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Hormesis: Fact or Fiction?

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Abstract

Hormesis is a phenomenon that until recently was not readily understood nor is it generally accepted. Through research and experimentation, we have gathered enough information to convince us to accept the validity and social impact of hormesis. We have related this possible phenomenon to other well-known research areas such as toxicology, acceptable risk, and free radicals. We believe that if the idea of hormesis were broadly accepted there would be many benefits to society.

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1 Introduction

To understand hormesis and be able to experiment and hypothesize about the topic, it is crucial to understand the building blocks that lead to hormesis. These include topics such as free radicals, toxicology, as well as a sense of risk management. The following is a review of the literature found, and on some topics, a more detailed description of that information.

1.1 Hormesis

"Hormesis is the production of beneficial effects in a population at low exposures and adverse effects at high exposures to a given chemical, or more generally, the effects produced at high exposures are the inverse or apparent inverse of those produced at low exposures." (Holland, 2003) This is stating that a little bit of a bad thing, could be good for you. The small dose of a chemical will have a positive effect, while the large dose of the same chemical will have a negative effect. One theory of hormesis is that the small amount of a "bad agent" will trigger a biological response to defend, creating a positive substance in the specimen, and since the dose was so small these positive substances remain useful to the body for other purposes other than combating the "bad agent" ultimately making the specimen more fit. It is also stated that he hormetic response results from an initial disruption in homeostasis to one which responds by overcompensation in an effort to re-establish homeostasis. (Holland 2003)

1.1.1 Evidence of Existence

After the atomic bomb explosions in Hiroshima and Nagasaki, studies concerning life span of atomic bomb survivors showed a linear relationship between cancer mortality and high doses of radiation (Pollycove, 1998). The United Nations Scientific Committee on the Effects of Atomic Radiation then proposed the linear no-threshold theory in 1958 (UNSCEAR, 1958). The LNT has two major points. First, "The effects of low doses of ionizing radiation can be estimated by linear extrapolation from effects observed by linear extrapolation from effects observed by high does." Secondly, "There is not any safe dose because even very low doses of ionizing radiation produce some biological effect." In 1959 the international commission on radiation protection adopted the LNT theory (ICRP, 1959). Obviously this is directly stating that there is no hormetic effect. Interestingly, the results of many investigations do not support the LNT theory. Furthermore several studies including Cohen's studies of the relationship between environmental radon concentration and lung cancer contradict this theory and clearly suggest that there is a hormetic effect.

Deeper into the report it explains that although radiation hormesis data is still incomplete, extensive epidemiological studies have indicated that radiation hormesis really exists. There were four Japanese studies discussed in Mortazavi's report. The first, according to an UNSCEAR report in 1994, stated, "Among A-bomb survivors from Hiroshima and Nagasaki who received doses lower than 200mSv, there was no increase in the number of total cancer death. Mortality caused by leukemia was even lower in this population at doses below 100mSv than age-matched control cohorts." The second involved Mifune and his co-workers and was done in 1992. "[They] indicated that in a

spa area, with an average indoor radon level of $35 \frac{Bq}{m^3}$, the lung cancer incidence was about fifty percent of that in a low-level radon region. (Mifune et al., 1992) Their results also showed that in the above mentioned high background radiation area; the mortality rate caused by all types of cancer was thirty-seven percent lower. The third study only included a brief statement that said the expected death rate was actually higher than the actual death rate amongst A-bomb survivors. The final study reported that, "according to their twenty five year follow up study of Japanese fishermen who were heavily contaminated by plutonium (hydrogen bomb test at bikini), no one died from cancer." (Kumatori et al., 1980)

The conclusion of the literature states, "Our radiation protection policy is based on a linear extrapolation from the dose-response data of high doses of ionizing radiating. According to the results of many worldwide studies, this assumption is not compatible with observed health effects of low levels of radiation. Obviously LNT and current radiation protection regulations exaggerate the risk of low-level ionizing radiation (in the range of 1-50 cGy) and cause radiophobia (Yalow RS, 1990). It is concluded that according to the new findings, the existence of radiation hormesis and adaptive response are not deniable and abandoning the LNT theory in low dose risk estimations will be a real necessity in the near future.

A quote from *Is Radiation Good for you?* agreeing with Mortazavi states in response to the title, "The Answer is yes but only in very small doses." It goes on to say "If this is right, environmental regulation will never be the same." (Hively, 2002)

1.2 Free Radicals

Free radicals are one topic that is closely related to our main research. Dr. Tamer Fouad, M.D. submitted a paper to the Doctor's Lounge titled "Free Radicals, Types, Sources and Damaging Reactions." The existence of free radicals in biological systems was not taken seriously until further investigational techniques were discovered. (Fouad, 1999) Now they are closely under study and are said to have a role in rheumatoid arthritis, Alzheimer's disease, hypertension, and myocardial ischemia among other diseases. A free radical is a "chemical species", as put in Fouad's paper, whose outer valence shell has an unpaired electron. With this unpaired electron it is highly reactive and can affect thousands of cells very efficiently and quickly. It is able to react with molecules such as proteins, lipids, carbohydrates, and DNA and the interesting part is that once it reacts with such a molecule, that affected molecule is now the free radical. (Fouad, 1999) Eliminating, or even simpler, locating this free radical becomes a difficult task because its form is always changing. Interestingly enough, there are some simple ways to help your body fight them.

Antioxidants such as vitamin E, a fat soluble vitamin present in nuts, seeds, vegetable and fish oils, whole grains, fortified cereals, and apricots, and vitamin C, an ascorbic acid that is water soluble present in citrus fruits and juices, green peppers, cabbage, spinach, broccoli, cantaloupe, kiwi, and strawberries, will attach to these free radicals before they are able to harm any cells, preventing damaged tissue. (NEJM, 1994) A report in Harvard magazine (Verdine, 1998) goes on to say that it may seem simple, but no matter how many vitamins or antioxidant you take, the free radicals in your body will always exist and do their process. Fortunately, Gregory Verdine a professor of Chemistry at Harvard says that the body creates a special protein called

hOGG1, or hog one, to fix damaged DNA. It's a large molecule antioxidant and acts by working with the products of oxidation. The oxidants perform their process on the DNA and the hOGG1 checks the DNA constantly eliminating the damaged portions. Verdine and his team were able to make an image of the process catching the protein in action. The image was a collection of single molecules because, due to the extremely small size, it was not possible for them to create high-resolution images of just one molecule. With the use of genetic engineering he and his team created bacteria that made large quantities of hOGG1. Next, they chemically synthesized DNA "indistinguishable from what you find in human cells". (Verdine, 1998) After combining DNA with the newly created hOGG1, the resulting mixture was crystallized. He goes on to state "In a crystal every molecule has the same orientation, so they create a uniform, repeating pattern. That way, when you shoot x-rays at the crystal, you get the cumulative signal from every molecule." (Verdine, 1998) Once Verdine and his students had established on Harvard's equipment that their crystal would generate a strong signal, they took it to a powerful synchrotron (particle accelerator) at Brookehaven Nation Laboratories. There they shot through the crystal a beam of x-rays so energetic that Verdine says, "If you put your hand in, it would fry instantly." The electrons of the crystal diffract the x-rays, creating a pattern. With the aid of computers, Verdine worked backward from this pattern to create a model of the molecule. Because the model shows every atom, it is too complex to create an easily recognizable image, so Verdine has created a simplified version. The result shows a strand of the familiar double helix with the protein hOGG1 poised over it, caught in the act of DNA repair. Thus, it eliminates the damage of free radicals on your DNA. (Verdine, 1998)

One may wonder where these free radicals come from. Well a simple answer is they are produced by your body, through what you eat and drink and breathe. Another cause is radiation. Reading "An Introduction to Radiation Hormesis" (Mortazavi, 2001) it explains how besides obvious external radiation, internal ionizing radiation can lead to the creation of free radicals. He goes on to say, "Some pioneer scientists reported that low-dose ionizing radiation is not only a harmless agent but often has a beneficial or hormetic effect." (Mortazavi, 2001) So something negative like radiation that causes free radicals could possibly create those same free radicals to do something good? The answer is yes, but such small amounts of these so-called "bad things" are needed to produce this hormetic affect, that it is very difficult to find positive data on the subject. Hormesis is defined in Martazavi's writings as any stimulatory or beneficial effect, induced by low doses of an agent that cannot be predicted by the extrapolation of detrimental or lethal effects induced by high doses of the same agent. He also goes on to write of the early 1900's where it was believed that ionizing radiation and X-rays had numerous beneficial effects. Bottles of drinking water with radium were highly popular and even women's' corsets contained radium. It was advertised that certain mixtures containing radium were able to treat over 150 diseases. It wasn't until later research that victims who exceeded 350Sv were linked to complications and other harmful effects. (Mortazavi, 2001)

1.3 Toxicology

Knowing the adverse effects of a certain chemical is essential in studying a possible case of hormesis. According to Webster's Dictionary (Parker, 2004), Pharmacology is "the science of drugs including materia medica, toxicology, and

therapeutics" or "the properties and reactions of drugs especially with relation to their therapeutic value." Toxicology is "a science that deals with poisons and their effect and with the problems involved (as clinical, industrial, or legal)." The *Basic Principles of Toxicology,* written by Elizabeth Casarez, goes into detail on the topic of toxins. A toxicant, in other words a poison, is capable of producing a deleterious response in a biological system if given too large a dose. Hormesis works on the principle that if you find the correct dose, a toxicant may no longer cause adverse effects, but stimulate a positive biological response making the organism more fit, as Darwin might put it. Unfortunately, it is difficult to find that correct dose.

