RETHINKING CARCINOGENS:
NEW VIEW OF CANCER DEVELOPMENT FOCUSES ON SUBTLE, COMBINED EFFECTS

EWG
JULY 2015

Curt DellaValle
EWG Senior Scientist

www.ewg.org
1436 U Street N.W., Suite 100
Washington, D.C. 20009

COMMONWEAL
www.commonweal.org
P.O. Box 316
Bolinas, CA 94924

Contents

www.ewg.org

Editor
Nils Bruzelius

Designers

Print Layout
Aman Anderson

Web Layout
Taylan Yalniz

About EWG
The Environmental Working Group is the nation's most effective environmental health research and advocacy organization. Our mission is to conduct original, game-changing research that inspires people, businesses and governments to take action to protect human health and the environment. With your help – and with the help of hundreds of organizations with whom we partner – we are creating a healthier and cleaner environment for the next generation and beyond.

HEADQUARTERS
1436 U Street N.W., Suite 100
Washington, D.C. 20009
(202) 667-6982

CALIFORNIA OFFICE
2201 Broadway, Suite 308
Oakland, CA 94612

MIDWEST OFFICE
103 E. 6th Street, Suite 201
Ames, IA 50010

SACRAMENTO OFFICE
1107 9th Street, Suite 625
Sacramento, CA 95814

RETHINKING CARCINOGENS: NEW VIEW OF CANCER DEVELOPMENT FOCUSES ON SUBTLE, COMBINED EFFECTS

By Curt DellaValle, Senior Scientist

EXECUTIVE SUMMARY

More than one in three Americans will be diagnosed with cancer in their lifetimes. Along with genetics, diet, lifestyle and viruses, exposures to toxic chemicals clearly contribute to this epidemic. This means it is critical to get the science and regulation of carcinogens right, but there is growing evidence that we may be overlooking crucial aspects of how combinations of chemicals may cause cancer.

That's the conclusion of the Halifax Project, a collaboration of researchers from around the world who have just published a series of groundbreaking papers in a special issue of the scientific journal *Carcinogenesis.*

Current regulatory policy focuses on identifying "complete carcinogens" – single chemicals that can cause cancer all by themselves, but the Halifax Project's work raises the strong possibility that complete carcinogens may be only the tip of the iceberg. New research is beginning to look at chemicals that are not carcinogenic in and of themselves but can affect normal cells in ways that make them more prone to becoming cancerous. Could exposures to multiple chemicals such as these over time also have the potential to cause cancer?

This simple yet profound hypothesis is being put forward by the Halifax Project's scientists, who were brought together by the non-profit organization Getting to Know Cancer. Their investigation of the relationship between cancer and low-dose exposures to chemical mixtures may fundamentally shift the way we think about carcinogenesis.

This idea is based on two well-accepted scientific concepts:

1. The development of cancer is a multistep process.
2. There is a set of aggressive characteristics and processes, called "hallmarks of cancer," that distinguish cancer cells from normal ones.

The "hallmarks" consist of a spectrum of changes to healthy cells that allow or cause them to divide and grow uncontrollably, eventually developing into cancer. These hallmarks include such factors as the ability of a cell to replicate endlessly and avoid biologically programmed cell death.

The Halifax Project team examined toxicity data on 85 chemicals that can trigger cancer-related hallmark processes to see if they might pose a risk at exposure levels people typically encounter in day-to-day life. Among the substances were phthalates, which are common plasticizers, and several pesticides. What they found was that 59 percent of the chemicals do affect cancer hallmark processes at low doses.

Although the study investigated only a small number of chemicals, the findings suggest that many of the hundreds of substances to which people are commonly exposed to in the environment may be capable of affecting cancer-related processes in human cells.

How great are the risks associated with chemical mixtures? An analysis by the Environmental Working Group found that 23 of the 85 chemicals investigated

by Halifax Project scientists have been measured at detectable levels in the bodies of people participating in the nationally representative National Health and Nutrition Examination Survey, which is conducted annually by the Centers for Disease Control and Prevention. Many questions remain, but if cancer in fact results from an accumulation of these "hallmark" processes, it would mean that exposure to multiple chemicals that act on different cellular pathways could likely cause cancer.

It is time to expand the definition of carcinogenesis beyond the idea of a single chemical acting alone. We must begin to consider how combinations of chemicals working in concert and affecting a cell's functioning in disparate ways may result in cancer.

As the President's Cancer Panel pointed out in its 2008-2009 annual report, federal environmental laws not only leave many known carcinogens completely unregulated, they also "fail to address the potential hazards of being exposed to combinations of chemicals".[1]

This needs to change for society to have any hope of success in preventing cancer.

