clearly more complicated than accounted for in threshold regulations. As a follow up, another study was done by University of Crete scientists on health effects associated with low levels of OPs and OCs. They discovered yet another pathway, the non-cholinergic mechanism, which links long-term exposure to minimal doses of chemicals to neurodegeneration (Androutsopolous et al. 2013, Flaskos 2012). And this year, studies moved outside of the realm of organo-pesticides, to test the most commonly used type of pesticide around the world, Glyphosate-based herbicides (GlyBH) such as RoundUp, for possible adverse effects caused by below regulatory level exposure. Although similar mechanisms, as found in the previous studies, were detected, including endocrine disruption and oxidative stress, these pathways interacted with different biological functions leading to altogether different health risks, including teratogenic and hepatorenal effects. Mesnage et al. also concluded that there was uncertainty in how pesticide exposure could cause different health problems using the same mechanisms that have been linked to other health risks (Mesnage et al. 2015). Thresholds are based on the theory that

the lowest level of exposure causing harm can be calculated through assessment; however, these studies all point to a reliable calculation being practically impossible. Because the mechanisms and resulting effects of pesticide exposure, both short-term and long-term, are still being understood and remain largely unknown, it cannot be accurately determined with thresholds at what specific levels various pesticides will cause harm (WARRANT).

Second, pesticides almost always contain a mixture of numerous chemicals, which can exhibit synergy or new toxic effects together, thus negating the known threshold of each chemical tested separately. To add to the inconclusive data on the mechanisms and risks of each individual chemical, the changes that occur when two or more of these chemicals are mixed together is also severely under researched. In the last few years, toxicologists have finally begun to test a mixture of chemicals and measure the effects of one added to another. Yet, this has been done with less than 100 chemicals out of an estimated 70,000 that have been produced and are used around the world, with no more than two tested together at one time (Hernandez et al. 2013, Keil 2014).

Currently, a calculated threshold for individual chemicals does not change when mixed together with other chemicals because the level is supposedly set low enough to offset any additive effects. Therefore, when the chemicals come into contact with each other, as long as they individually remain below their respective set limits, the mixture as a whole can also be theoretically considered safe. Many studies have supported this theory, mixing two chemicals at a time and determining that the overall toxicity of the mixture was as predicted. In 2011, two such studies by Koster et al. and Rennen et al. independently supported that the threshold for chemical mixtures should be set at 540 micrograms per person, about the same as the limit for the same class of individual chemicals by themselves (Koster et al. 2011, Rennen et al. 2011, Leeman et al. 2013). They predicted that this would hold true for all other classes and types of chemicals as well, and that the threshold theory was reliable even for the mix of chemicals found in pesticides.

However, other studies have been published which challenge this assumption. In 2008, Boobis et al. carried out one of the first assessments which directly analyzed various pesticide residues containing a mixture of chemicals and their subsequent toxic risk. The results showed that the toxicity levels in the residues did not always match what they expected, having assumed that the effects of the various chemicals would be additive. They suggested the need to pursue the possibility of chemical synergy, a process that occurs when two chemicals interact to become more toxic than they would if their effects were simply added together (Boobis 2008). Hernandez et al. also supported this concept in their recent article covering the toxic effects of pesticide mixtures, focused on the molecular level of chemicals. Concluding that not all mixtures only produce additive effects, they state, "if [the molecules] act on multiple sites they can elicit different toxic effects, with some mixtures having the potential of producing greater toxicity than would be predicted based on the potencies of the individual compounds." Further, Hernandez et al. also poses that the molecules of pesticide chemicals interact on an "agent-to-agent" level, meaning that they can change the expected relationship between the dose and the amount of the chemical that reaches the target biological function, thus changing the threshold level necessary to cause adverse effects (Hernandez et al. 2013). These studies are significant because they demonstrate that the chemical reactivity of pesticides is not as simple as the threshold theory accounts for. In many of the studies which support the threshold theory, two chemicals are singled out and tested, and the possibility of synergy was never considered. However, as numerous studies support that synergy can occur between toxic chemicals, it is important to recognize that the current threshold theory cannot account for these effects. There is no way, using the traditional threshold concept, to predict what mixture of chemicals will be toxic at lower doses without testing every combination of the 70,000 possible chemicals.[1]

One recent, potential solution that was proposed to this problem was the Mixture Risk Assessment (MRA), an additional threshold test

[1] Testing every possible combination of 70,000 chemicals would require approximately 1040000 separate toxicological assessments.