Casarez states five axioms of toxicology. The first being there is essential uniformity in the biochemistry in similar species among biological mechanisms in mammals. This allows for extrapolation from animal data for predictions in humans. This explains why animal testing can be relevant to a product for humans. Secondly, any substance can provoke a dysfunction or injury at some degree of exposure, the dose makes the poison. Attenuation of injury can be achieved by dilution; i.e., lowering the dose of the agent. Complications can occur when there is exposure to more than one agent, even at non-toxic doses. That opens the doorway to even more experimentation, dealing with low-doses of multiple toxins, to provoke a hormetic response. Next, there is a dosage or exposure level that has no effect on the health of animals, as measured by the methods which have finite sensitivity to measure dysfunction or injury. The fourth axiom states toxicological data from animal experiments can be used to assess the degree of exposure or dosage that will not adversely affect human health. However, potential or real differences in animals or

humans (as well as variations in species) each mandate that judgmental factors be applied when extrapolating from animal threshold doses in order to insure an adequate margin of safety for humans. The final axiom says that the single most important factor that determines the potential harmfulness of a chemical is the relationship between the concentration of the chemical at its site of action and the effect that is produced. With these facts clearly established, it is possible to move forward with getting a grasp on the subject of hormesis.

The potential toxicity (harmful action) inherent in a substance is exhibited only when that substance is exposed to a living biological system. The potential toxic effect increases as the exposure, time, and or concentration increases. All chemicals will exhibit a toxic effect given a large enough dose. The toxic potency of a chemical is thus ultimately defined by the dose (the amount) of the chemical that will produce a specific response in a specific biological system.

Hazardous chemicals enter the body mainly in four different ways; inhalation, ingestion, dermal contact, or percutaneously. Most exposure standards such as the Threshold Limit Values (TLVs) and Permissible Exposure Limits (PELs) are based on the inhalation route of exposure. TLVs are guidelines not standards which are prepared by the American Conference of Governmental Industrial Hygienists, Inc (ACGIH) to assist industrial hygienists in making decisions regarding safe levels of exposure to various hazards found in the workplace. PELs are regulatory limits on the amount or concentration of a substance in the air. They may also contain a skin designation. PELs are enforceable. OSHA sets them to protect workers against the health effects of exposure to hazardous substances. These limits are normally

expressed in terms of either parts per million (ppm) or milligrams per cubic meter ($\frac{mg}{m^3}$) concentration in air. If a significant route of exposure for a substance is through skin contact, the PEL and/or TLV will have a "skin" notation. There are several types of effects; an acute effect has sudden and severe exposure and rapid absorption of the substance. Normally a single large exposure is involved. Health effects are often reversible. A chronic effect has prolonged or repeated exposures usually measured in days, months, or years. Symptoms may not be immediately apparent and health effects are often irreversible. In addition, there are local and systemic effects. Local effects usually have adverse health effects only at the location of the contact. Systemic effects usually have adverse health effects away from the location of the contact. So many factors affect what and how the toxin affects the body. With vapors and gases the solubility of the substance is a key factor. Particle size is also a factor in the effect of the substance, larger particles deposit in different places then smaller ones.

There are several classes of chemicals that affect the body. Irritants are materials that cause inflammation of the mucous membranes with which they come in contact. Irritants can also affect the mechanics of respiration and lung functions. Asphyxiates are gases that reduce the bodies ability to absorb or process oxygen, usually very active at low concentrations. Anesthetics have a depressant effect on the central nervous system, particularly the brain. Hepatotoxins cause damage to the liver, Nephrotoxins cause damage to the kidneys, and neurotoxins cause damage to the nervous system. Some toxic agents act on the blood or hematopoietic system. The blood cells can be affected directly or the bone marrow (which produces the blood

cells) can be damaged. There are toxic agents that produce damage of the pulmonary tissue (lungs) but not by immediate irritant action. Fibrotic changes can be caused by free silica and asbestos. Other dusts can cause a restrictive disease called pneumoconiosis. Carcinogens are agents that can initiate or increase the proliferation of malignant neoplastic cells or the development of malignant or potentially malignant tumors. A mutagen interferes with the proper replication of genetic material (chromosome strands) in exposed cells. If germ cells are involved, the effect may be inherited and become part of the genetic pool passed onto later generations. A teratogen (embryo toxic or feto-toxic agent) is an agent which interferes with normal embryonic development without causing a lethal effect to the fetus or damage to the mother. Effects are not inherited. A sensitizer is a chemical which can cause an allergic reaction in normal tissue after repeated exposure to the chemical. The reaction may be as mild as a rash (allergic dermatitis) or as serious as anaphylactic shock.

1.4 Avoidable and Unavoidable Social Risks

A man is driving home from work in his car during a heavy rainstorm. He is driving the speed limit; however, when it is raining the speed limit could now be construed as excessive by law enforcement. Thinking about the risk of driving brings to mind many different factors of life that we take for granted in our everyday life. Risk is "the possibility of suffering harm or loss; danger" (Parker, 2004). The first obvious risk is that of driving. Regardless of speed, death is an inherent risk while operating an automobile. For the majority of people, driving to work is not an option, because most jobs are not within walking distance, but in theory, he could find a job

closer to his house, use public transportation, or even work out of his home. Although all of these might be a solution to a prior problem, they now present new risks, for example, now that he is not driving himself, he leaves his life in the hands of another driver who is driving a bus with 40 people on it. Who do you trust more, yourself or someone else who you have never met before? Driving when the roads are dry is thought to be safer than driving in more hazardous conditions such as rain, snow, or sleet. This is a risk that the man can choose to accept or decline. Another risk that the man has control over, is whether or not he drinks alcohol, smokes cigarettes, does drugs, or has promiscuous sex. This now brings forth the question of the relative degree of risk associated with each activity.

Henceforth, if driving a car, being out in the rain, and drinking a diet soda are considered dangerous, what is considered safe? "Safety is defined as a judgment of the acceptability of risk, and risk as a measure of probability and severity of harm to human health" (Bartel, 2004). Even as a definition, safety is still a subjective idea. How safe is safe enough? Who decides on what is safe and what is not safe? "Safety is the degree to which risks are judged acceptable" (Bartel, 2004). Even the Environmental Protection Agency (EPA) has not identified a universal way to decide on acceptable risk. "No fixed level of risk could be identified as acceptable in all cases and under all regulatory programs" (Fischhoff, 2004). The EPA is saying that the level of acceptable risk is variable depending on the situation.

The first thing to consider would be whom the risk involves. This assumes that we know all factors pertaining to the risk and its outcomes. "In actual fact there are no agreed upon ways for assessing nervous system damage, immune system damage,

or damage to the genes. Furthermore, science has no way to evaluate the effects of exposure to several chemicals simultaneously. Because everyone in the real world is exposed to multiple chemicals simultaneously, risk assessment is never describing the real world, yet almost always PRETENDS to describe the real world" (Montague, 2004).

So who does the pretending? Bill Bartel, chief for the Safety and Occupational Health Office says that "Safety is not measured; risks are" (Bartel, 2004). Risks are measured in many different ways. "The certainty and severity of the risk; the reversibility of the health effect; the knowledge or familiarity of the risk; whether the risk is voluntarily accepted or involuntarily imposed; whether individuals are compensated for their exposure to the risk; the advantages of the activity; and the risks and advantages for any alternatives" (Fischhoff, 2004). This introduces the task of balancing benefits and risks.

