nobody@al289.g.akarnai.net
05/28/2002 01:25:58 PM

Please respond to nobody@a1289.g.akamai.net

Record Type: Record

To: John Morrall@EOP

cc:
Subject: Suggestion for Guidance Document Improvements

Name:
George **E.** Parris, Ph.D.

Address:

Telephone No.:
703-204-0500 W

E-mail address:
gparris@awpi.org

Name of Guidance:
EPA Risk Assessment Policy

Regulating Agency:
EPA et al.

Subagency (if any):

Citation (Code of Federal Regulation):

Authority (Statute/Regulation):

Description of Problem (Nature of Impact and on Whom):

Almost all of the regulatory standards promulgated by the USEPA and applied throughout that agency and the Federal and State governments are based on the one-hit or multiple-hit theory of cancer causation that leads to the linear no-threshold risk model.

This is simply wrong.

Critique of the Target Theory of Cancer Causation
and the

Linear No-Threshold Risk Model that Follows from It

Origins of the Linear No-Threshold Model of Cancer Risk Assessment:

The linear, no-threshold LNT risk model used by the USEPA is based on the target theory of cancer causation. The target theory assumes that one or more hits on the chromosomes i.e., incidents of genotoxicity are necessary and sufficient to produce mutations that would cause cancer.

DNA and#61560 Damaged DNA and#61560 Mutation and#61560 Tumor
The original theory circa 1930-1940 was developed to explain the observed mutagenicity of x-rays, which can damage the DNA in living cells without traversing the many chemical and physical barriers separating the DNA from the environment. X-rays have on the order of 10,000 kcal/mole compared to typical bond strengths of 100 kcal/mole. Absorption of one x-ray should be adequate to create about 100 free radicals, any one of which could damage DNA . Thus, in the limited case of x-rays, a dose to the outside of the tissue is tantamount to the dose to the DNA i.e., x-rays are attenuated by a linear shielding factor related to the gross properties of the tissue, not the specific chemical or biological processes that occur in the tissue. At that time prior to 1960, it was scientifically reasonable to assume that genotoxicity, mutations, and cancer would vary linearly with dose for x-rays. However, it is not clear how target theory could account for different susceptibility of different tissues to cancer. It may have been presumed that the tissue receiving the highest dose would show effects first, in which case lungs would be the natural target of air pollutants and the liver would be the major internal organ showing cancer from ingested chemicals. Overall, it has never been clear, based on this theory, why different tissues have different susceptibility after accounting for pharmacodynmaics.

The structure of DNA was not understood until 1953.
Linear Extrapolation of the Target Theory from X-rays to Chemicals Was Never Justified:

Circa 1960-1970, the USEPA and others inappropriately extrapolated the target theory of cancer causation from x-rays to chemical substances. Implicitly this expansion of the target theory to chemical substances assumes that there is a linear relationship between external dose e.g., S of any chemical substance and the active dose that is experienced at the DNA. While this is true for x-rays, it is not true for chemical substances.

Chemical molecules unlike x-rays must traverse the chemical and physical barriers of the body and cell before interacting with DNA. In some cases, the chemical substance must be metabolized i.e., activated along the way. The efficiencies of these processes are generally not independent of dose. For example, chemical processes mediated by enzymes e.g., transport across membranes, activation and detoxification of chemical compounds typically follow Michaelis-Menten kinetics non-linear and this would apply to various transport and metabolism steps:

Rate of biochemical process = V = Vmax S / Km S
e.g.,
http://jeffline.tju.edu/CWIS/DEPT/biochemistry/kinetics/HTML/ ->
PAGE5.HTML.

There are also gene induction processes that are involved in metabolism of chemicals in vivo.

Classical toxicology had discovered that virtually all experimental data the observable summation of all the physical and chemical steps for chemical toxicity follows an S-shaped dose-response curve. This behavior probably represents an effective detoxification process at low concentrations although it might also arise from key roles played by allosteric enzymes e.g., http://www.biology.arizona.edu/biochemistry/problem_sets/energy_enzymes_catalysis/14t.html. Genotoxicity i.e., primary damage to the DNA is not fundamentally different from any other type of toxicity and an S-shaped dose-response curve is expected for all chemical carcinogens, even those that directly interact with DNA as contrasted to the situation with x-rays.