RETHINKING CARCINOGENS: NEW VIEW OF CANCER DEVELOPMENT FOCUSES ON SUBTLE, COMBINED EFFECTS

By Curt DellaValle, Senior Scientist

FULL REPORT

1. The Halifax Project: Complete vs. Partial Carcinogens

Cancer takes an enormous personal and economic toll on individuals, families and society as a whole. The numbers are startling. Nearly one in every two men and one in every three women will be diagnosed with cancer over their lifetimes.[2] The evidence is now compelling that chemicals in the environment are a significant factor in the risk of developing cancer, and a new series of reports from an international scientific collaboration called the Halifax Project suggests that the risk may be greater than we realize.

Current thinking about the known links between environmental toxics and cancer suggest that many cancers could be prevented through effective regulation and lifestyle changes. Until now, however, that has meant identifying and attempting to reduce exposures to "complete carcinogens" – chemicals that can cause cancer all by themselves. But they may only be one piece of the puzzle. What could we be missing?

For starters, we know very little about the long-term effects of continuous low-dose exposures to a wide array of chemicals. And we know little about how those exposures might interact over time to affect the working of healthy cells.

It was with that gap in scientific knowledge in mind that the non-profit organization Getting to Know Cancer brought together researchers from around the world to investigate the combined effects of low-dose exposures to chemicals and cancer risk, in an initiative they called the "The Halifax Project."

Getting to Know Cancer was co-founded in 2011 by Leroy Lowe and Michael Gilbertson in Nova Scotia, Canada. The goal of the organization is to inspire new approaches to research on cancer causes and therapies. Backed by a scientific advisory board, they initiated the Halifax Project by bringing together more than 300 scientists from research institutions in 31 countries to form two teams. One team focused on new approaches to cancer therapy, while the other one investigated low-dose exposure to everyday chemicals and their role in cancer development.

The research of the latter team, published in the scientific journal *Carcinogenesis*,[3] shows that many common and widespread chemicals can affect cancer-related mechanisms in the body at the low doses people typically encounter in the environment. Although these chemicals are not known to cause cancer on their own, the reports present the novel idea that they can combine in ways that have synergistic carcinogenic effects. The findings suggest that it may be time for fundamental change in the way we think about chemical carcinogens.

Cancer does not develop all at once. It happens through a series of mutations and genetic changes that collectively transform normal cells into aggressive cancer cells – the "multiple hits" model. Many chemicals that can interfere with individual cancer-related processes are not complete carcinogens, but exposure to combinations of these substances could interfere with multiple cancer-related processes, overwhelm the body's defense mechanisms, and result in cancer. That is the underlying hypothesis the Halifax Project is exploring.

Its scientists are asking three questions:

- Are there such things as partial carcinogens?
- Can partial carcinogens cause adverse health effects at low doses?
- Can exposure to the right (or wrong) combinations of partial carcinogens have synergistic, cancer-causing effects?

In effect, they are applying the ideas of the multiple-hit model of cancer development to the concept of chemical carcinogenesis. In doing so, they may bring about a fundamental shift in the way we think about carcinogens – advancing beyond the model of single chemical "bad actors" to a model that considers the combined effects of biologically disruptive chemicals that have historically been deemed to be non-carcinogenic.

Every day people are exposed to a chemical cocktail: volatile chemicals in the air we breathe, disinfection by-products and other contaminants in our water, numerous synthetic chemicals in the food we eat and the consumer products we buy. Most of them are present in only small amounts. The Halifax Project examined toxicity information on 85 widely used chemicals (see a full list in Appendix 1) that are not considered classically carcinogenic and found that the majority (50) were able to disrupt cancer-related mechanisms at these low doses.[3]

This important discovery challenges the prevailing tenet of toxicology that "the dose makes the poison," i.e., that in small enough amounts even something known to be toxic is unlikely to hurt you. Although the Halifax Project scientists investigated only a small number of chemicals, the findings suggest that many of the hundreds of substances people are exposed to daily at low levels may be capable of affecting cancer-related processes.

CHEMICALS IN OUR BODY

The logical next question is: What role do the combined effects of chemicals that interfere with cancer-related processes play in the actual development of cancer?

TABLE 1.

BIOLOGICALLY DISRUPTIVE CHEMICALS INVESTIGATED BY THE HALIFAX PROJECT THAT HAVE BEEN MEASURED IN NHANES BIOLOGICAL SAMPLES

2,2-bis-(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE)	Iron
Acrylamide	Lead
Alloy particles (tungsten/nickel/cobalt)[1]	Lindane (gamma-hexachlorohexane)
Bisphenol A (BPA)	Mercury
Cadmium	Methoxychlor
Cobalt	Methylmercury
Copper	Perfluorooctane sulfonate (PFOS)
Cotinine	Phthalates
DDT	Polybrominated diphenyl ethers (PBDEs)
Dibutyl phthalate (DBP)	Triclosan
Diethylhexyl phthalate (DEHP)	Tungsten
Hexacholorobenzene	

[1] cobalt, nickel and tungsten measured independently in NHANES biological samples

This is especially important when you consider that many chemicals are known to accumulate and remain in the body for long periods of time. The National Biomonitoring Program, conducted through the Centers for Disease Control and Prevention, has found and measured 265 environmental chemicals in human blood and urine samples collected as part of the National Health and Nutrition Examination Survey (NHANES).[4] We know that many of these chemicals will be present in the body at the same time, even if the exposures do not occur simultaneously.