Everyday people balance benefit and cost throughout their lives. Buying a lottery ticket is a great example. The person buying the ticket realizes that the odds are against them of winning the grand prize, but still takes the risk of losing the one-dollar for the chance of a lifetime. People that go running in the day most likely take into consideration the dangers of running in the streets with the cars driving along side of them so closely. However, to reduce the risk, they run during the day, instead of at nighttime, or possibly at night, but with reflective gear and bright clothing. All of these examples follow one general idea, which is that of compromise. It does not make compromise the best means of dealing with every situation, but it explains why a person is able to justify their decision to accept certain risks.

For induced risks, people must rely on the person(s) imposing the risk upon them. The risk of terrorism has had the people of the United States very concerned after 9/11. That will certainly be a day that no one will ever forget. The level of risk of terror is determined by a color system where red is the highest level of risk and green is the lowest. The description in the levels of risk from highest to lowest are: severe, high, elevated, guarded and low. In a country that is concerned with statistical numbers and evaluations, this has no quantitative value, which makes it hard to understand the precise differences between levels. We have been on high alert and nothing has happened, while we were not on any alert when 9/11 occurred. The question remains as to where society and each individual draw the line for acceptable. People generally will accept higher levels of risk for voluntary activity than for induced situations.

Alcohol is an excellent example of a voluntary risk. No one forces another individual to have a drink. The level of risk is very high for this activity because of things like drunk driving, alcohol poisoning, and even date rape. We feel that the level of risk is modified depending on the level of intoxication. If an individual is intending on driving home from a bar on any given night, the level of risk for having an accident is greatly increased with every drink consumed. "The use of illicit drugs and the abuse of alcohol also affect emotional equilibrium, mental well-being, and the ability to make critical decisions. Such use also impairs judgment, which in turn increases one's vulnerability and risk-taking behavior, including engaging in unprotected sex, which may lead to exposure to HIV and other sexually transmitted diseases and unplanned pregnancy" (University of Chicago, 2001). Women have an

added risk while consuming alcohol because it is possible for them to be taken advantage of while under the influence. This is a problem because it could lead to unwanted pregnancy, sexually transmitted diseases, or even brutal rape. Alcohol is not the only voluntary risk that many people accept everyday.

Many people in the world smoke cigarettes. Smoking cigarettes has been proven to directly increase a person's risk of getting cancer. "The risk of getting cancer is generally greater for smokers than non-smokers by a factor of 2.24" (Petrie, 2004) It has also proven to decrease life expectancy in most individuals. "Research has shown that smoking reduces life expectancy by seven to eight years. An interesting calculation predicts that on average, each cigarette shortens the life of the smoker by around seven to eleven minutes" (Petrie, 2004). The risk to them is unclear, non-threatening at the time, or irrelevant. Not only is smoking detrimental to a person's health, but it also leads to problems in the workforce. "Generally smokers have 25 per cent more sick days per year than non-smokers" (Petrie, 2004). This can lead to an inability to "climb the ladder" at work or even to lose an existing job due to recurrent absences. Being in the presence of cigarette smoke is almost as deadly as actually smoking the cigarette. It is a risk that creates all the same health problems of actually smoking, without the jolt of adrenaline. Smokers also hurt their unborn children, causing numerous complications with the delivery process. Babies born to mothers who smoke "are twice as likely to be born prematurely and with a low birth weight (below 2.5kg or 5lb 8oz)" (Petrie, 2004).

Drugs, recreational or prescribed, can create serious risks for an individual. Recreational drugs do not only create health issues, but also legal issues. The risk of

getting caught using or selling drugs is a chance people are willing to take because of the benefits from it. "The legal age of responsibility is 10" ("Risks of Using Drugs", 2004). They believe that the money they spend on the drugs and the time they are affected by them are worthwhile. What they are not thinking about is the serious damage they are inflicting to themselves and the risk they run of being caught, which could lead to jail time. Even prescribed drugs cause additional health issues. Although they may be curing one disease, they may be hurting an organ, or damaging tissue at the same time. These are all risks that people accept by choosing to use drugs whether they realize it or not.

One area of voluntary risk that most people do not normally take into consideration is that of promiscuous behavior. For the most part, no one is forced into having sex, which makes it a voluntary activity. The dangerous part about sex is the ability to acquire a myriad of sexually transmitted diseases in the course of 30 minutes to an hour. This risk is prominently associated with unsafe sex, but safe sex is not always as safe as people believe it to be. Some could be life threatening while others are just annoying. The thought of teen or pregnancy could ruin somebody's life in an instant because of the inability to continue school for the woman, the responsibility of being a father for the man, the financial hardship of taking care of a newborn or even family. It all can happen so fast, while many people accept this great risk everyday.

Although people choose to endure many voluntary risks, let us take a second to look at the unavoidable risks that many people incur everyday. A smaller scale risk is breathing in the outside air which contains pollution. No matter what part of the

country a person lives in, there is always the risk of air pollution. "In the city, air pollution may be caused by cars, buses and airplanes, as well as industry and construction. Air pollution in the country may be caused by dust from tractors plowing fields, trucks and cars driving on dirt or gravel roads, rock quarries and smoke from wood and crop fires" ("Outdoor Air Pollution: Possible Health Effects", 2004). The effect of pollution is different depending on certain groups of people. Pollution can lead to many illnesses and various diseases. "Children probably feel the effects of pollution at lower levels than adults. They also experience more illness, such as bronchitis and earaches, in areas of high pollution than in areas with cleaner air" ("Outdoor Air Pollution: Possible Health Effects", 2004). This could in turn create future health problems such as asthma, deterioration of the immune system, and even cancer.

The level of acceptability is very unclear. Where humans draw the line between acceptable and unacceptable risks varies upon situations due to their experiences, culture, age and many other factors. If a person is able to justify their reasoning for acting in a manor as they do, they are more likely to continue to accept the risks surrounding their actions. No matter what questions remain, there is one thing that is certain, which is that voluntary actions are able to have higher risks than that of induced situations.

2 Hormesis

2.1 Literary Review

Although the entire mechanisms of radiation hormesis are not known, the following theories help to explain this process.

According to the DNA repair theory, low doses of ionizing radiation induce the production of special proteins, which are involved in DNA repair processes (Ikushima, 1996). Studies using two-dimensional gel electrophoresis indicated new proteins in cells irradiated with low doses of radiation. In addition, it was further shown that cycloheximide; a protein synthesis inhibitor, blocks this hormetic effect. The function and importance of these radiation-induced proteins is still unknown. Furthermore, it was found that inhibitors of poly ADP-ribose polymerase, an enzyme implicated in DNA strand break rejoining, could prevent the induction of adaptive response.

A second theory involves free radical detoxification. In 1987 Feinendengen and his co-workers indicated that low doses of ionizing radiation cause a temporary inhibition in DNA synthesis (the maximum inhibition at five hours after irradiation). This temporary inhibition of DNA synthesis would provide a longer time for irradiated cells to recover (Feinendengen et al., 1987). This inhibition also may induce the production of free radical scavenger, so irradiated cells would be more resistant to any further exposures.

The third theory is of the stimulation of the immune system. It states, "Despite the fact that high doses of ionizing radiation are immunosuppressive, many studies have indicated that low doses of radiation may stimulate the

function of the immune system." (Russ VK, 1909) In 1909 Russ first showed that mice treated with low-level radiation where more resistant against bacterial disease (Russ VK, 1909). Later in 1982 Luckey published a large collection of references supporting immunostimulatory effects of low doses ionizing radiation (Luckey TD, 1982).