Linear Extrapolation of the Target Theory from Mutations to Cancers Was Never Justified:

It was assumed in the target theory that all mutations either lead to cell death or some sort of tumor. We now know that many mutations have no effect on biological functions of cells. The mutations range from single nucleotide polymorphisms SNPs to inclusion of viruses in the human genome.

Even among mutations that lead to cancer several independent types of mutations must be accumulated in the same cell to fully transform it to cancer. It is currently believed that at least three unrelated mutations are required. Cancer cells transformed cells and the clones to which they belong are defined by the facts that:

i They divide without the normal inhibitions concerning neighboring cells and attachment i.e., loss of external control on cell cycle and programmed cell death

ii They attempt to divide without regard to fidelity of DNA replication or nutrient/respiration status i.e., loss of internal control of cell cycle. Note: many tumor cell clones divide frequently, but the frequency of division is not a defining characteristic of cancer per se

and

iii They are not limited in the number of divisions generations, passages that they can accomplish i.e., the cell clones are immortal.

It usually takes mutations in each of these areas to convert a normal cell into a fully transformed cell e.g., see R.A. Weinberg et al. 1999. Nature London 400: 464-468. All of these mutations may occur in somatic tissue clones or some of the mutations may be inherited, which makes certain individuals more susceptible to developing cancer than others.

Thus, there are many types of partially transformed i.e., mutant cell clones in the body that never progress to cancers. Thus, multiple hits on the genome would be required for cancer causation. While a single x-ray might cause multiple damaging events hits chemical carcinogens are likely to act on a stoichiometric basis i.e., one active molecule in the nucleus for one hit or mutation. The requirement for multiple chemical hits on the same DNA for full transformation means that the mutation response must at least be a polynomial function of dose:

Response mutations = AS BS2 CS3

and the cancer response requires at least three hits on the same cell:

Response cancer = AS BS2 CS3 ...

where A and B are essentially zero and C is the lowest non-zero term.

When this is done, it is very hard to fit data that essentially form a linear function y = mx b. The common practice in using multi-hit models is to assume that both the single hit and higher numbers of hits are effective. This allows the coefficients A and B to be non-zero and obviously better mathematical fits will usually be obtained with a third degree polynomial than with a simple linear function. This improved fit seems to mislead analysts to believe that they have some how improved the model. In actual fact, it still just a linear model and because the data at likely high doses only fit the linear function y = mx b better than they fit the cubic function y = mx3 b. If data were available at low doses and not at high doses, then the cubic form would likely fit them better and incorrectly project the effects at high doses.

DNA Repair Discovered First Fundamental Flaws in the Target Theory:

About the same time that the target theory was unjustifiably generalized as explained above to include chemical carcinogens and the linear, no-threshold risk model was adopted without appropriate corrections to account for non-linearity of the dose of active agent delivered to the **DNA** compared to the applied dose or the essentiality of multiple hits to achieve cancer, the first of two discoveries was made that show that DNA damage i.e., genotoxicity is not sufficient to ensure mutations i.e., inheritable genotoxicity much less cancer.

Prior to about 1968-72, damage to DNA was assumed to be irreversible. However, in the 1960s, study of individuals that had the condition known as xeroderma pigmentosum revealed that these individuals had inherited genetic damage that disabled to varying degrees and in various ways a previously unrecognized system of DNA repair. This system would, thus, prevent low frequencies of genotoxic events from ever being manifest as mutations. In short, in normal people, there is a threshold below which the frequency of genotoxicity will not produce mutations because DNA can be repaired before the genotoxicity is inherited in a new cell clone.

and#61566 Genotoxicity and#61570
DNA
Damaged DNA and#61556 DNA Replication and#61556 Mutation
and#61572 DNA Repair and#61571

It was subsequently understood that, rather than being rare and irreversible, primary damage to DNA is common and readily repairable. Thus, contrary to the target theory, low frequencies of genotoxicity are not sufficient to cause mutations.