Each year, NHANES evaluates about 5,000 adults and children from across the United States to assess the health and nutritional status of the nation. Biological samples taken as part of the survey provide a good "snapshot" of chemical exposures in the population. The Environmental Working Group found that 23 of the 85 "partial carcinogens" investigated by the Halifax Project have been detected in the blood and urine sampled from the NHANES population (Table 1). These 23 chemicals – mostly metals, plasticizers (BPA and phthalates) and pesticides – circulate in the body and are known to disrupt certain cancer-related pathways. EWG has independently measured many of these same chemicals in biological samples, including in umbilical cord blood, showing that exposure to these chemicals may be passed from a mother to her unborn child.[5,6]

The 23 chemicals listed in Table 1 represent only those directly measured in NHANES biological samples. There are other chemicals that are quickly eliminated from the body and unlikely to be analyzed or detected in a non-specific survey such as NHANES. Just because a chemical passes quickly through the body, however, does not mean it poses no health risk. For example, the pesticide glyphosate, recently classified as probably carcinogenic by the World Health Organization, remains in the body for only a few hours after exposure.

Chemicals can also be metabolized in the body and transformed into other substances as part of the natural process of detoxification. These metabolites are indicators that chemicals have been present and interacted with the body's chemistry, and they, too, can be toxic. Metabolites such as atrazine mercapturate, a breakdown product of the pesticide atrazine, have been measured in biological samples but are not included in the list above.

NHANES does not provide an exhaustive list of chemicals found in the general population. EWG's review of the scientific literature found data on 12 of the other 62 chemicals studied by the Halifax Project that have been directly measured in humans (Table 2).[7-29] The Halifax Project also lists three medications – diethylstilbestrol, phenobarbital and reserpine – and melatonin, a hormone produced by the body naturally that can also be taken as a dietary supplement. The scientific data clearly shows that chemicals in the environment end up in the body and interact in ways we don't fully understand.

TABLE 2.

ADDITIONAL BIOLOGICALLY DISRUPTIVE CHEMICALS INVESTIGATED BY THE HALIFAX PROJECT THAT HAVE BEEN DIRECTLY MEASURED IN BIOLOGICAL SAMPLES

4-Nonylphenol	Chlorpyrifos
Acrolein	Cypermethrin
Atrazine	Diazinon
Benzo(a)pyrene	Nickel
Bisphenol AF	Nickel derived compounds[1]
Chlorothalonil	Nitric oxide

[1] measured as nickel

2. "Hallmarks of Cancer:" How Normal Cells Turn into Cancer Cells

Cancer develops over time as mutations and genetic changes accumulate in cells. The traits a normal cell acquires as it slowly transforms into a precancerous one and ultimately into cancer are called the "Hallmarks of Cancer".[30,31] They are the characteristics that distinguish cancer cells from normal cells. Although each hallmark contributes to cancer, it is not until a cell exhibits the complete set of characteristics that cancer has fully developed. This framework illustrates that cancer develops through a set of discrete transformations (genetic changes). This is known as the multi-hit model of carcinogenesis because it takes multiple alterations or "hits" to cellular processes for cancer to develop.

To fend off cancer, the human body has many layers of safeguards to control cell division and prevent DNA damage. A chemical that interferes with a single cancer-related hallmark process, therefore, is unlikely to cause cancer. But combine a chemical that interferes with the cell division cycle with one that interferes with the cellular death cycle and you begin to see how exposures to chemical mixtures have the potential to overwhelm the body's defenses. Understood in this way, it is easy to see how chemicals that interfere with one or more hallmark processes could combine to form carcinogenic mixtures that apply multiple "hits" to cellular processes.

THE HALLMARKS OF CANCER

In two landmark scientific papers, Douglas Hanahan of the University of California, San Francisco and Robert Weinberg of the Massachusetts Institute of Technology described the Hallmarks of Cancer this way:[30, 31]

1. Self-sufficient cell division

Cells are organized into tissues and tissues are organized into organs with specific functions, such as the heart, lungs and skin. The cells of each organ must work and communicate as a team to function properly. When growth is necessary, cells collectively send signals to other cells to divide. Cancer cells, on the other hand, do not behave as team members. They control their own proliferation by producing growth signals themselves or by having overactive signal receptors.