It is important to note an organization which is taking steps in the direction to making hormesis mainstream. The year 2000 was the 10^{th} anniversary of the BELLE (Biological Effects of Low Level Exposures) initiative. The purpose of BELLE was "to explore the nature of the dose response in the low-dose zone, including linear, sublinear, threshold, and U-shaped (i.e., hormetic) dose-response relationships." (Calabrese, 2001) In 1986 Dr. Leonard Sagan held a conference on radiation Hormesis, and Health Physics published a peer-reviewed proceeding in 1987. There was no organized follow-up activity, but in 1989 Sagan and University of California, San Francisco professor Sheldon Wolff, participated in a point-counterpoint debate in the journal *Science* on the issue of radiation hormesis. Later on a decision was made to organize a meeting at UMass of the top scientists to develop a focus on the topic. In May of 1990, BELLE was created, "establishing a focused leadership function on low-dose effects in general, including the hormetic perspective." (Calabrese, 2001)

During the early years of the BELLE initiative, it was clear that the idea of hormesis needed to be experimented and explored and put in scientific context with other more known features of dose-response relationships that had been institutionalized within scientific and regulatory frameworks. Early BELLE

newsletters emphasized a goal to enhance the scientific assessment of hormesis as seen with papers by various scientists. First, Davis and Svendsgaard (Davis, 1990), of the EPA, dealing with the frequency of U-shaped dose-response relationships published within toxicological journals which were used to establish some EPA-Reference Doses. Second, Gaziano of Harvard Medical School submitted a paper on epidemiological evidence supporting the U-shaped dose-response relationship of alcohol and cardiovascular disease. Third, Hattori from Japan included his topic on the extensive research program funded by the Electric Power Institute of Japan in the area of radiation hormesis. A fourth topic by an Australian named Parsons discussed the evolutionary expectation of hormesis. (Calabrese, 2001) Although the BELLE Advisory Committee supported the need to explore the concept of hormesis in the early 1990s, it was evident that there appeared to be "no unanimous conviction that hormesis was real, reproducible, broadly generalizable, and a fundamental aspect of evolutionary/biological processes." (Calabrese, 2001)

Despite the longstanding impediments to the assessment and acceptance of hormesis, there have been developments in the field that have created incentive to study hormesis. In 1996 the Texas Institute for Advancement of Chemical Technology, Inc (TIACT) provided funding to the University of Massachusetts to assess hormesis as a biological hypothesis. The grant permitted the opportunity to explore, collect, assess, and integrate scientific data concerning hormesis. An effort was focused on the reconstruction of the historical foundations of the nature of the dose response for chemicals and radiation and the detailing of

pharmacologically based mechanisms that may account for the numerous U-shaped, dose-response relationships obtained. (Calabrese, 2001)

TIACT undertook this study in order to bring together biological evidence in the scientific literature on the phenomenon of hormesis. Hormesis was formulated as the Arndt-Schultz Law in the late 1800s (Shulz, 1877), and it asserts that poisons stimulate biological processes at low doses and inhibit them at high doses. The term hormesis was given in 1943 by Southam and Ehrlich and was defined as the stimulation of biological processes at subinhibitory dose levels of toxicants. (Holland 2003)

Hormetic responses are characterized as proposed by Davis and Svendsgaard (Davis 1990) by two curves, the β-curve, and U-shaped curve.

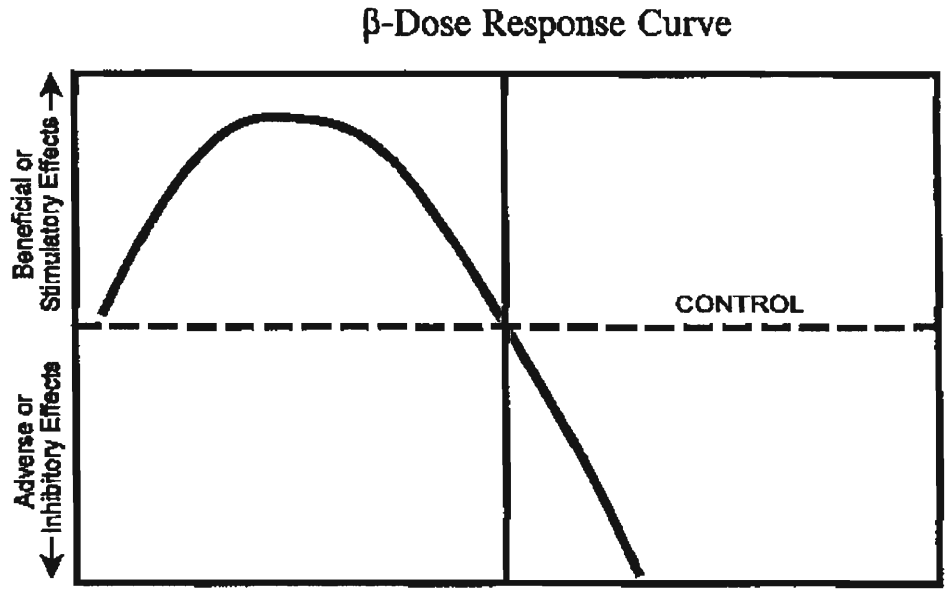


Figure 2.1.1 Beta Dose Response Curve

The β-curve represents the situation where low doses of substance promote an improvement in an endpoint such as growth rate, longevity, reproduction or some other desirable health effect. As the dose is increased, there is an adverse or an inhibitory effect. (Holland 2003)

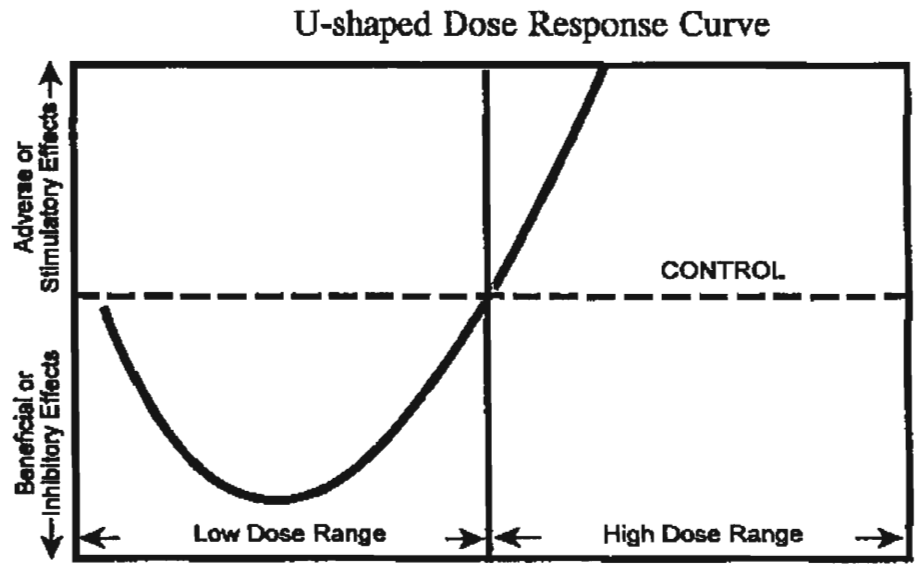


Figure 2.1.2 U-shaped Dose Response Curve

The U-shaped curve represents the situation where low doses of a substance give a decrease in an endpoint such as mutations, cancer, birth defects, or other harmful effects. As the dose is increased, adverse effects such as an increase in cancer deaths begin to occur.

Over several centuries, biological processes in bacteria plants and animals have been reported to exhibit hormetic responses when exposed to chemicals at low levels. Observations of the characteristic dose responses over high and low-dose ranges shown in Figure 2.1.1 and Figure 2.1.2 led to the fundamental statement of toxicology that the dose determines the poison. This was originally stated by a physician known as Paracelsus (1493-1541): "All things are poison, and nothing is without poison: the Dose alone makes a thing not poison". Paracelsus, who was a German physician and alchemist, is known as "the father of toxicology". It is obvious to think that the dose determines the poison when considering known poisons such as cyanide, arsenic, lead and pesticides, but this statement is true for substances such as vitamins, minerals, and even oxygen, which can all be toxic at excessive doses.

A recent review of toxicological literature from the late 19th century to mid 1930s has revealed the publication of numerous papers indicating that the shape of the dose response curve often displayed a low dose stimulatory response followed by an inhibitory response at higher doses (Calabrese 1999). This was especially the case with respect to the responses of plants, bacteria, and fungi. The endpoints measured typically involved growth rate, colony number, germination rate, time to germination, and physiological responses such as carbon dioxide production, sugar production and utilization, waste product generation, ammonification, nitrification and nitrogen-fixation (Calabrese 1999). These low dose stimulatory responses became viewed as reproducible and broadly generalizable. The papers were published in leading scientific journals by

investigators with notable reputations from outstanding institutions and universities. These leading researchers in low dose stimulatory science involved Nobel Prize winners.

Growth hormesis is one of the most studied endpoints, which obviously has to do with its importance in the agriculture, animal, and fishing industries. Calabrese and Baldwin (Calabrese 1997) found numerous reports of growth hormesis in the agricultural, toxicological, and biomedical literature. The growth hormesis phenomenon was observed over a wide range of plants, microbe and animal species, and it was induced by agents representing a wide range of chemical classes. Numerous studies were found in which low-dose stimulation was followed by high-dose inhibition.