Programmed Cell Death Discovered Second Fundamental Flaw in the Target Theorv:

Later, circa 1972-1990, it became apparent from studying individuals with the condition known as ataxia telangiectasia sustained high rates of cancer because, cells that carry mutations were not being directed to undergo programmed cell death and recycling apoptosis as in normal individuals. In short, in normal people, there is a threshold of frequency of mutations below which the mutated cells are killed off rather than allowed to proceed to cancer clones. There are several processes through which the DNA is monitored for mutations so that abnormal cells i.e., mutations can be induced to undergo programmed cell death. One of the major processes involved the protein coded by the p53 gene. Defects in the p53 gene or related genes are observed in most cancer clones

Proposed Solution:

Almost all of the regulatory standards promulgated by the USEPA and applied throughout that agency and the Federal and State governments are based on the one-hit or multiple-hit theory of cancer causation that leads to the linear no-threshold risk model.

This is simply wrong.

Critique of the Target Theory *of* Cancer Causation
and the
Linear No-Threshold Risk Model that Follows from It

Origins of the Linear No-Threshold Model of Cancer Risk Assessment:

The linear, no-threshold LNT risk model used by the USEPA is based on the target theory of cancer causation. The target theory assumes that one or more hits on the chromosomes i.e., incidents of genotoxicity are necessary and sufficient to produce mutations that would cause cancer.

DNA and#61560 Damaged DNA and#61560 Mutation and#61560 Tumor
The original theory circa 1930-1940 was developed to explain the observed mutagenicity of x-rays, which can damage the DNA in living cells without traversing the many chemical and physical barriers separating the **DNA** from the environment. X-rays have on the order *of* 10,000 kcal/mole

compared to typical bond strengths of 100 kcal/mole. Absorption of one x-ray should be adequate to create about 100 free radicals, any one of which could damage DNA . Thus, in the limited case of x-rays, a dose to the outside of the tissue is tantamount to the dose to the DNA i.e., x-rays are attenuated by a linear shielding factor related to the gross properties of the tissue, not the specific chemical or biological processes that occur in the tissue. At that time prior to 1960, it was scientifically reasonable to assume that genotoxicity, mutations, and cancer would vary linearly with dose for x-rays. However, it is not clear how target theory could account for different susceptibility of different tissues to cancer. It may have been presumed that the tissue receiving the highest dose would show effects first, in which case lungs would be the natural target of air pollutants and the liver would be the major internal organ showing cancer from ingested chemicals. Overall, it has never been clear, based on this theory, why different tissues have different susceptibility after accounting for pharmacodynmaics.

The structure of DNA was not understood until 1953.

Linear Extrapolation of the Target Theory from X-rays to Chemicals Was Never Justified:

Circa 1960-1970, the USEPA and others inappropriately extrapolated the target theory of cancer causation from x-rays to chemical substances. Implicitly this expansion of the target theory to chemical substances assumes that there is a linear relationship between external dose e.g., S of any chemical substance and the active dose that is experienced at the DNA. While this is true for x-rays, it is not true for chemical substances.

Chemical molecules unlike x-rays must traverse the chemical and physical barriers of the body and cell before interacting with DNA. In some cases, the chemical substance must be metabolized i.e., activated along the way. The efficiencies of these processes are generally not independent of dose. For example, chemical processes mediated by enzymes e.g., transport across membranes, activation and detoxification of chemical compounds typically follow Michaelis-Menten kinetics non-linear and this would apply to various transport and metabolism steps:

Rate of biochemical process = V = Vmax S / Km S
e.g.,
http://jeffline.tju.edu/CWlS/DEPT/biochemistry/kinetics/HTML/ ->
PAGE5.HTML.

There are also gene induction processes that are involved in metabolism of chemicals in vivo.

Classical toxicology had discovered that virtually all experimental data the observable summation of all the physical and chemical steps for chemical toxicity follows an S-shaped dose-response curve. This behavior probably represents an effective detoxification process at low concentrations although it might also arise from key roles played by allosteric enzymes e.g.,
http://www.biology.arizona.edu/biochemistry/
problem_sets/energy_enzymes_catalysis/14t.html. Genotoxicity

i.e., primary damage to the DNA is not fundamentally different from any other type of toxicity and an S-shaped dose-response curve is expected for all chemical carcinogens, even those that directly interact with DNA as contrasted to the situation with x-rays.

Linear Extrapolation of the Target Theory from Mutations to Cancers Was Never Justified:

It was assumed in the target theory that all mutations either lead to cell death or some sort of tumor. We now know that many mutations have no effect on biological functions of cells. The mutations range from single nucleotide polymorphisms SNPs to inclusion of viruses in the human genome.