2. Insensitivity to signals to stop cell division

Just as there are signals that stimulate cell proliferation, there are signals that put the brakes on cell growth and proliferation. Cancer cells are able to interrupt or ignore these inhibitory messages. Usually this is a result of mutations or alterations to genes known as tumor suppressor genes, which normally control a cell's response to external and internal cues to exit the cell division cycle.

3. Resisting cell death

When cells become old or damaged they are programmed to die in a process called apoptosis. This is the body's way of limiting growth and discarding cells with damaged DNA in order to prevent propagation of DNA errors. Cancer cells are dangerous because they avoid the normal cell death cycle and continue to accumulate in the body. Apoptosis signals can be disrupted when tumor suppressor genes suffer mutations or other damage.

4. Limitless reproductive potential

The accumulation of the billions of cells it takes to form a tumor requires uncontrolled cell division, avoidance of apoptosis *and* the ability to replicate an unlimited number of times. In normal cell division, a small portion of the end of each chromosome, in a region called the telomere, is lost every time DNA is

TABLE 3:

CHEMICALS WITH EVIDENCE OF AFFECTING CANCER HALLMARK PROCESSES

Hallmark Process	Chemicals[1]
Self-sufficient cell division	Low Dose Effect: bisphenol A (BPA), etoxazole, imazalil, methoxychlor, perfluorooctane sulfonate (PFOS), phthalates, polybrominated diphenyl ethers (PBDEs), prochloraz, trenbolone acetate (anabolic steroid) Threshold effect (no low dose effect): cyprodinil, edible oil adulterants, pyridaben Low Dose Effect Unknown: lactofen, maneb, phosalone
Insensitivity to signals to stop cell division	Low Dose Effect: atrazine, BPA, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT), folpet
Resisting cell death	Low Dose Effect: BPA, dibutyl phthalate, dichlorvos, methoxychlor Threshold effect (no low dose effect): chlorothalonil, diethylhexyl phthalate, lindane, oxyfluorfen Low Dose Effect Unknown: linuron
Limitless reproductive potential	Low Dose Effect: acetaminophen, cotinine, diethylstilbestrol, lead, nickel-derived compounds, nitric oxide, phenobarbital, sodium selenite Threshold effect (no low dose effect): reserpine *Note: potential compounds (limited research available)
Creating their own blood supply	Low Dose Effect: chlorothalonil, 2,2-bis-(p-hydroxyphenyl)-1,1,1-trichloroethane, PFOS Threshold effect (no low dose effect): dinicon-azole, ziram Low Dose Effect Unknown: biphenyl, bisphenol AF, C.I. solvent yellow 14, tributyltin chloride, methylene-bis(thiocyanate)

Ability to invade other organs	Low Dose Effect: hexachlorobenzene, phthalates, tetrabromobisphenol A (and metabolites: BPA, tetrabromobisphenol A dimethyl ether) Low Dose Effect Unknown: biorhythms/melatonin, iron, sulfur dioxide
Ability to survive with little oxygen	Low Dose Effect: acrolein, cadmium, copper, cypermethrin, diazinon, iron, nickel, rotenone Low Dose Effect Unknown: hexythiazox, malathion
Evading the immune system	Low Dose Effect: BPA, maneb, triclosan Threshold effect (no low dose effect): diethylhexyl phthalate, pyridaben Low Dose Effect Unknown: atrazine, azamethiphos, fluoxastrobin, pyraclostrobin
Genomic instability	Low Dose Effect: alloys (containing: tungsten, nickel, and cobalt), carbon nanotubles, cobalt, mercury, nickel Threshold effect (no low dose effect): benomyl, BPA, lead Low Dose Effect Unknown: acrylamide, halobenzoquinones (quinones), titanium dioxide nanoparticles
Inflammation	Low Dose Effect: BPA Threshold effect (no low dose effect): PBDEs Low Dose Effect Unknown: 4-nonylphenol, atrazine, phthalates, vinclozolin

Source: Goodson WH, Lowe L, et al. (2015).
[1] Dose-response effects (low dose, threshold-level effect, unknown dose-response) specific to each hallmark process

copied. Eventually the loss of telomere reaches a critical point and the cell can no longer divide and replicate. In this way, healthy cells self-limit their replication, but activation of an enzyme called telomerase can maintain telomeres and allow the cell to continue to replicate indefinitely. More than 90 percent of "immortalized" cancer cells have activated telomerase, while most normal cells do not.

5. Creating their own blood supply

In order for a tumor to grow it needs a greater and greater blood supply to provide oxygen and nutrients to the increasing number of cells. A tumor is able to stimulate formation of new blood vessels, a process known as angiogenesis, to supply it with adequate nutrients and promote its growth.

6. Ability to invade other organs

Cancer cells, unlike normal cells, can metastasize – break through tissue barriers and spread from one organ to another. Sometimes they do this by entering the newly formed blood vessels created by the tumor.

