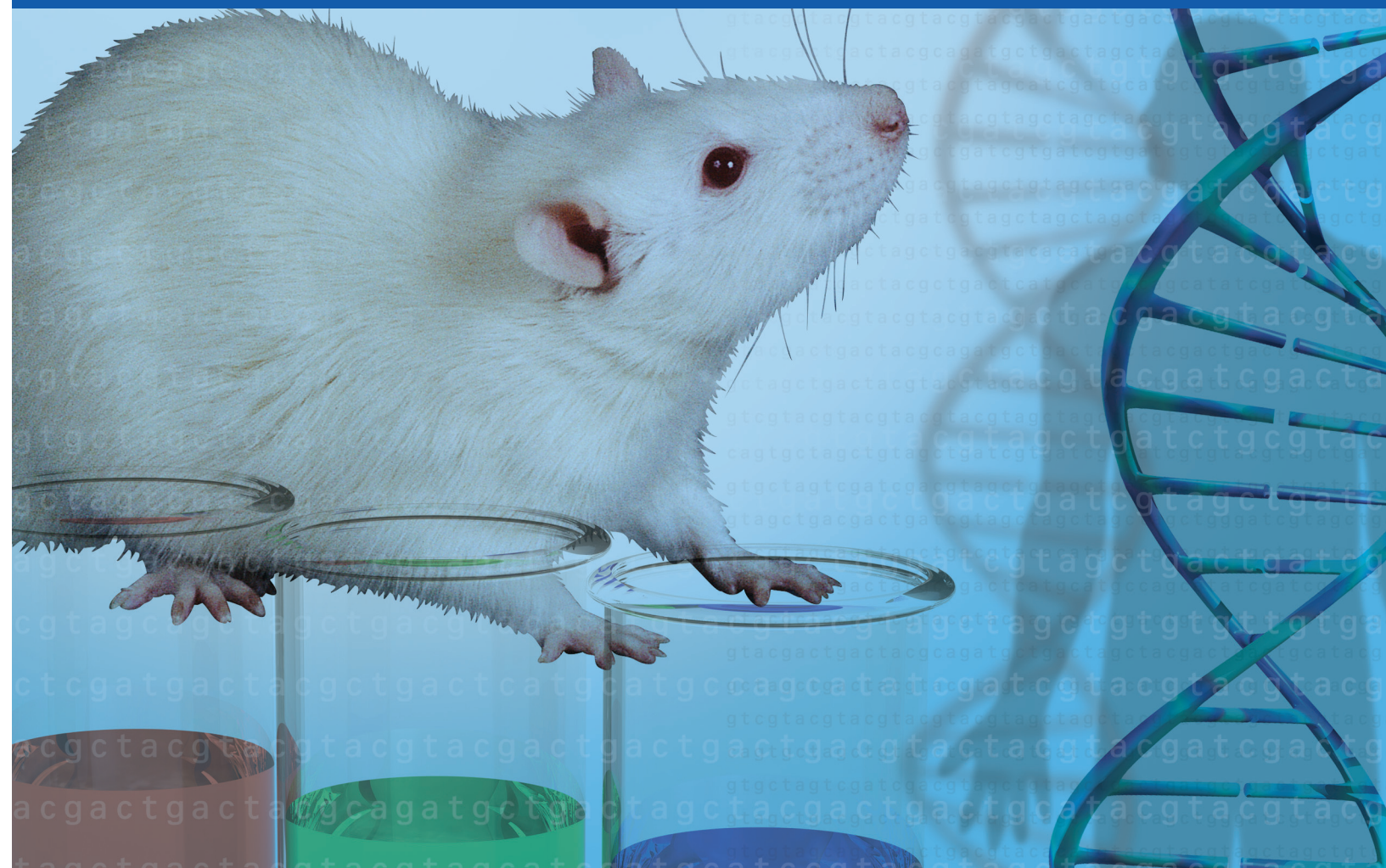


WASTED MONEY, WASTED LIVES

A Layperson's Guide to the Problems With Rodent
Cancer Studies and the National Toxicology Program



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EXECUTIVE SUMMARY

Established in 1980, People for the Ethical Treatment of Animals (PETA) is the world's largest animal rights organization, with 1.3 million members and supporters who share the belief that animals are not ours to eat, wear, experiment on, use for entertainment, or exploit in any way. For the past decade, PETA has been at the forefront of global efforts to modernize regulatory toxicology testing by documenting the scientific failings of conventional approaches and by financially supporting and promoting valid and humane alternatives that reduce or eliminate reliance on animal testing while better protecting public health and the environment. As a founding member of the International Council on Animal Protection at the OECD and at the ICH (ICAPO and ICAP, respectively), PETA joins with animal protection organizations across North America, Europe, and Asia to ensure that animals have an effective voice within the Organization for Economic Cooperation and Development and the International Conference on Harmonization, as they establish and harmonize test guidelines and standards for the safety testing of chemicals and pharmaceuticals that affect the use of animals in laboratories the world over.