Despite this substantial development and publication of reproducible scientific data the concept of hormetic dose-response relationships became rapidly marginalized during the mid-decades of the 20th century in the field of toxicology and its related disciplines. It involved the assessment of the effects of pesticides, disinfectants, environmental toxins, and radioactivity. "Such has been the case of its marginalization that the concept of hormesis rarely, if ever, merits even an historical note in any leading toxicological textbook." (Calabrese 1999) That being said generations of toxicologists don't get exposed to the science of hormesis and therefore is detrimental to the progress of it as an accepted science.

3 Experiments

While researching toxicology and the study of hormesis, we decided that the only way to prove to ourselves once and for all that hormesis was a legitimate science, was to conduct our own experiments to add to evidence that hormesis exists. We first had to decide what living organism to choose for our experiment. It was decided that we would grow lawn grass and spray it with different concentrations of Round-Up® (Figure 1.1) to see a positive effect of hormesis. Our hypothesis for the experiment was that the plants sprayed with the lower concentrations of Round-Up® would exhibit a higher growth rate than the plants sprayed only with water. We then brainstormed on a way to produce accurate results in a semi-controlled environment. In the end, we decided that we would do an initial "range finding" experiment in which we would try a large variety of concentrations to hopefully determine the approximate concentration of interest for a latter experiment.

3.1 Methods

We used eight, four-inch diameter, plastic pots filled with potting soil (Table 3.1.2) and grass seed (Table 3.1.3) on top, which we allowed to grow for three weeks. Afterwards, we trimmed the plants down to a height of one inch using a ruler and a pair of scissors. Next we made six different concentration levels (Table 3.1.4) of Round-Up® mixed with dechlorinated tap water. We used one pot as a control, spraying it with dechlorinated tap water only. The pots were placed under a Philips agro light (120 volt, 60 watt) which was turned on for exactly eight hours a day. Every pot was relocated into one of eight positions under the agro light every other day in order for all pots to occupy each location for an equivalent time. This allowed

us to keep a more consistent amount of light from the agro light on each pot. All the pots were sprayed with four sprays of dechlorinated tap water (Approximately 1.35mL per spray), from six inches above the pots, roughly every other day for two months. After roughly two months, we discontinued the experiment and collected the data that we could. We lined up all eight pots side by side and visually judged the relative greenness of each pot versus the rest. We then recorded the results on a basis from eight to one, with eight being the greenest, and one being the least green. After collecting that data, we then visually determined and recorded the relative number of plants alive in each pot on the same eight to one basis. The collected data can be found in Figure 3.1.1 and Figure 3.1.2.

From the results in the first experiment we determined that it would be beneficiary to conduct another experiment. This time we used concentration levels which best achieved the presence of hormesis in our experiment (Table 3.1.5). In the second experiment, we used fifteen, four-inch diameter, plastic pots filled with potting soil (Table 3.1.2) and one tablespoon of grass seed (Table 3.1.3) on top, which we allowed to grow for three weeks. This enabled us to over-seed the pots, which allowed us to achieve a more uniform amount of plants across all of the pots. We then allowed the grass to grow for approximately three weeks at which point we cut the grass to one inch tall with a pair of scissors and a one-inch diameter cardboard dowel cut to 4.13 inches tall. We placed the dowel on a flat surface and cut the grass. This in essence cut the grass to a height of 0.63 inches above the soil level. We then weighed the grass clippings with an electronic balance. The results can be found in Table 3.2.1. We waited for a period of ten days and re-cut the grass to one inch tall

using the same method as before. With the clippings from each pot, we took the total wet weight and recorded this data in order to normalize our final growth data. We repeated these methods, starting with cutting and spraying, twice to attain our data.

Active Ingredients	
Glyphosate, isopropylamine salt	1.92%
Other Ingredients	98.08%

Table 3.1.1 Round-Up® Weed & Grass Killer

Total Nitrogen	**0.07%**
Ammoniacal Nitrogen	0.04%
Nitrate Nitrogen	0.03%
Available Phosphate (P2O5)	0.01%
Soluble Potash (K2O)	0.03%

*A portion of the nitrogen, phosphate, and potash sources have been coated to provide 0.06% slow-release nitrogen (N) 0.003% slow-release phosphate (P_2O_5) and 0.014% slow-release (K_2O).

Table 3.1.2 Scotts® Potting Soil Plus Osmocote®

Pure Seed	Variety/Kind	Germination	Origin
44.40%	Crestlawn Creeping Red Fescue	87%	OR
29.05%	Ascend Perennial Ryegrass	90%	NZ
12.61%	Buckingham Kentucky Bluegrass	85%	OR
11.72%	Coventry Kentucky Bluegrass	90%	WA/ID

Other Ingredients	
0.15%	Other Crop Seed
2.06%	Inert Matter
0.01%	Weed Seed

Table 3.1.3 Scotts® Pure Premium™ Shady™ Grass Seed Mixture

Bottle	Round-Up®	Water	Concentration
1	NONE	ALL	0.000
2	5 ml	500 ml	0.010
3	25 ml	500 ml	0.050
4	37.5 ml	500 ml	0.075
5	50 ml	500 ml	0.100
6	75 ml	500 ml	0.150
7	100 ml	500 ml	0.200
8	ALL	NONE	1.000

Table 3.1.4 Experimental Concentrations

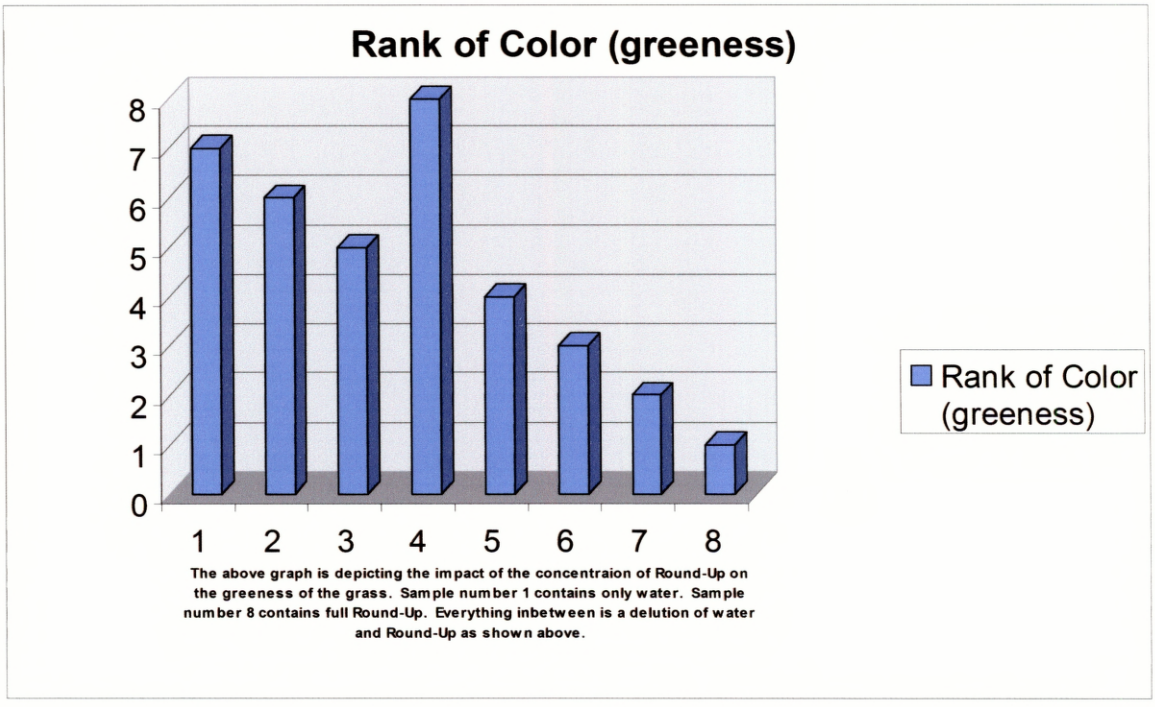


Figure 3.1.1 Rank of Color (greenness)