7. Ability to survive with little oxygen

Even with an increased blood supply, cells in the interior of a tumor may be oxygen- and nutrient-deprived. This would be detrimental to normal cells, which use oxygen to convert glucose to energy through the process of aerobic metabolism. Cancer cells have the ability to switch from aerobic to anaerobic (oxygen-free) glucose metabolism (glycolysis) to allow oxygen-deprived cells to continue to produce energy and survive.

8. Evading the immune system

When functioning properly, the body's immune system detects and destroys foreign and abnormal cells. Although the process is not fully understood, there is evidence that cancer cells are able to evade destruction by the body's immune defenses to some degree, allowing them to proliferate and invade other tissues.

These eight hallmark characteristics that distinguish cancer cells from normal ones are made possible by two final characteristics that enable the alterations necessary for a cell to become cancerous:

9. Genomic instability

Genes are segments of DNA that provide the instructions for all cellular activity. The accumulation of changes to specific genes that promote cell proliferation (e.g., activating oncogenes) or disrupt control mechanisms (e.g., tumor suppressor genes) can result in normal cells acquiring hallmark characteristics and transforming into cancer cells.

10. Inflammation

Chronic inflammation can result in conditions that promote proliferation, cell survival and angiogenesis. Inflammation can also enhance production of free radicals that can damage DNA.

Table 3 lists chemicals found by the Halifax Project team to alter the cancer-related hallmark processes. The list represents just a sample of potentially hundreds of chemicals that may interfere with these processes. Many of the chemicals are in pesticide residues on the foods we eat or are ingredients in personal-care products we use daily. These chemicals are ubiquitous in the environment and many can cause potentially harmful effects at low doses.

A SHORT PRIMER ON CANCER BIOLOGY

The hallmarks of cancer provide a framework for the idea that chemicals that interfere with discrete cancer-related mechanisms may combine to create carcinogenic combinations in a manner consistent with the multi-hit model of carcinogenesis. In order to better understand the role that chemical exposures, specifically chemical mixtures, play in the risk of developing cancer, it is helpful to understand the biology of cancer and how the disease develops.

Cells divide (i.e. replicate) in order for the body to grow and maintain itself. Cancer happens when abnormal cells begin to divide and proliferate uncontrollably. Unlike normal cells, cancer cells do not respond to the signals that control cell division. Because cancer cells grow and divide uncontrollably, they rapidly accumulate. In most cases, tumors eventually form as cancer cells become crowded within tissues and organs. In the late stages of cancer, malignant tumors can metastasize – break through tissue boundaries and form new tumors in other organs. It is the growth and spread of tumors that can lead to the shutdown of vital organ systems, which is the primary cause of death from cancer.

The process of cell division is carefully regulated by two main categories of genes. One category provides signals that stimulate cell proliferation, while the other provides signals that inhibit it. These genes also detect damaged cells and signal them to enter apoptosis, or programmed cell death. A proper balance between growth and inhibitory signals is critical to ensure that tissues and organs function as they should. Mutations or other changes in these two categories of genes are the major cause of healthy cells transforming into cancerous ones.

Our current understanding of cancer is that it is a multistep process and not a disease that develops all at once – the multi-hit model. For example, a mutation to a gene that promotes cell growth can allow a cell and all its offspring to replicate faster than normal. A second mutation to a gene that inhibits proliferation can allow a cell to break free from the normal constraints on cell division. One by one, this accumulation of mutations and gene alterations causes a normal cell to take on the traits of a cancer cell until eventually the transformation is complete.

3. Comparing Cancer Risk Factors: Should We Be Concerned?

The reports of the Halifax Project demonstrate that the universe of cancer-causing chemicals may be much larger than the list of known complete carcinogens. There may be such a thing as partial chemical carcinogens that play a role. But even if chemicals and combinations of chemicals can cause cancer, is that a big concern? How many cancers can be attributed to chemical exposures rather than other risk factors such as inheritance and lifestyle choices?

We know that inherited genetic variability – the genes we're born with – can increase our risk of cancer. For example, breast cancer rates are much higher among women who inherited mutations in the BRCA1 and BRAC2 tumor suppressor genes. However, we are learning that only a relatively small proportion of cancers can be attributed solely to heredity.

One study in twins showed that, among the cancers the researchers investigated, at most 42 percent of cancer incidence was due to heritable factors.[32] Studies of people who migrated from one country to another also demonstrate the importance of lifestyle and environmental factors. These studies have found that cancer rates among migrants more closely resemble those in the country they move to than their country of origin.[33, 34] Clearly, a large proportion of cancers are caused by something other than inheritance.