BAD SCIENCE = BAD DECISIONS

PETA firmly supports the National Toxicology Program's (NTP) motto of "good science for good decisions." However, the NTP's uncritical reliance on toxicity tests on animals undermines this important goal. In addition to being of unproven reliability and relevance to humans, most animal tests are also costly and inefficient. The NTP's rodent cancer-testing program is a case in point. The NTP recently celebrated the publication of its 500th rodent cancer study as "a landmark in a series that has influenced public policy on air, water, food and drug quality" and a "milestone of health protection."¹ However, in contrast to the fanfare with which this announcement was made, the history of NTP rodent cancer studies is one of controversy spanning several decades, with top federal officials having made the following admissions:

"We have been concerned about the predictivity of 2-[year] [rodent cancer studies] for the past 10 [years], as our experience and knowledge have expanded."

—Drs. Bernard Schwetz and David Gaylor²

Office of the Director/National Center for Toxicological Research
Food and Drug Administration (FDA)

"The problem is we don't know what the findings really mean."³

—Dr. Robert Maronpot, chief, Laboratory of Experimental Pathology,
National Institute of Environmental Health Sciences (NIEHS)

"Even if a chemical is found to be nontoxic in animal studies, the safety of the chemical cannot be assured."⁴

—Dr. Barbara Shane, NTP executive secretary

"My overall assessment is that the national cancer program must be judged a qualified failure."⁵

—Dr. John Bailer, 20-year veteran of the National Cancer Institute

PETA recently conducted its own investigation, in which we compiled and analyzed the results from all 502 federally funded and conducted lifetime rodent cancer studies published on the NTP Web site as of January 2006. On the basis of this analysis, together with more than 25 years of evidence published in scientific journals, we have determined the following:

■ **The great majority of the U.S. government's more than \$1 billion investment in the NTP rodent cancer-testing program has been wasted** on studies that:

- are judged by the NTP itself to be "inadequate" or to produce "equivocal" (ambiguous) results, which are then disregarded by health authorities (\$121 million).
- produce such dubious and conflicting results that more than 75 percent of tested chemicals remain either unclassified as to their cancer risk to humans or lumped into such meaningless categories as "possible" human carcinogens or "unclassifiable" as to human cancer risk—designations that do nothing to enhance public health or worker protection (\$460 to \$720 million).
- have been shown by other scientists to produce consistent and reproducible results only 57 percent of the time when the same chemicals are tested more than once using the same method—a result that could be achieved by simply tossing a coin.

■ Critical public health and worker protection measures related to cigarette smoke, asbestos, benzene, and other cancer-causing substances were delayed for many years because of misplaced trust in animal tests, which for years could not replicate cancerous effects that had already been documented in people.^{6,7,8,9} If standard animal tests failed to readily identify these well-known human carcinogens, how many other dangerous chemicals are Americans being exposed to today as a result of misleading animal data?

■ Conversely, substances such as saccharin and ethyl acrylate (used in making latex paints and textiles) have been branded as "probable" human carcinogens and stigmatized on the basis of animal data later dismissed as irrelevant or otherwise inapplicable to humans.¹⁰ Such false alarms can cost society billions in terms of loss of viable products in commerce, decreased international competitiveness, job loss, litigation, and unnecessary public anxiety.