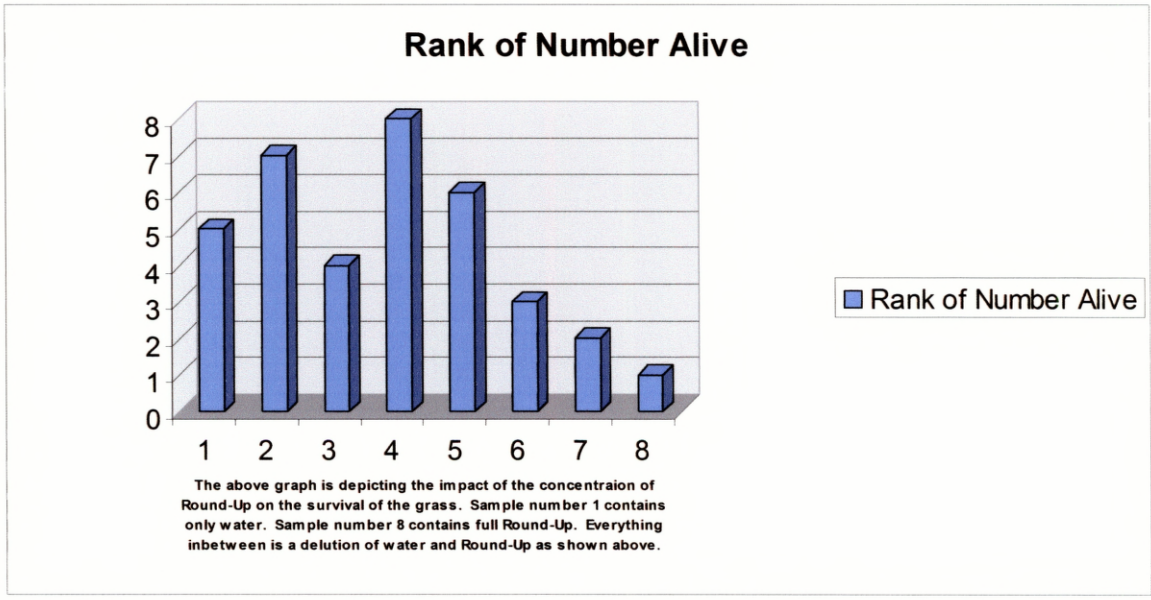


Figure 3.1.2 Rank of Number Alive

Bottle	Round-Up®	Water	Concentration
1	0 ml	ALL	0
2	5 ml	500 ml	0.01
3	25 ml	500 ml	0.05
4	37.5 ml	500 ml	0.075
5	50 ml	500 ml	0.1

Table 3.1.5 Second Experiment Concentration Levels

3.2 Results

With the described methods, we were able to acquire the data found in Table 3.2.1 from our second experiment.

Pot Number	Bottle	Bottle Number	Weight 1	Weight 2
5	Water	1	1.993	1.246
10	Water	1	2.380	0.843
15	Water	1	1.695	0.807
1	1	2	1.430	1.175
6	1	2	0.872	0.400
11	1	2	1.230	0.216
2	2	3	1.581	0.225
7	2	3	1.670	0.074
12	2	3	1.176	0.115
3	3	4	0.996	0.500
8	3	4	1.093	0.051
13	3	4	0.893	0.065
4	4	5	0.334	0.010
9	4	5	1.085	0.030
14	4	5	0.963	0.030

Table 3.2.1 Weights

	Average Weight	
Bottle Number	Cut 1	Cut 2
1	2.023	0.965
2	1.177	0.597
3	1.476	0.138
4	0.994	0.205
5	0.794	0.023

Table 3.2.2 Average Weights

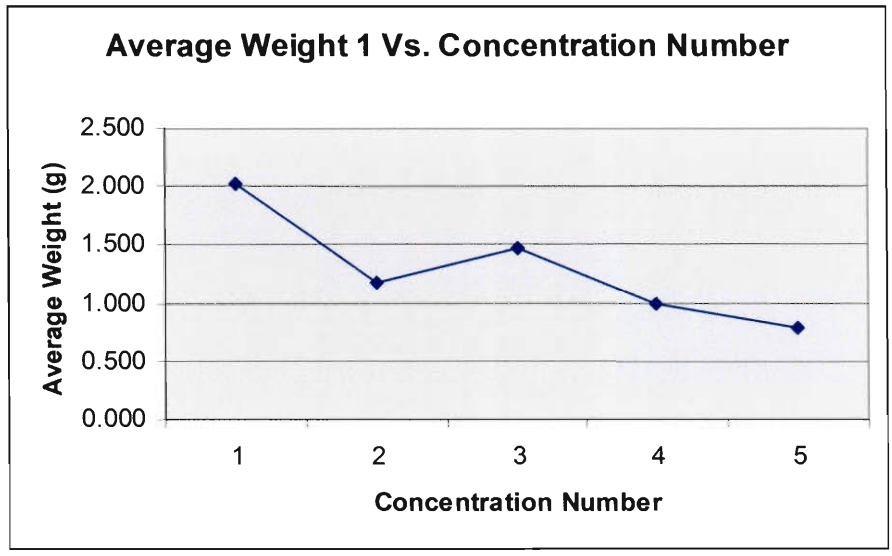


Figure 3.2.1 Weight One Graph

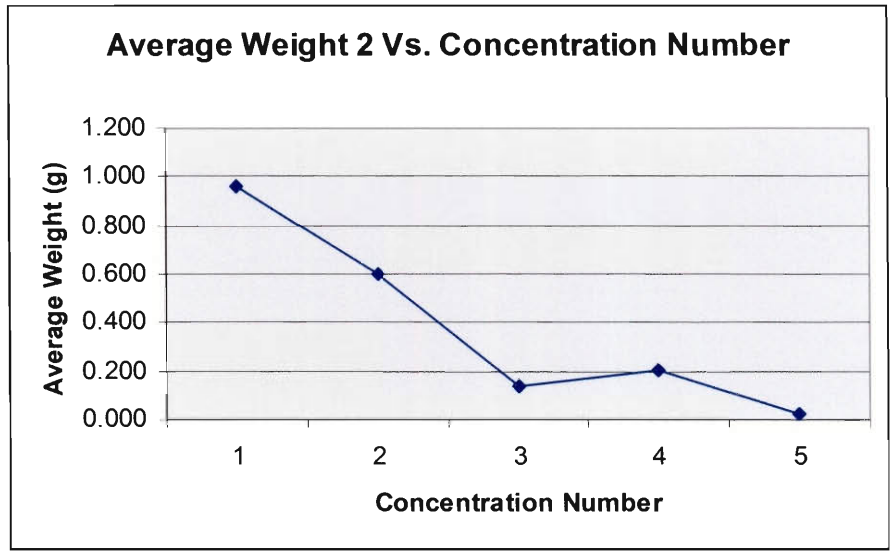


Figure 3.2.2 Weight Two Graph

3.3 Discussion

Based on our results one might conclude, hormesis might not exist, however we feel our resources inhibited us in conducting an experiment that was precise enough to detect the effect of hormesis. Furthermore, we are able to determine that the effect of hormesis is very minimal, if existent at all. We would like to believe that the effect of hormesis does exist but are unable to with great certainty within our experimental results. Both experiments raised questions as to the validity of the results. The first

experiment showed a possible hormetic effect in relation to the length of the grass and the color of the grass. However in our second experiment the weights did not increase with minimal concentrations of Round-Up®. This could be due to human error, as in us not using low enough concentrations or the conditions were not able to be controlled strictly enough. These were all due to lack of materials and resources. Hormesis could quite possibly exist, but not with these particular set of conditions. The toxic agent we used might not exhibit a hormetic effect because of the way it affects the plants. Therefore we cannot conclude that hormesis does not exist, however we can determine that hormesis was not applicable in this situation.

3.4 Further Experiments

Any experiment conducted has limitations due to time and monetary constraints. With additional time, materials, and resources, we would be able to conduct a more extensive and accurate experiment to test the theory of hormesis. In an additional experiment we would like to use a larger sample of living organisms with many different concentration levels. We would use different toxic materials in order to test their hormetic effect on plants and other organisms. For better results we would need to control the variables to a further extent then what was possible with the available resources that we had for these experiments at this particular time. Results might also be attained by looking at the living organisms at a system or cellular level instead of a total body level. The secret might lie within the cellular changes that the organism undergoes. This research would also require a much more extensive background in the biological or genetic field. For example, we could devise another experiment using mice which could more accurately depict a relation to humans.