Even among mutations that lead to cancer several independent types of mutations must be accumulated in the same cell to fully transform it to cancer. It is currently believed that at least three unrelated mutations are required. Cancer cells transformed cells and the clones to which they belong are defined by the facts that:

i They divide without the normal inhibitions concerning neighboring cells and attachment i.e., loss of external control on cell cycle and programmed cell death

ii They attempt to divide without regard to fidelity of DNA replication or nutrient/respiration status i.e., loss of internal control of cell cycle. Note: many tumor cell clones divide frequently, but the frequency of division is not a defining characteristic of cancer per se

and

iii They are not limited in the number of divisions generations, passages that they can accomplish i.e., the cell clones are immortal.

It usually takes mutations in each of these areas to convert a normal cell into a fully transformed cell e.g., see R.A. Weinberg et al. 1999. Nature London 400: 464-468. All of these mutations may occur in somatic tissue clones or some of the mutations may be inherited, which makes certain individuals more susceptible to developing cancer than others.

Thus, there are many types of partially transformed i.e., mutant cell clones in the body that never progress to cancers. Thus, multiple hits on the genome would be required for cancer causation. While a single x-ray might cause multiple damaging events hits chemical carcinogens are likely to act on a stoichiometric basis i.e., one active molecule in the nucleus for one hit or mutation. The requirement for multiple chemical hits on the same DNA for full transformation means that the mutation response must at least be a polynomial function of dose:

Response mutations = AS BS2 CS3

and the cancer response requires at least three hits on the same cell:

Response cancer = AS BS2 **CS3** ...

where A and B are essentially zero and C is the lowest non-zero term.

When this is done, it is very hard to fit data that essentially form a linear function y = mx b. The common practice in using multi-hit models is to assume that both the single hit and higher numbers of hits are effective. This allows the coefficients A and B to be non-zero and obviously better mathematical fits will usually be obtained with a third degree polynomial than with a simple linear function. This improved fit seems to mislead analysts to believe that they have some how improved the model. In actual fact, it still just a linear model and because the data at likely high doses only fit the linear function y = mx b better than they fit the cubic function y = mx3 b. If data were available at low doses and not at high doses, then the cubic form would likely fit them better and incorrectly project the effects at high doses.

DNA Repair Discovered First Fundamental Flaws in the Target Theory:

About the same time that the target theory was unjustifiably generalized as explained above to include chemical carcinogens and the linear, no-threshold risk model was adopted without appropriate corrections to account for non-linearity of the dose of active agent delivered to the DNA compared to the applied dose or the essentiality of multiple hits to achieve cancer, the first of two discoveries was made that show that DNA damage i.e., genotoxicity is not sufficient to ensure mutations i.e., inheritable genotoxicity much less cancer.

Prior to about 1968-72, damage to DNA was assumed to be irreversible. However, in the 1960s, study of individuals that had the condition known as xeroderma pigmentosum revealed that these individuals had inherited genetic damage that disabled to varying degrees and in various ways a previously unrecognized system of DNA repair. This system would, thus, prevent low frequencies of genotoxic events from ever being manifest as mutations. In short, in normal people, there is a threshold below which the frequency of genotoxicity will not produce mutations because DNA can be repaired before the genotoxicity is inherited in a new cell clone.

and#61566 Genotoxicity and#61570
DNA
Damaged DNA and#61556 DNA Replication and#61556 Mutation
and#61572 DNA Repair and#61571

It was subsequently understood that, rather than being rare and irreversible, primary damage to DNA is common and readily repairable. Thus, contrary to the target theory, low frequencies of genotoxicity are not sufficient to cause mutations.

Programmed Cell Death Discovered Second Fundamental Flaw in the Target Theory:

Later, circa 1972-1990, it became apparent from studying individuals with the condition known as ataxia telangiectasia sustained high rates of

cancer because, cells that carry mutations were not being directed to undergo programmed cell death and recycling apoptosis as in normal individuals. In short, in normal people, there is a threshold of frequency of mutations below which the mutated cells are killed off rather than allowed to proceed to cancer clones. There are several processes through which the DNA is monitored for mutations so that abnormal cells i.e., mutations can be induced to undergo programmed cell death. One of the major processes involved the protein coded by the p53 gene. Defects in the p53 gene or related genes are observed in most cancer clones

Estimate of Economic Impacts (Quantified Benefits and Costs if possible / Qualified description as needed):

Almost all of the regulatory standards promulgated by the USEPA and applied throughout that agency and the Federal and State governments are based *on* the one-hit or multiple-hit theory of cancer causation that leads to the linear no-threshold risk model.