■ At least 15 types of rodent tumors are now recognized as having little or no relevance in predicting human cancer risk because of species-specific physiological mechanisms and/or entire organs that are found in rodents but not in humans. In addition, a number of

tumors are believed to occur simply as a result of the chemical overdose given to animals in NTP studies, which can overwhelm the body's natural defense mechanisms independently of the chemical's cancer-causing potential.¹¹

- In addition to their dubious scientific validity, NTP rodent cancer studies are also highly inefficient, requiring four to five years to design, conduct, and interpret and consuming 860 animals and \$2 to \$4 million per chemical tested. As a result, the NTP has only been able to conduct an average of 12 such studies per year over the past several decades. At this rate, it would take the NTP more than 32,000 years, 68 million animals, and \$160 billion to test the more than 80,000 environmental chemicals whose cancer-causing potential has not yet been specifically assessed.¹²

These findings reinforce and amplify the criticisms voiced by top federal officials and call into question the wisdom of continued federal appropriations to the NTP rodent cancer-testing program. **Taxpayer dollars would be better spent developing more reliable, relevant, and cost-effective non-animal methods for assessing chemical safety.**

RECOMMENDATIONS

1. **Federal appropriations to the rodent cancer-testing program at the NTP/NIEHS should cease.**
2. **Funding that would otherwise have been spent on animal-based cancer studies should be redirected to the following two areas:**
 - **The NTP “21st Century Vision” program (described below in “Summary and Recommendations”), with a specific proviso that funds be spent on the development and validation of *non-animal* methods and testing strategies to detect chemicals that present a genuine risk of cancer or other serious health effects in humans.**
 - **Human epidemiology (population) studies to identify additional human carcinogens as well as human noncarcinogens.**
3. **The U.S. Environmental Protection Agency, Food and Drug Administration, and other agencies that continue to require or recommend long-term cancer studies should limit this requirement to a single species or a “reduced protocol,” described below, and commit to replacing this requirement with a battery of non-animal methods as soon as practicable.**

INTRODUCTION

Toxicology is the study of the nature, effects, and treatment of poisonous substances. During the 1960s and '70s, as vast numbers of new chemicals were being produced and used in agriculture, manufacturing, food preparation, and virtually every other aspect of modern life, the public became increasingly concerned that these chemicals were finding their way into the environment and food supply. The National Toxicology Program (NTP) was established in 1978 to provide information about potentially toxic chemicals and to coordinate toxicity testing programs within the federal government, strengthen the science of toxicology, and develop and validate improved testing methods. The NTP's activities are funded through the U.S. Department of Health and Human Services at an annual level of approximately \$500 to \$600 million.¹³

NTP TOXICOLOGY EVALUATIONS

The NTP regularly solicits public nominations of chemicals and other substances to undergo toxicity testing. These chemical nominations are made available for public comment and are subsequently reviewed by various federal advisory committees. Yet despite these reviews, the NTP still conducts and/or calls for a number of highly questionable animal-poisoning studies—both for substances already well established to be hazardous, such as lead, ethylene glycol (antifreeze), acrylamide, methanol, and chromium, as well as natural substances that have been used safely for centuries, including echinacea, aloe vera, ginseng, and green tea.¹⁴

The NTP conducts and/or calls for additional dubious animal studies under the auspices of its Center for the Evaluation of Risks to Human Reproduction. In 2005, for example, the NTP proposed to send the drug Prozac® back for more animal testing despite the drug's nearly 20-year history of human use overseen by the U.S. Food and Drug Administration (FDA). A Freedom of Information Act request by PETA revealed that the nomination of Prozac® was made by a single, anonymous individual and “no reason for the nomination [was] provided.”

NTP CANCER EVALUATIONS

Much of the public anxiety regarding chemicals relates to their potential to cause cancer, or “carcinogenicity.” In response to public concern, the U.S. federal government instituted a program to test chemicals on rats and mice to determine whether they caused cancer in these species. The program grew exponentially after the Nixon administration declared its “war on cancer” in 1971, and a standardized rodent cancer study was developed by the National Cancer Institute (NCI). Since 1978, the rodent cancer-testing program has been

FACTS & FIGURES:
NTP LIFETIME
CANCER STUDIES
IN
RATS & MICE

Cost per study:
\$2-4 million

Animals used per study:
860

Chemicals tested as of
Jan. 2006: **476**

Chemicals tested more
than once: **24**

Total cost to U.S.
taxpayers: **>\$1 billion**

Total animals used to
date: **430,000**

administered by the NTP from its headquarters at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina.