that can theoretically be used with the traditional threshold approach in order to quickly account for these mixture variances. In an evaluation of this assessment, 67 different pesticide chemicals were tested together in various combinations, and the data were used to identify whether a standard could be statistically determined, so that every possible combination of mixtures would not need to be tested. However, researchers encountered significant problems; they simply could not get enough data to make reliable determinations. It would have taken entirely too long to evaluate just 67 chemicals, making it inefficient and impossible to use for the rest of the 70,000. As well, they concluded that there were too many variables, which they could not account for using the MRA and the threshold theory alone (Evans et al. 2015). This study, in combination with the previous, raises the question of whether the threshold theory's framework is inherently flawed, as it cannot accommodate new and necessary aspects of pesticide risk. When chemicals are mixed together to make pesticides, potential increases in toxicity are unpredictable, making certain combinations dangerous despite the threshold limits which say they are safe. And if all aspects of pesticide risk and thus possibilities of adverse effects in human populations cannot be modeled, the threshold theory must be regarded as ineffective (WARRANT).

A third problem with the threshold concept is that rather than a single event of exposure as assessed in toxicology safety assessments, body burden is a combination of personal exposure to toxic chemicals accumulated throughout an entire lifetime as well as the chemically-induced epigenetic changes in our DNA that are inherited across generations. In calculating all chemical thresholds, exposure is assumed to be a single event. Or conversely, extended periods of exposure to a chemical are not considered or accounted for in the toxicological tests. As argued by many in favor of traditional threshold assessments, this is an unnecessary component because all experimental values are reduced by two orders of magnitude to determine the set limits. By erring on the side of caution, the variable of duration could not be enough to cause harm, so it does not need to be considered. In a study done this year by the European Food Safety Authority using the Threshold of Toxicological Concern (TTC) test, results supported that the threshold theory is conservative for 96.2% of chronic exposure to pesticide chemicals. Chronic exposure to 311 out of 328 chemicals at levels below traditional thresholds did not cause adverse health effects. However, they include in their conclusion that for 17 of the 328 pesticides they tested, the levels recommended for NOAEL were too high, implying that chronic exposure to these pesticides at doses lower than the threshold were still linked with significant health effects (Feigenbaum et al. 2015). Although the results were written to emphasize the chemicals for which the threshold theory proved reliable, it is significant that several of the pesticide chemicals did not confirm this theory. If toxicologists are relying on erring on the side of caution, yet 17 separate chemicals were still shown to be dangerous at the recommended dose with chronic exposure—considering that these levels were already reduced to be extremely cautious—it seems that these levels are not always exceedingly safe. Further, the researchers were not able to distinguish why these 17 chemicals did not follow the threshold concept. Thus, out of the 70,000 man-made toxic chemicals, we have no way of determining which 5% (assuming no other factors increase this number) are currently causing significant health problems around the world.

Other studies have also shown that chronic exposure to pesticides at levels below the NOAEL can lead to negative health effects, including Pohl et al. who completed a chemical risk assessment in their 2010 study on the effects of duration on priority toxic substances. Although the threshold theory held for volatile organic compounds (VOCs), their data for Organophosphate and Organochlorine pesticides supported that doses well below NOAEL limits can be safe for acute exposure, but chronic exposure may cause neurodevelopmental complications (Pohl et al. 2010). This further supports that the threshold theory is insufficient for chronic exposure to all pesticides, and therefore new models and theories are needed which can accurately limit every pesticide chemical to safe levels.

Additionally, an extremely new field of study in pesticide exposure is transgenerational environmental epigenetics. This is the theory that "chronic" exposure to chemicals is not limited to a single lifetime, but

rather, through DNA changes, chemical exposure is "passed down" through generations with heritable genes (Thayer and Kudzawa 2011). By inducing changes in phenotypes through hormones, DNA methylation, and histone modification, exposure to chemicals can "build up" in our bodies for generations, making us infinitely more susceptible to personal chemical exposure in our lifetime (Hou et al. 2012). Recently, the Center of Molecular and Genetic Epidemiology in Italy published a study on pesticide exposure and mechanisms of epigenetic-induced adverse health effects in various populations. Supporting research done by Chiu and Blair in 2009, they concluded that the strongest link between pesticide exposure and epigenetics is through DNA methylation directly leading to blood cancers. These epigenetic changes may also be passed down through generations, making agricultural workers and their families extremely vulnerable (Collotta et al. 2013, Chiu and Blair 2009). If pesticides can induce changes to DNA, which are different for every person, as well as if these changes can be passed down through generations which are unique to every family, it would be impossible to measure at what level pesticide exposure is harmful for each individual. The model of measuring a threshold and then reducing it to be cautious could no longer be considered safe for entire populations with the possibility of agricultural families whose tolerance for pesticides is so low that any exposure might cause significant health effects. The threshold theory cannot account for either chronic exposure across a single lifetime, or for exposure passed down through generations, severely limiting the protection that it claims to provide (WARRANT).