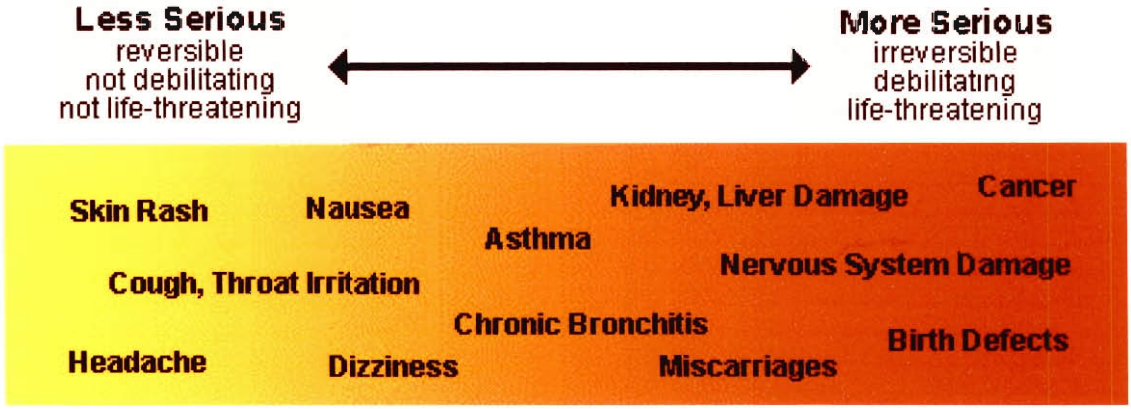
To accurately measure the effects, if any, of hormesis, we would require sufficient lab space, more accurate measurements, and sufficient funding.

4 General Conclusions and Recommendations

4.1 Acceptable Risks

Making good decisions in life is one of the best things a person can learn how to do. Deciding which risks to take and not take is vital to everyone's well being. Risk assessment is a good way to make decisions that will keep you from unwanted risk. Risk assessment as described by the National Academy of Sciences is a four-step process. Step one is **hazard identification**.

> "This step is supposed to estimate chemical damage from acute (single dose), sub chronic (a few doses), or chronic exposures for each possible toxic endpoint. Toxic "endpoints" include cancer, damage to organs (liver, kidney, heart, etc.), developmental disorders, damage to the immune system, central nervous system, reproductive system, and genes. Because organisms (whether hamsters or people) react differently at different stages of development, particularly while in the womb, dozens of "endpoints" must be considered. In actual practice, most endpoints are simply ignored." (Montague, 2004)



(EPA, 1991)

Figure 4.1.1: Air Toxin Effects

Figure 4.1.1: Air Toxin Effects describes the different effects that can come about from toxins found in the air. Because of these, **risk assessment** is necessary. The first step allows a person to assess the everyday information that they receive through all their senses and decide what is best for them at anytime. They can decide what is safe and what isn't and how to live their lives the best way they can. For instance; if a man is walking down the street and he sees a hitchhiker, there is a risk involved with picking up that hitchhiker. It has to go through the man's head that the hitchhiker could be potentially dangerous to his health. In addition, hitchhiking might be illegal in the state the man is in and the man might be arrested for that. All these thoughts have to come into play for risk assessment. The second step is **dose response assessment**.

> "Dose-response assessment means determining what damage, and to which bodily systems, will occur as the dose of a chemical increases. Most people are familiar with the concept of dose-response; think of

effects from drinking one, two, or three glasses of wine. In general, greater dose leads to greater effect. Usually assessing dose-response for a chemical requires estimating ("extrapolating") from data about laboratory animals, which have been given high doses, to effects in humans who typically receive low doses from environmental exposures. There are many different ways of "extrapolating" from high-dose animal data down to low-dose human estimates." (Montague, 2004)

Dose-assessment allows a person to decide that if they want to take a risk by using a harmful substance, how much they can use without causing serious damage. This is essential within a society controlled by law, because the government will set a limit on how much a person is able to purchase in a day, or if they can purchase it at all. This isn't just for immediate effectors. The government will not allow certain chemicals into the environment which will cause permanent or severe effects to a person or the ecosystem. If a chemical kills all of a certain species of animal or plant, it will be banned from ground disposal. The dose-response assessment adds to the assessment of all risks. If the dose is a risk then it has to be factored into the total risk assessment. The third step in risk assessment is **exposure assessment**.

"Exposure assessment tries, or should try, to determine how much of a chemical is absorbed from all sources. Example: if the chemical is a pesticide, exposures might occur through food, water, air, and perhaps even skin, through home and occupational uses. (In practice, many sources of exposure are usually ignored)" (Montague, 2004)

Exposure to a risk can be given as statistical information. There are chances that you will be exposed to risks and they can determine the risk from that exposure. Exposure isn't just the chance that you are exposed but also the way you absorb whatever it is. You can be exposed to extreme amounts of vitamin C but it won't be harmful because your body can only absorb a certain amount and all the rest is excreted. The following figure is a chart of risk exposures and the chances of the exposures.

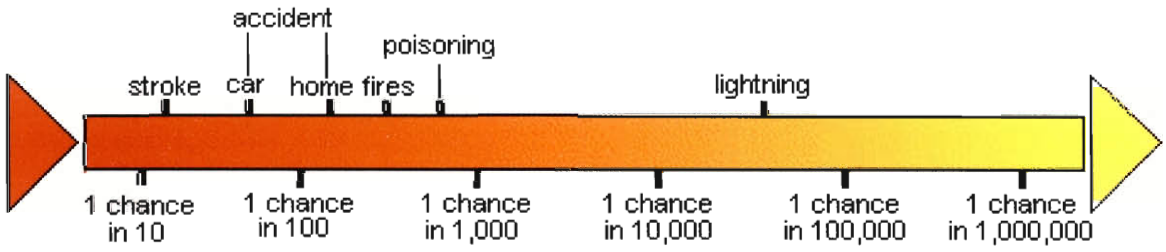


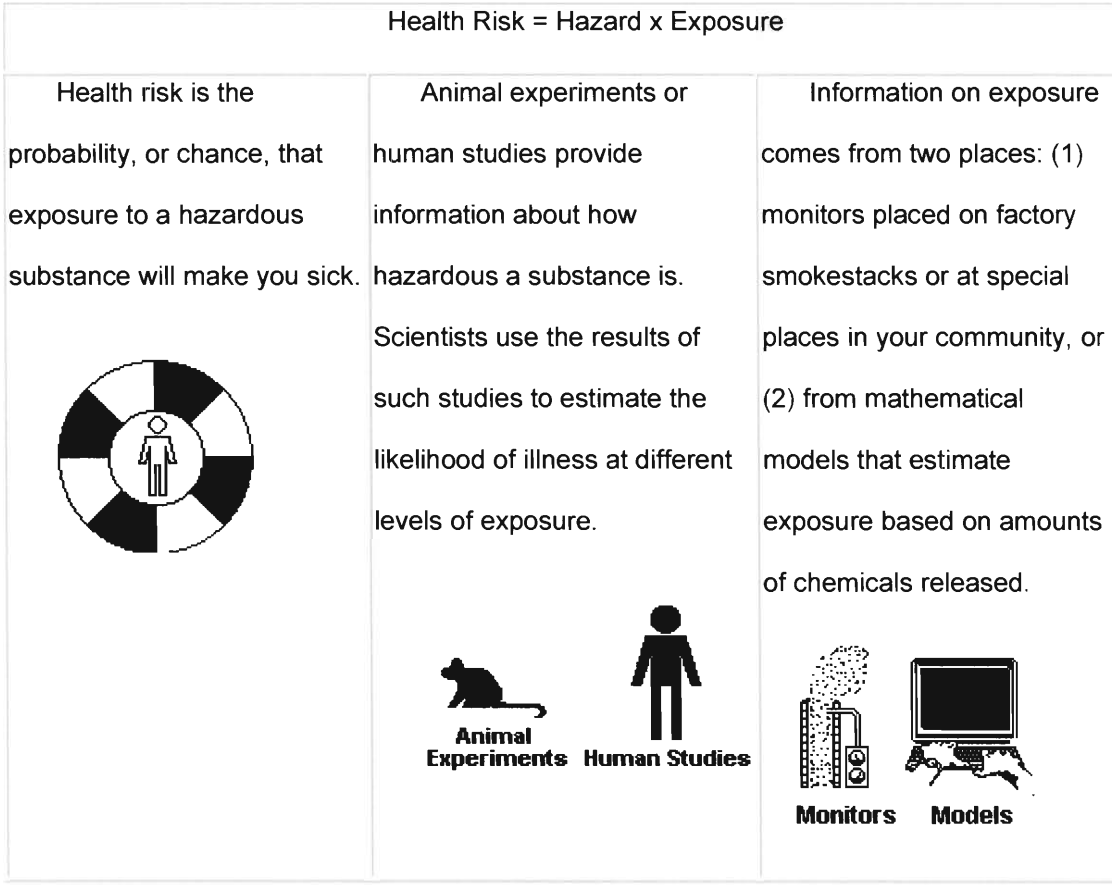
Figure 4.1.2: Exposure Risks

Furthermore, the risk of exposure is assessed through how many times you will absorb a given thing. If you absorb one thing through your skin, the air, and water; then another thing just through the air the risk of the first is much, much greater then the second. The final step is **Risk characterization.**