In fact, we know that diet, lifestyle choices, viral infections, radiation, environmental contaminants and all things *not* genetic play a role in cancer causation and may cause up to 95 percent of certain cancers.[35] It's hard to know exactly how many cases of cancer are the result of exposures to toxic chemicals, but occupational exposures alone are estimated to cause 2-8 percent of all cancers.[36]

The bad news is that the environment in which

we live and work is increasing the risk of cancer. The good news is that cancers caused by environmental contaminants are preventable. However, as the reports of the Halifax Project make clear, our understanding of the interplay between cancer and environmental exposures, particularly to chemicals, is incomplete. This has important implications for the regulation of potential environmental carcinogens. As the 2008-2009 report of the President's Cancer Panel said, federal environmental laws "fail to address the potential hazards of being exposed to combinations of chemicals."

Another weakness of current environmental laws is that for many chemicals, there is either a lack of political will to enact meaningful regulation or a lack of information on toxicity. Environmental chemicals have been known to cause cancer since as far back as 1775, when an English surgeon, Sir Percivall Pott, made the connection between high rates of scrotal cancer among chimney sweeps and exposure to soot.[37] Today the International Agency for Research on Cancer and the U.S. Environmental Protection Agency (EPA) have classified hundreds of chemicals as having carcinogenic potential, but we know these lists are incomplete.

According to the EPA's Chemical Hazard Data Availability Study, only about 7 percent of approximately 3,000 chemicals produced or imported in high volumes (at least one million pounds a year) have complete toxicity profiles. Even more alarmingly, the Halifax Project team found no existing dose-response information for 22 (26 percent) of the 85 chemicals it examined. The vast numbers of chemicals in the environment that have not been properly tested for carcinogenic potential represents an immediate public health threat that demands an organized approach to prioritize testing of chemicals with the greatest likelihood of causing cancer.

When you consider that there are thousands of chemicals and millions of possible combinations, it is clear that testing chemical mixtures for toxicity is a monumental task.[38] We need new tools to help identify chemicals and chemical mixtures that may be linked to cancer. One approach urged by the Halifax Project reports is to use the hallmarks of cancer to identify the chemical mixtures with the greatest potential to cause disease. Screening for chemicals that interfere with hallmark processes could be a highly efficient way to target carcinogenicity testing of the thousands of chemicals for which we lack toxicity information.

CONCLUSION AND RECOMMENDATIONS:

It is clear that reducing or eliminating exposures to carcinogenic chemicals in the environment could prevent a large number of cancers. However, the hallmarks of cancer framework suggests that complete carcinogens may only be one piece of the total cancer risk. Development of cancer is a multistep, multi-hit process that occurs through the accumulation of cancer hallmarks in a cell. The understanding of this model of cancer development is applied in the Halifax Project's new ideas about how combinations of chemicals can cause cancer. It identified 85 chemicals common in the environment that can disrupt one or more cancer-related hallmark process. Combinations of such chemicals could very well have synergistic carcinogenic effects, which we are only beginning to discover. Focusing exclusively on complete carcinogens fails to consider the possibility that combinations of chemicals could work in concert to lay the groundwork for cancer and knock out the body's defenses against it.

Just as troubling are the Halifax Project's findings that low doses of a large number of partial carcinogens can affect cancer-related pathways. This calls into question whether current safety standards, which are generally based on high-dose toxicity testing, are sufficiently protective.

When you consider the vast number of possible chemical combinations, many of which act at low doses, the relationship between exposures and cancer gets even more complex. Although this makes the study and regulation of chemical mixtures an extremely daunting task, the findings of the Halifax Project suggest that the hallmarks of cancer framework can provide a blueprint for setting priorities based on the mixtures' carcinogenic

potential. Continuing to identify and regulate only complete carcinogens ignores the serious threat that chemical mixtures can pose to public health.

Recommendations for research and health:

- The hallmarks of cancer should be used to set priorities for screening chemicals and chemical mixtures for carcinogenic effects.
- Further study is necessary to determine the effects of chronic lifetime exposure to chemical mixtures, including the accumulation of chemicals in the body, with particular attention to chemicals that disrupt cancer-related hallmark processes.
- Chemical safety standards should be revisited so as to carefully consider low-dose health effects.

Recommendations for policy, with special consideration for reform of the Toxic Substances Control Act (TSCA):

- Federal and state regulation should extend beyond "complete carcinogens" and take into account the effects of chemical mixtures on specific modes of cancer causation – the hallmarks of cancer.
- Reform of TSCA should not hinder EPA from adopting new risk assessment models based on the Halifax Project's insight that combinations of hallmark-disrupting chemicals can have synergistic carcinogenic effects, as this information becomes available.
- TSCA should include provisions for EPA to consider cumulative exposures to single chemicals and chemical combinations.
- Chemicals that disrupt hallmark processes should be given special consideration, since these chemicals are unlikely to be regulated under EPA's current risk assessment and cost/benefit analyses.
- Reform of TSCA should include a special section providing research funding and an evaluation process for the health effects of chemical combinations.