A conventional NTP rodent cancer study consumes 860 rats and mice at a cost of \$2 to \$4 million per chemical tested.¹⁵ The study exposes three groups of animals to three different doses of a test chemical, while a fourth group (known as the “control” group) receives no chemical exposure. The chemically exposed animals receive daily doses of a test substance for their entire 18- to 24-month life span. If these animals develop more tumors than the nonchemically exposed controls, this is taken as evidence that a chemical causes cancer. To date, the NTP has tested hundreds of substances in rodent cancer studies, including pharmaceuticals, pesticides, plastics, industrial chemicals, and even plant extracts.

Recently, the NTP celebrated the publication of its 500th rodent cancer study, declaring it the “gold standard of animal toxicology.” In reality, however, the history of these studies is one of controversy and contentious scientific debate spanning more than 25 years:

- **1979:** The year after the NTP rodent cancer-testing program began, the White House Office of Science and Technology warns that the results of cancer studies in one animal species are not necessarily relevant to other animal species, let alone humans.¹⁶
- **1984:** An expert panel of the NTP Board of Scientific Counselors questions the use of the B6C3F1 mouse strain as the standard for NTP cancer studies.¹⁷
- **1994:** The NTP Board of Scientific Counselors concludes that the assumptions upon which the rat and mouse research are based “do not appear to be valid.”¹⁸
- **1996:** The NTP hosts an international scientific workshop to respond to widespread concern regarding the use of rodent cancer study results in the assessment of cancer risks to humans.¹⁹
- **2002:** The NIEHS journal *Environmental Health Perspectives* publishes the article “Assessing Assays,” which sparks heated criticism of the NTP’s two-year rodent cancer studies.^{20,21,22,23}
- **March 2005:** The Society of Toxicology devotes its annual “Great Debate” to the hot topic: “The 2-[Year] Rodent Carcinogenesis Bioassay: Relevant or Relic?”²⁴
- **June 2005:** Ongoing problems with the strains of rats and mice generally used in its cancer studies prompt the NTP to host a workshop, “Animal Models for the NTP Rodent Cancer Bioassay: Strains & Stocks—Should We Switch?”
- **August 2005:** The American Council on Science and Health and the Washington Legal Foundation challenge the relevance of the rodent cancer study with a legal petition calling on the Environmental Protection Agency (EPA) to “stop declaring chemicals ‘carcinogens’ based on rodent tests alone.”²⁵

THE CASE AGAINST RODENT CANCER TESTS

“The current 2-year rodent carcinogenicity study was never validated ... and there is little evidence supporting the repeatability and reproducibility of the current rodent carcinogenicity study.”²⁶

—Drs. Joseph Contrera, Abigail Jacobs, and Joseph DeGeorge
FDA, Center for Drug Evaluation and Research

Assessments of cancer risk and other human health hazards have traditionally relied heavily on the results of animal testing. However, animal studies suffer from many scientific limitations, are costly and time-consuming, and inflict pain, distress, and, ultimately, death upon hundreds of thousands of sentient creatures. A key limitation is the fact that NTP rodent cancer studies, like virtually all other animal tests, have never been properly validated.²⁷ A “scientifically valid” test for human risk assessment is one that (1) produces results that are relevant to actual human health risk, and (2) gives consistent results when the test is repeated.²⁸ Test method validation is a legal requirement in the U.S., with the ICCVAM Authorization Act of 2000 stipulating: “Each Federal agency shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method.”²⁹ However, noncompliance with this statutory requirement is rampant among U.S. federal agencies, which require and accept many animal studies that do not satisfy internationally accepted criteria for test method validation. Indeed, there is a preponderance of evidence, presented below, that suggests that rodent cancer studies would fail a properly conducted validation study, because the results of these studies are often both inconsistent and irrelevant to humans.

MILLIONS DOWN THE DRAIN—MEANINGLESS TEST RESULTS AND CLASSIFICATIONS

“The problem is we don’t know what the findings really mean.”³⁰

—Dr. Robert Maronpot, NIEHS Laboratory of Experimental Pathology

An NTP rodent cancer study consists of concurrent tests in four different “species/gender groups” (i.e., male rats, female rats, male mice, and female mice). Thus, PETA’s analysis of all NTP rodent cancer studies published as of January 2006 involved separate reviews of 1,872 individual species/gender group tests on 476 distinct chemicals, each consuming approximately \$500,000 and 215 animals. Of these, a total of 243 individual species/gender group tests—or approximately **one in every seven**—were found to produce either

“equivocal [ambiguous] evidence of carcinogenic activity,” or were written off altogether as being “inadequate studies.” Either way, these studies contributed nothing of value to the understanding of whether or not the tested chemicals cause cancer in rodents, let alone in humans—thus wasting in excess of 121 million tax dollars and more than 50,000 animal lives (Table 1).