This is simply wrong.

Critique of the Target Theory of Cancer Causation
and the
Linear No-Threshold Risk Model that Follows from It

Origins of the Linear No-Threshold Model of Cancer Risk Assessment:

The linear, no-threshold LNT risk model used by the USEPA is based on the target theory of cancer causation. The target theory assumes that one or more hits on the chromosomes i.e., incidents of genotoxicity are necessary and sufficient to produce mutations that would cause cancer.

DNA and#61560 Damaged DNA and#61560 Mutation and#61560 Tumor
The original theory circa 1930-1940 was developed to explain the observed mutagenicity of **x-rays,** which can damage the DNA in living cells without traversing the many chemical and physical barriers separating the DNA from the environment. X-rays have on the order of 10,000 kcal/mole compared to typical bond strengths of 100 kcal/mole. Absorption of one x-ray should be adequate to create about 100 free radicals, any one of which could damage DNA . Thus, in the limited case of x-rays, a dose to the outside of the tissue is tantamount to the dose to the DNA i.e., x-rays are attenuated by a linear shielding factor related to the gross properties of the tissue, not the specific chemical or biological processes that occur in the tissue. At that time prior to 1960, it was scientifically reasonable to assume that genotoxicity, mutations, and cancer would vary linearly with dose for x-rays. However, it is not clear how target theory could account for different susceptibility of different tissues to cancer. It may have been presumed that the tissue receiving the highest dose would show effects first, in which case lungs would be the natural target of air pollutants and the liver would be the major internal organ showing cancer from ingested chemicals. Overall, it has never been clear, based on this theory, why different tissues have different susceptibility after

accounting for pharmacodynmaics.

The structure of DNA was not understood until 1953.

Linear Extrapolation of the Target Theory from X-rays to Chemicals Was Never Justified:

Circa 1960-1970, the USEPA and others inappropriately extrapolated the target theory of cancer causation from x-rays to chemical substances. Implicitly this expansion of the target theory to chemical substances assumes that there is a linear relationship between external dose e.g., S of any chemical substance and the active dose that is experienced at the DNA. While this is true for x-rays, it is not true for chemical substances.

Chemical molecules unlike x-rays must traverse the chemical and physical barriers of the body and cell before interacting with DNA. In some cases, the chemical substance must be metabolized i.e., activated along the way. The efficiencies of these processes are generally not independent of dose. For example, chemical processes mediated by enzymes e.g., transport across membranes, activation and detoxification of chemical compounds typically follow Michaelis-Menten kinetics non-linear and this would apply to various transport and metabolism steps:

Rate of biochemical process = V = Vmax S / Km S
e.g.,
http://jeffline.tju.edu/CWIS/DEPT/biochemistry/kinetics/HTML/ -> PAGE5.HTML.

There are also gene induction processes that are involved in metabolism of chemicals in vivo.

Classical toxicology had discovered that virtually all experimental data the observable summation of all the physical and chemical steps for chemical toxicity follows an S-shaped dose-response curve. This behavior probably represents an effective detoxification process at low concentrations although it might also arise from key roles played by allosteric enzymes e.g.,
http://www.biology.arizona.edu/biochemistry/problem sets/energy_enzymes_catalysis/14t.html. Genotoxicity i.e., primary damage to the DNA is not fundamentally different from any other type of toxicity and an S-shaped dose-response curve is expected for all chemical carcinogens, even those that directly interact with DNA as contrasted to the situation with x-rays.

Linear Extrapolation of the Target Theory from Mutations to Cancers Was Never Justified:

It was assumed in the target theory that all mutations either lead to cell death or some sort of tumor. We now know that many mutations have no effect on biological functions of cells. The mutations range from single nucleotide polymorphisms SNPs to inclusion of viruses in the human genome.