And finally, fourth, a complex set of psychosocial differences in individuals, particularly allostatic load, have the ability to modify vulnerability to chemical exposure, implying that a single threshold for an entire population is useless. Disease susceptibility is commonly quantified by the total amount of stressors placed on the body. Thus, the accumulation of all types of stress over a lifetime, termed allostatic load, is often used when calculating individual or population sensitivity to certain risks. The more stress the body endures, the more vulnerable it is to adverse health effects. However, when calculating thresholds for pesticide exposure, the only stress that is considered is chemical stress, or the direct influence of the chemicals on the body. The theory neglects all other types of stress that are experienced or have been experienced, such as psychosocial and physical stress (Olden et al. 2014).

In 2012, a study by Crews et al. analyzed the relationship between stress response and exposure to a chemical commonly found in fungicides and pesticides. They found that when rats were exposed to the pesticide chemical, the concurrent three generations responded to stressful situations differently than the control group of rats which was not exposed to the pesticide (Crews et al. 2012). These results support that there is a link between the stress placed on the body by chemical exposure and the psychosocial stress from seemingly unrelated events. Two further studies done by toxicologists on stress and chemical exposure have also concluded that psychosocial stress "[has] the potential to modify the response to environmental exposures", and combinations of stress "…coordinately increase toxicological assaults on health". They further conclude that, "In addition to concomitant chemical exposures having agonistic and/or antagonistic interactions, the physical and psychological status of the individual can influence exposure outcomes" (Schwartz et al. 2011, Friedman and Lawrence 2002). In other words, the effect of chemicals on the body is influenced by many other physiological and psychological states and thus cannot be adequately predicted unless all stressors are considered. Yet, the cumulative impact of all of the interacting stressors has received little to no attention from toxicologists despite recent technological tools made available to measure allostatic load (Olden et al. 2014). They prefer instead to hold to the threshold theory and its inability to measure stressors beyond chemical exposure.

A common counterargument to this debate over the threshold concept is that the level of exposure to pesticides can still be limited to the most vulnerable in society. Therefore, it doesn't matter how complicated and diverse an entire population's response to chemical exposure would be, as it only needs to be concerned with those who will react first and the worst. Safe and effective thresholds are those

which intend to protect the infants and the sick, and by doing so, protect the rest of the population as well (Munro et al. 2008). Yet, as the previous studies have demonstrated, the threshold for chemical stressors is also dependent upon the body's allostatic load, making the threshold for each individual extremely variable. Psychosocial stressors and other physical stressors, such as past traumatic events, chronic stress due to poverty, or stress to the body caused by a lack of nutrients could interact with chemical exposure stress, making particular adults more vulnerable to pesticides than even infants. Because there are many other variables involved in calculating risk to chemical exposure beyond just the chemical itself, the 'threshold' will be constantly, incalculably changing as people change, depending on their respective stress levels. And as the threshold theory is a constant limit set for an entire population based on the vulnerability of infants, it is unable to predict or protect those who are even more susceptible to chemical exposure due to stress (WARRANT).

In conclusion, though at one point in history the threshold theory was a sufficient concept, it needs to be reconsidered given what we now know and what we realize that we don't fully understand about chemical exposure to pesticides. Thresholds are unable to predict and account for the chemically-induced mechanisms leading to adverse biological effects. And because these mechanisms are not well understood, it is impossible to assume the ability to predict safe levels. As well, thresholds do not consider the possible synergistic effects of mixing two or more toxic pesticide chemicals, and currently we have no way of determining what mixture of chemicals will exhibit synergy and thus could be hazardous at levels lower than the NOAEL threshold. Further, most threshold assessments only test acute exposure, and even tests done to attempt to determine chronic exposure thresholds cannot predict or measure epigenetic changes across generations affecting chemical exposure vulnerability. And finally, due to the varying influences of psychosocial and physical types of stress on the potency of chemical exposure to the body, the threshold theory is incomplete as it does not allow for combinations of multiple stressors. Thresholds are too simple of a concept bidding to model a tremendously complicated process. In an attempt to force an outdated theory into practice for the sake of industrial economics and politics, human health is being knowingly compromised. And the vast majority of the public is unaware of the risk they are taking, and the precautions they are forsaking, because of the trust they place in political regulation of toxicology. It remains unknown whether an effective theory for pesticide exposure regulation can be modeled, and if so, what models will amply serve to protect populations from toxic chemicals. Therefore, much research is needed in this area, taking into consideration all of the concerns raised in this paper. Still, it must be said that it may never be possible to accurately predict and prevent all adverse effects caused by chemical exposure. Do we then choose to reduce our usage and production of these chemicals, or are there human lives that we are willing to sacrifice for economic prosperity and the increase of benefits somewhere else? Perhaps it is time to begin thinking about the true costs of pesticide usage without the justifications that thresholds provide.

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