Species		Ambiguous or inadequate tests	Animal lives (215/test)	U.S. tax dollars (\$500,000/test)
Rat	Male	72	15,480	\$36,000,000
	Female	64	13,760	\$32,000,000
Mouse	Male	67	14,405	\$33,500,000
	Female	40	8,600	\$20,000,000
Total		243	51,245	\$121,500,000

Table 1 U.S. tax dollars and animal lives wasted on NTP rodent cancer studies producing ambiguous or inadequate results.

A variety of national and international agencies classify chemicals according to their perceived cancer risk to humans, including the World Health Organization’s International Agency for Research on Cancer (IARC), the EPA, and the NTP itself, through its biennial *Report on Carcinogens* (RoC). Although classification schemes vary somewhat among these agencies, there are essentially five broad categories in which a chemical may be placed:

- **Known** human carcinogen
- **Probable** human carcinogen
- **Possible** human carcinogen
- **Unclassifiable** as to human carcinogenicity
- **Probably not** carcinogenic to humans

In order for a chemical to be classified as a *known* human carcinogen, there must generally be “sufficient evidence of carcinogenicity in humans” (*emphasis added*).³¹ In other words, animal data alone are never enough to classify, let alone regulate, a chemical as a human carcinogen. The most that can be said on the basis of animal test results is that a substance may be a *probable* human carcinogen—and even this classification generally requires there to be evidence of cancer risk in *both* rats and mice, as well as some level of evidence of cancer risk in humans.³² The lack of weight given to NTP rodent cancer data is clearly illustrated in Figure 1, which contrasts the hundreds of NTP-tested chemicals found to produce “positive” evidence of cancer in one or more rodent species/gender groups (light blue bars) with the tiny proportion of these that have been classified as *known* (dark blue bars) or *probable* (white bars) human carcinogens by the NTP, EPA, and IARC.^{33,34,35}