APPENDIX 1

HALLMARK-DISRUPTING CHEMICALS INVESTIGATED BY THE HALIFAX PROJECT

12-O-Tetradecanoylphorbol-13-acetate (TPA)	Cypermethrin	Methylmercury
2,2-bis-(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE)	Cyprodinil	Na-selenite
4-Nonylphenol	DDT	Nickel
Acetaminophen	Diazinon	Nickel-derived compounds, (e.g. Nickel chloride)
Acrolein	Dibutyl phthalate (DBP)	Nitric oxide
Acrylamide	Dichlorvos	Oxyfluorfen
Alloy particles (tungsten/nickel/cobalt)	Diethylhexyl phthalate (DEHP)	Paraquat
Atrazine	Diethylstilbestrol	Perfluorooctane sulfonate (PFOS)
Azamethiphos	Diniconazole	Phenobarbital
Benomyl	Edible oil adulterants	Phosalone
Benzo(a)pyrene	Etoxazole	Phthalates
Biorhythms/Melatonin	Fluoxastrobin	Polybrominated diphenyl ethers (PBDEs)
Biphenyl	Folpet	Pyraclostrobin
Bisphenol A	Hexacholorobenzene	Pyridaben
Bisphenol AF	Hexythiazox	Quinones
Butyltins (such as TBT)	Imazalil	Reserpine
C.I. solvent yellow 14	Iron	Rotenone
Cadmium	Lactofen	Sulfur dioxide
Carbendazim	Lead	Tetrabromobisphenol A
Carbon black	Lindane	Tetrabromobisphenol A dimethyl ether
Carbon nanotubes	Linuron	Titanium dioxide nanoparticles
Chlorothalonil	Malathion	Tributyltin chloride
Chlorpyrifos	Maneb	Triclosan
Cobalt	Mercury	Tungsten
Copper	Methoxychlor	Vinclozolin
Cotinine	Methylene bis(thiocyanate)	Ziram

Source: Goodson WH, Lowe L, et al. (2015).

REFERENCES

1. (HHS) U.S. Department of Health and Human Services. Reducing Environmental Cancer Risk: What We Can Do Now. President's Cancer Panel, 2008-2009 Annual Report(year). By Suzanne H. Reuben. Bethesda, MD. April 2010.
2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300.
3. Goodson III W, Lowe L, Carpenter D, et al. Assessing the carcinogenic potential of low dose exposures to chemical mixtures in the environment: the challenge ahead. *Carcinogenesis*. 2015
4. Centers for Disease Control and Prevention (CDC). Forth national report on human exposure to environmental chemicals. Atlanta, GA. 2015http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf
5. Houlihan J, Kropp T, Wiles R, Gray S, Campbell C, Greene A. (2005, July 14). Body burden: the pollution in newborns. Retrieved from http://www.ewg.org/research/body-burden-pollution-newborns
6. (EWG) The Environmental Working Group. (2009, Nov. 23). Pollution in people: cord blood contaminants in minority newborns. Retrieved from http://www.ewg.org/research/minority-cord-blood-report
7. Arrandale VH, Beach J, Cembrowski GS, Cherry NM. Urinary metal concentrations among female welders. *Ann Occup Hyg*. 2015 Jan;59(1):52-61.
8. Asimakopoulos AG, Thomaidis NS, Koupparis MA. Recent trends in biomonitoring of bisphenol A, 4-t-octylphenol, and 4-nonylphenol. *Toxicol Lett*. 2012 Apr 25;210(2):141-54.
9. Asimakopoulos AG, Thomaidis NS. Bisphenol A, 4-t-octylphenol, and 4-nonylphenol determination in serum by Hybrid Solid Phase Extraction-Precipitation Technology technique tailored to liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2015 Apr 1;986-987:85-93.
10. Barr DB, Ananth CV, Yan X, et al. Pesticide concentrations in maternal and umbilical cord sera and their relation to birth outcomes in a population of pregnant women and newborns in New Jersey. *Sci Total Environ*. 2010 Jan 15;408(4):790-5.
11. Buckley TJ, Geer LA, Connor TH, et al. A pilot study of workplace dermal exposures to cypermethrin at a chemical manufacturing plant. *J Occup Environ Hyg*. 2011 Oct;8(10):600-8.
12. Chen B, Xia G, Cao XM, et al. Urinary levels of nickel and chromium associated with dental restoration by nickel-chromium based alloys. *Int J Oral Sci*. 2013 Mar;5(1):44-8.
13. Chevrier C, Limon G, Monfort C, et al. Urinary biomarkers of prenatal atrazine exposure and adverse birth outcomes in the PELAGIE birth cohort. *Environ Health Perspect*. 2011 Jul;119(7):1034-41.
14. Clough GF, Bennett AR, Church MK. Measurement of nitric oxide concentration in human skin in vivo using dermal microdialysis. *Experimental Physiology*. 1998; 83: 431-434
15. Darsow U, Fedorov M, Schwegler U, et al. Influence of dietary factors, age and nickel contact dermatitis on nickel excretion. *Contact Dermatitis*. 2012 Dec;67(6):351-8.
16. Garrett MC, McCullough-Hicks ME, Kim GH, et al. Plasma acrolein levels and their association with delayed ischemic neurological deficits following aneurysmal subarachnoid haemorrhage: a pilot study. *Br J Neurosurg*. 2008 Aug;22(4):546-9.
17. Hinwood A, Callan AC, Heyworth J, et al. Children's personal exposure to PM10 and associated metals in urban, rural and mining activity areas. *Chemosphere*. 2014 Aug;108:125-33.
18. Kasper-Sonnenberg M, Sugiri D, Wurzler S, et al. Prevalence of nickel sensitization and urinary nickel content of children are increased by nickel in ambient air. *Environ Res*. 2011 Feb;111(2):266-73.
19. Li LX, Chen L, Meng XZ, et al. Exposure levels of environmental endocrine disruptors in mother-newborn pairs in China and their placental transfer characteristics. *PLoS One*. 2013 May 7;8(5):e62526.
20. Madhavan ND, Naidu KA. Polycyclic aromatic hydrocarbons in placenta, maternal blood,umbilical cord blood and milk of Indian women. *Hum Exp Toxicol*. 1995;14:503-506.
21. Persoons R, Arnoux D, Monssu T, et al. Determinants of occupational exposure to metals by gas metal arc welding and risk management measures: a biomonitoring study. *Toxicol Lett*. 2014 Dec 1;231(2):135-41.
22. Sancini A, De Sio S, Gioffrè PA, et al. Correlation between urinary nickel and testosterone plasma values in workers occupationally exposed to urban stressors. *Ann Ig*. 2014 May-Jun;26(3):237-54.
23. Singh VK, Patel DK, Ram S, et al. Blood levels of polycyclic aromatic hydrocarbons in children of Lucknow, India. *Arch Environ Contam Toxicol*. 2008;54:348-354.