Even among mutations that lead to cancer several independent types of

mutations must be accumulated in the same cell to fully transform it to cancer. It is currently believed that at least three unrelated mutations are required. Cancer cells transformed cells and the clones to which they belong are defined by the facts that:

i They divide without the normal inhibitions concerning neighboring cells and attachment i.e., loss of external control on cell cycle and programmed cell death

ii They attempt to divide without regard to fidelity of DNA replication or nutrient/respiration status i.e., loss of internal control of cell cycle. Note: many tumor cell clones divide frequently, but the frequency of division is not a defining characteristic of cancer per se

and

iii They are not limited in the number of divisions generations, passages that they can accomplish i.e., the cell clones are immortal.

It usually takes mutations in each of these areas to convert a normal cell into a fully transformed cell e.g., see R.A. Weinberg et al. 1999. Nature London 400: 464-468. All of these mutations may occur in somatic tissue clones or some of the mutations may be inherited, which makes certain individuals more susceptible to developing cancer than others.

Thus, there are many types of partially transformed i.e., mutant cell clones in the body that never progress to cancers. Thus, multiple hits on the genome would be required for cancer causation. While a single x-ray might cause multiple damaging events hits chemical carcinogens are likely to act on a stoichiometric basis i.e., one active molecule in the nucleus for one hit or mutation. The requirement for multiple chemical hits on the same DNA for full transformation means that the mutation response must at least be a polynomial function of dose:

Response mutations = AS BS2 CS3

and the cancer response requires at least three hits on the same cell:

Response cancer = AS BS2 CS3 ...

where A and B are essentially zero and C is the lowest non-zero term.

When this is done, it is very hard to fit data that essentially form a linear function y = mx b. The common practice in using multi-hit models is to assume that both the single hit and higher numbers of hits are effective. This allows the coefficients A and B to be non-zero and obviously better mathematical fits will usually be obtained with a third degree polynomial than with a simple linear function. This improved fit seems to mislead analysts to believe that they have some how improved the model. In actual fact, it still just a linear model and because the data at likely high doses only fit the linear function y = mx b better than they fit the cubic function y = mx3 b. If data were available at low doses and not at high doses, then the cubic form would likely fit them better and incorrectly project the effects at high doses.

DNA Repair Discovered First Fundamental Flaws in the Target Theory:

About the same time that the target theory was unjustifiably generalized as explained above to include chemical carcinogens and the linear, no-threshold risk model was adopted without appropriate corrections to account for non-linearity of the dose of active agent delivered to the DNA compared to the applied dose or the essentiality of multiple hits to achieve cancer, the first of two discoveries was made that show that DNA damage i.e., genotoxicity is not sufficient to ensure mutations i.e., inheritable genotoxicity much less cancer.

Prior to about 1968-72, damage to DNA was assumed to be irreversible. However, in the 1960s, study of individuals that had the condition known as xeroderma pigmentosum revealed that these individuals had inherited genetic damage that disabled to varying degrees and in various ways a previously unrecognized system of DNA repair. This system would, thus, prevent low frequencies of genotoxic events from ever being manifest as mutations. In short, in normal people, there is a threshold below which the frequency of genotoxicity will not produce mutations because DNA can be repaired before the genotoxicity is inherited in a new cell clone.

and#61566 Genotoxicity and#61570
DNA
Damaged DNA and#61556 DNA Replication and#61556 Mutation
and#61572 DNA Repair and#61571

It was subsequently understood that, rather than being rare and irreversible, primary damage to DNA is common and readily repairable. Thus, contrary to the target theory, low frequencies of genotoxicity are not sufficient to cause mutations.

Programmed Cell Death Discovered Second Fundamental Flaw in the Target Theory:

Later, circa 1972-1990, it became apparent from studying individuals with the condition known as ataxia telangiectasia sustained high rates of cancer because, cells that carry mutations were not being directed to undergo programmed cell death and recycling apoptosis as in normal individuals. In short, in normal people, there is a threshold of frequency of mutations below which the mutated cells are killed off rather than allowed to proceed to cancer clones. There are several processes through which the DNA is monitored for mutations so that abnormal cells i.e., mutations can be induced to undergo programmed cell death. One of the major processes involved the protein coded by the p53 gene. Defects in the p53 gene or related genes are observed in most cancer clones

.