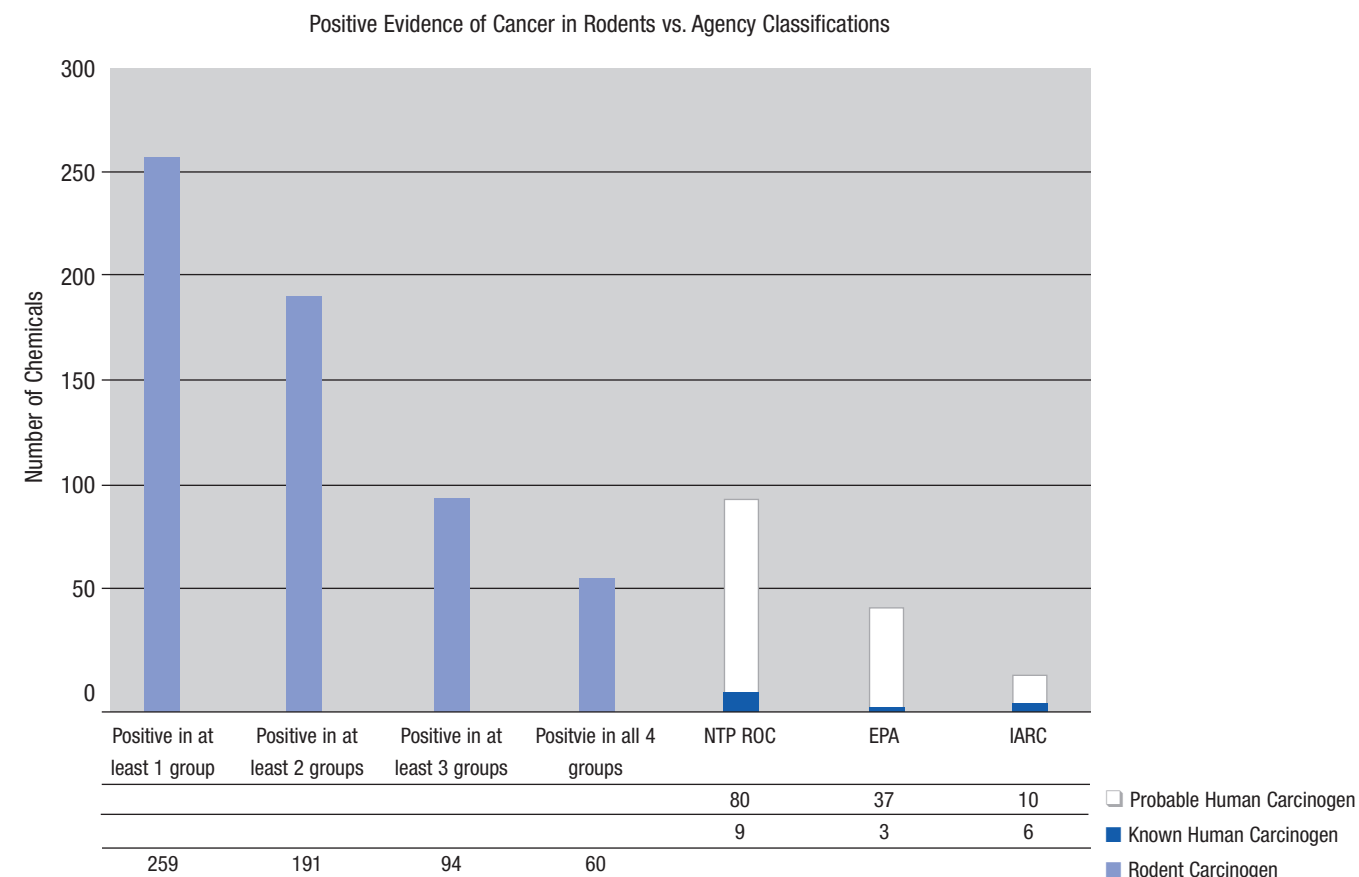


Figure 1 NTP-tested chemicals producing positive evidence of cancer in one or more rodent species/gender groups relative to NTP-tested chemicals classified as known or probable human carcinogens by the NTP (Report on Carcinogens), EPA, and IARC.

Although chemicals classified as *known* or *probable* human carcinogens are more likely to be subject to meaningful regulatory controls, PETA’s analysis determined that such classifications have only been assigned to a small fraction of the chemicals that yielded positive evidence of cancer risk in NTP studies (Figure 1). For example, the EPA has yet to classify more than 85 percent of the chemicals tested in NTP rodent cancer studies as to their cancer risk to humans, and IARC has classified less than 45 percent. And of the NTP-tested chemicals that these agencies have classified, most have simply been lumped into such uninformative and noncommittal categories as *possible* human carcinogen or *unclassifiable* as to human cancer risk (Figure 2).^{36,37} In fact, more than 82 percent of all chemicals evaluated to date by IARC have been so classified.³⁸ **Such designations fail to address the central question of whether a substance does or does not cause cancer in humans and are therefore virtually meaningless from a public health perspective.**