> "Ideally, risk characterization takes information from hazard assessment, dose-response assessment, and exposure assessment, then adds information about the characteristics of the affected population – How old are they? Are they generally malnourished? Overweight? – And combines it all together to determine an estimate of hazard (called "risk"). (In practice, the characteristics of a particular population are usually ignored and averages are used instead.) Hazard (called "risk") is

> expressed as a probability of a particular kind of harm to a specific group of people during a stated period. For example, a typical estimate of "risk" might be expressed this way: a particular group of people is expected to endure one additional cancer for every 100,000 people, over and above the normal risk of cancer, as a result of chronic exposure to some toxic chemical in their drinking water during their lifetimes of 70 years." (Montague, 2004)

The risk characterization is to bring together all the other steps in assessing risk and make an educated guess on who will be affected and how they will be affected. Trying to take this information and make it into law is what the Environmental Protection Agency (EPA) does. They assess the risk of releasing certain chemicals into the environment and decide if it is acceptable. They look at all the social and economical implications of what that chemical does to everyone and everything.



(EPA, 1991)

Figure 4.1.3: How a health risk is identified

The EPA uses the method in the figure above to determine the health risk of a given substance. There is a rating for the health risks of chemicals. From zero to four with zero being the least risky.

0	Material that on exposure under fire conditions would offer no hazard beyond that of ordinary combustible material.	Example: peanut oil
1	Material that on exposure would cause irritation but only minor residual injury.	Example: turpentine
2	Material that on intense or continued but not chronic exposure could cause temporary incapacitation or possible residual injury.	Example: ammonia gas
3	Material that on short exposure could cause serious temporary or residual injury.	Example: chlorine gas
4	Material that on very short exposure could cause death or major residual injury.	Example: hydrogen cyanide

(Grant, 1998)

Figure 4.1.4: Health Hazards

This rating comes from the OSHA hazard communication standard. Eliminating all public exposure to hazardous chemicals would be economically impossible. All major manufacturers would have such high operating costs they would be unable to make a profit and hence go out of business. "Ideally, regulators would like to eliminate all pollution and its risks, but this is usually not a realistic expectation. Regulators must address the most important risks and decrease them to the level at which they believe the risks are smaller than the benefits of the activity causing the pollution" (EPA, 1991). Everyday people do the same thing. They assess how dangerous something is in their lives and determine if they want to risk doing it. All things come with risk, however it is how much of a risk it is, and how much of a risk you are willing to take that will affect your everyday life.

There are several different reasons that risk assessment has become more important in the last few years. Because of advancements in technology we can measure smaller amounts of what is risky "One explanation for increased social conflict over questions of risk is that technological advances allow substances to be measured in ever-smaller quantities" (Clarke, 1989). Since we can measure smaller amounts of what is considered risky, it means we can measure an increased number of things that are risky. Some substances that are dangerous to a person's health might not have been able to be measured 30 years ago. But today they can be measured because of the accuracy of modern instruments "Dioxins, for example, simply could not be studied twenty years ago, even though they were undoubtedly as dangerous then as they are now" (Clarke, 1989). Since there are more toxins to be measured, there is more of a chance to find a toxic risk. If the limitations set on these risks are too small then nothing will ever get done. This is where limitations need to be set as to what is too risky. "One significant organizational response to this change in the social, economic, and political environments of corporations was the institutionalization of explicit, formal risk assessment as a method for balancing benefits and costs" (Clarke, 1989).

Risk Assessment has many different ways of affecting the economy. If a company finds that a process is "too risky"; they might not find it economical to provide funds for that process. "Cost-Benefit analysis is a method of collecting information, processing it, and providing a systematic approach to choosing between alternatives." (Dorfman, 1972). When this happens it will affect the overall economy because the "risky" process might be a civilization changing idea. "Expenditure on

treatment and loss of revenue on foregone production of incremental units may be in the interest of the firm either to avoid a charge on effluent or to obtain a payment for reducing discharge" (Dorfman, 1972). If the government finds that the good has beneficial effects on society then they might offer to help pay for the cost to manufacture the product.

Cost-benefit analysis helps companies to determine if it will be economical to produce the item. "It requires two things: clearly established alternatives, and a net-benefits or welfare function, which allows one to quantify the benefits from the various available choices. This second requisite is the most difficult and most arbitrary for it requires the specification of the order of priority of goals for society, i.e., it requires us to define quantitatively social welfare" (Dorfman, 1972). The company needs to find alternatives to the problems which will be either more cost effective or less harmful. After finding these they can determine the benefits and detriments that come from the production of the good. Usually the company will assess the alternatives as to which are most applicable, because the secondary goals are prioritized by the societal needs they can change as time goes on which in turn will cause need for further cost-benefit analysis. They will also change as a societies view of what is "risky" changes. Furthermore, risk assessment will change on every product as time goes on, giving need for more money spent on risk and cost-benefit assessments. "Three criteria for identifying significant impacts on the environment were suggested in the World Conservation Strategy. The first concerns the length of time and geographic area over which the effect will be felt. This criterion would include an assessment of the numbers of people affected, how much of a particular

resource would be degraded, eliminated, or – depending on what action is taken – conserved." (Carpenter et al, 1986). When determining the geographic area that is affected there is a study done as to how large of an area the product will be dispersed. If the area is small then the risk is lower, however if the area is large then the risk will go up.

With increased area comes increased cost, all of which will be included in the cost-benefit analysis of the product. "The second criterion is that of urgency. It is important to establish just how quickly a natural system might deteriorate and how much time is available for its stabilization or enhancement" (Carpenter et al, 1986). If it takes years for things to be affected then the company might not include the risk in their analysis. In addition, if it takes a few hours or days for the risk to be come evident it might keep the company from releasing the product. All of it depends on the analysis done on the situation. "Finally, it is important to assess the degree of irreversible damage to communities of pants and animals, to life-support systems, and to soil and water. (Carpenter et al, 1986). If a product is released and it causes extreme immediate damage to the ecosystem, then it is possible for a federal agency to initiate strict regulations as to when and how the product will be allowed to be produced.

If the by-products are the harmful, there will be a need for them to be processed. The processing of the by-products might be the most expensive part of the production. Eventually all of the assessments will be evaluated as to which route is most economical for production. When it is found to be uneconomical the production will stop or a new product will be developed to be economical.

4.2 Conclusion

Hormesis could bring about a revolution in how things are manufactured and how the economy runs within the confines of risk and toxicity. If hormesis does exist then risk assessment will change along with toxicology and many other fields of science. When a hormetic effect is found in a chemical the companies that have waste of that chemical might be allowed to release a small percentage of their waste into the environment, which would decrease the cost for them to dispose of the waste and put more money back into the development of new goods, for higher wages, or for the good of the entire company.

The effects of hormesis could be monumental, with people living longer around the world and being healthier overall. Although it is incomprehensible to quantify the effects of hormesis, we feel that it essential to the forward progress of science and technology especially in the environment. Furthermore, the proof that hormesis does exist would contradict many presently believed thoughts such as the need to reduce the amount of exposure to toxins to zero. In doing so it would decrease the cost of waste disposal and make manufacturing more cost effective in the United States. This will bring more companies back to the country after having moved out due to the expense of waste disposal.

Companies such as Eastman Kodak and General Electric might start moving more jobs back to the U.S. from India (Companies, 2004). With more companies moving back to the U.S. there will be a larger required workforce which will increase the economic growth of the country. With more people having better jobs there will be an increase in the spending of the average citizen which will provide greater profit for

companies and will cause them to spend more on research and development of better goods and services.

Risk assessment will change because there will be new definitions as to what is risky. If any amount of a chemical is currently too risky and it is found that small doses are healthful, the risk associated with it will decrease due to the allowable amount thus changing Dose Response Assessment.

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