24. Singh VK, Singh J, Anand M, et al. Comparison of polycyclic aromatic hydrocarbon levels in placental tissues of Indian women with full and preterm deliveries. *Int J Hyg Environ Health*. 2008; 211:639-647.

25. Toriba A, Kuramae Y, Chetiyanukornkul T, et al. Quantification of polycyclic aromatic hydrocarbons (PAHs) in human hair by HPLC with fluorescence detection: a biological monitoring method to evaluate the exposure to PAHs. *Biomed Chromatogr*. 2003; 17:126-132.

26. Vallance P, Patton S, Bhagat K, et al. Direct measurement of nitric oxide in human beings. *Lancet*. 1995 Jul 15;346(8968):153-4.

27. Wang H, Yan H, Wang C, et al. Analysis of phenolic pollutants in human samples by high performance capillary electrophoresis based on pretreatment of ultrasound-assisted emulsification microextraction and solidification of floating organic droplet. *J Chromatogr A*. 2012 Aug 31;1253:16-21.

28. Yang J, Chen W, Li X, et al. Relationship between urinary nickel and methylation of p15, p16 in workers exposed to nickel. *J Occup Environ Med*. 2014 May;56(5):489-92.

29. Yang Y, Guan J, Yin J, Shao B, Li H. Urinary levels of bisphenol analogues in residents living near a manufacturing plant in south China. *Chemosphere*. 2014 Oct;112:481-6.

30. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000; 100(1):57-70

31. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144(5):646-674

32. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343(2):78-85.

33. Kolonel LN, Altshuler D, Henderson BE. The multiethnic cohort study: exploring genes, lifestyle and cancer risk. *Nat Rev Cancer*. 2004;4(7):519-527.

34. McCredie M. Cancer epidemiology in migrant populations. *Recent Results Cancer Res*. 1998;154:298-305.

35. Anand P, Kunnumakkara AB, Kunnumakara AB, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res*. 2008;25(9):2097-2116.

36. Purdue MP, Hutchings SJ, Rushton L, Silverman DT. The proportion of cancer attributable to occupational exposures. *Ann Epidemiol*. 2015;25(3):188-192.

37. Pott, P. Chirurgical observations relative to the cataract, the polypus of the nose, the cancer of the scrotum, the different kinds of ruptures, and the mortification of the toes and feet. *CA: A Cancer Journal for Clinicians*. 1974; 24: 110–116

38. Koppe JG, Bartonova A, Bolte G, et al. Exposure to multiple environmental agents and their effect. *Acta Paediatr Suppl*. 2006;95(453):106-113