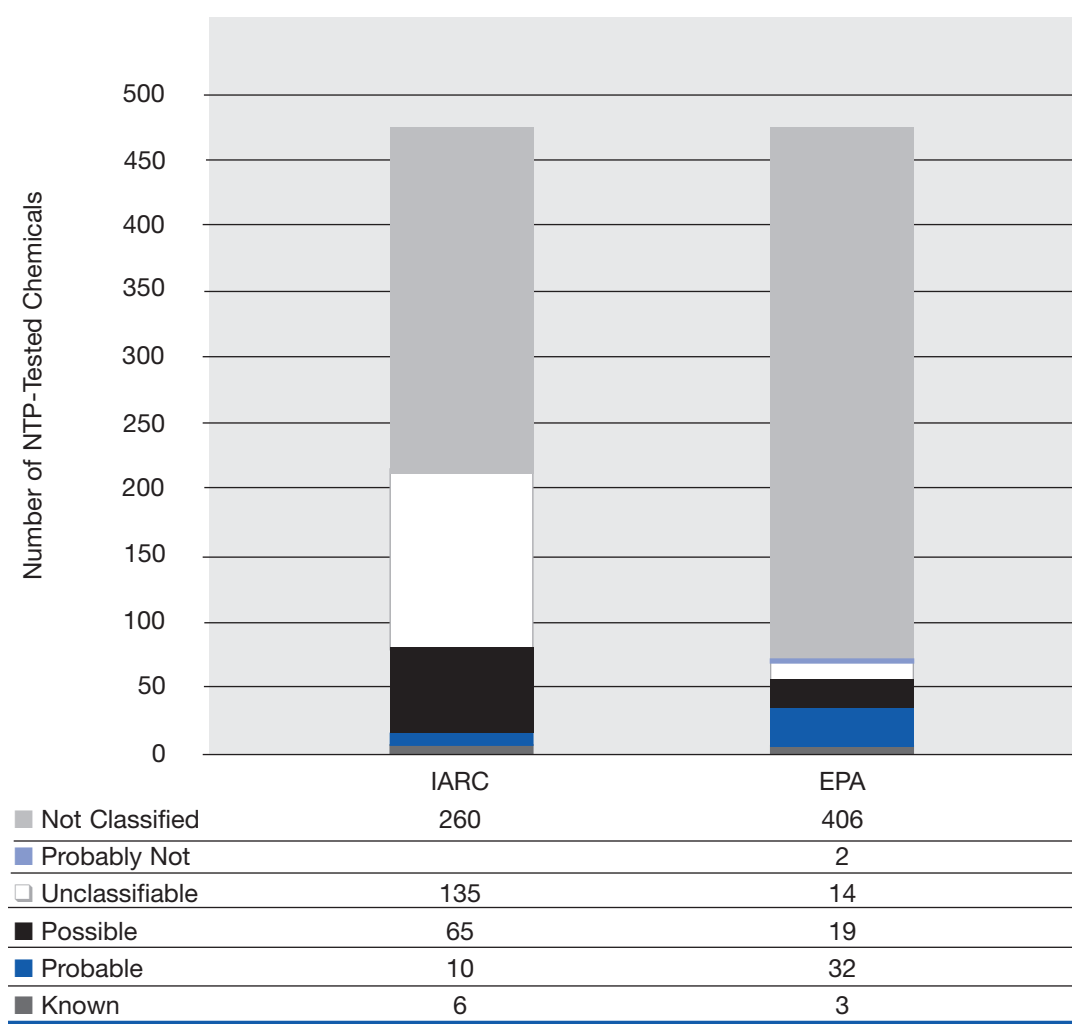


Figure 2 The vast majority of NTP-tested chemicals have not even been classified by IARC or the EPA as to their cancer risk to humans, and of those that have, most are deemed either unclassifiable or possible human carcinogens.

Even when evidence of cancer is found in both rats and mice (which suggests that a chemical hazard is not unique or limited to a single species), cancer authorities may disregard these findings when making their determinations regarding human risk. For example, only 62 of the 114 NTP-tested chemicals yielding this level of evidence (54 percent) have been classified as *known* or *reasonably anticipated* human carcinogens in the NTP’s *Report on Carcinogens*. The remaining 46 percent have simply not been classified by the NTP. If studies producing evidence of cancer in two species are so freely dismissed, public health authorities will be even less confident in making meaningful classifications or regulatory decisions based on evidence from *only one* rodent species, which is all that is available for 383 (80.5 percent) of the 476 NTP-tested chemicals examined in this report.

The majority of these 383 chemicals have not even been classified by IARC or the EPA (59 percent and 80.7 percent, respectively). Only 54 have been evaluated by the EPA, of which 32 (59.3 percent) have been labeled either *possible* human carcinogens or simply *unclassifiable*. IARC, on the other hand, has written off fully 94.2 percent of the 139 NTP chemicals that it evaluated as *unclassifiable* or *possible* human carcinogens. Thus, even after hundreds of \$2 million rodent studies, regulators are still stuck in limbo as to the actual human cancer risk posed by most NTP-tested chemicals. In practical terms—assuming that approximately 80 percent of NTP-tested chemicals fail to produce positive evidence in both rats and mice and that between 59 and 94 percent of these chemicals are ultimately lumped into categories that provide no meaningful insight as to the real-world danger that they pose to people—we estimate that **the \$460 to \$720 million used to underwrite these unenlightening NTP rodent cancer studies has been a complete waste of taxpayers’ money.**

Setting aside the high proportion of NTP rodent cancer studies that are either written off entirely or lumped into a meaningless “catch-all” classification, there is also considerable doubt as to whether study results are even consistent and repeatable. Repeatability refers to the degree to which a test method can be performed reproducibly within and among laboratories over time and is a precondition of a scientifically valid toxicity test.³⁹ Ideally, if a chemical is tested in several laboratories, each following the same protocol, variability in test results will be low and agreement between toxicity classifications will be high. However, when a European research team compared 121 replicate rodent cancer studies from the NTP database with those in the published scientific literature, they found that the studies produced consistent and repeatable results only 57 percent of the time, which is about the statistical equivalent of tossing a coin. As the scientists reported in the NIEHS journal *Environmental Health Perspectives*: “These results indicate that rodent carcinogenicity assays are much less reproducible than previously expected.”⁴⁰

THE TEST THAT CRIES WOLF—PERPETUALLY MISJUDGING HUMAN CANCER RISK

When animal tests produce inaccurate results, they can either give a “false positive,” in which they predict cancer risk where there is actually no risk to humans, or a “false negative,” in which they do not detect an actual health risk to humans. The problem of false negatives—true human carcinogens that go undetected—is clearly of great concern from a public health perspective, as they allow for potentially widespread human exposure to dangerous chemicals. For example, **critical public health and worker protection measures related to cigarette smoke, asbestos, benzene, and other cancer-causing substances were delayed for many years because of misplaced trust in animal tests**, which for years could not replicate cancerous effects that had already been documented in people.^{41,42,43,44} In addition, many of the known causes of human cancer are viruses, radiation, and chemical mixtures that would not normally be tested using conventional NTP rodent

cancer studies, which have historically been used only to assess one chemical substance at a time.⁴⁵

PETA analyzed the ability of one species/gender group (e.g., male mice) to predict the cancer risk for other groups of rodents exposed to the same chemical. We found that across all 502 published NTP rodent cancer studies, results in one species and gender frequently underestimated cancer incidence in the other species and genders, with the average false negative rate being 27.5 percent, but ranging as high as 40 percent in one case. Given that rats and mice are more similar to one another than either is to humans, these figures are likely an underestimate of the actual rate of false negative predictions of human risk by rodent studies. Indeed, Dr. David Salsburg of Pfizer reported in 1983 that rodent studies

showed no cancer-causing effects for 12 of 19 chemicals listed by IARC as *known* human carcinogens, which suggests that the false negative rate may be as high as 63.2 percent.⁴⁶ Similarly high estimates have also been reported elsewhere in the scientific literature.^{47,48} **Such dangerous underestimates of cancer risk could expose millions of people to very real health risks and incur societal costs of hundreds of millions of dollars.**⁴⁹

Turning to false positive results, the most famous example of this problem is the artificial sweetener saccharin. In 1981, saccharin was given the dubious distinction of being listed in the NTP’s *Report on Carcinogens* among substances “reasonably anticipated to be a human carcinogen” because it caused bladder cancer in rats. Naturally, the sugar industry capitalized on this finding, and for a time the FDA required saccharin packets and foods containing the sweetener to bear the warning: “Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals.”⁵⁰ Two decades later, government regulators were forced to admit that “observed

HUMAN CARCINOGENS UNDETECTED IN RODENT CANCER TESTS

Cigarette smoke—Despite ample human evidence of the link between smoking and cancer, the tobacco industry was successful in using the results of experiments—in which rodents and other animals were forced to inhale smoke but did not develop cancer—to delay health warnings about smoking for more than 20 years. As Dr. Clarence Little wrote in the *New England Journal of Medicine* in 1961: “There have been many such experiments here and abroad, and none have been able to produce carcinoma of the lung in animals.”

Asbestos—Hundreds of animal tests of asbestos have been conducted, including more than 20 rodent cancer studies, yet the significance of the test results to humans has been debated and disputed for decades. In 1995, a paper reanalyzed rat and human data and concluded that humans are 300 times more susceptible than rats to lung cancer (mesothelioma) from inhaled asbestos fibers. This led the scientists to conclude that “inhalation studies in rats are not sufficiently sensitive for the detection of hazards and risks to humans exposed to man-made fibers.”⁷⁷

Benzene—The causal link between benzene and human leukemia was established as early as 1928, yet 14 subsequent animal studies failed to replicate benzene’s cancer-causing effects. Only during the late 1980s were researchers ultimately able to induce cancer in animals by overdosing them with benzene, yet even this has not stopped researchers from continuing to use public funds to subject thousands of animals to lethal tests with this chemical, its derivatives, and its byproducts.⁸

bladder tumors in rats arose from a mechanism that is not relevant to humans,” which led to the de-listing of saccharin from the *Report on Carcinogens* in 2000.⁵¹

Saccharin’s regulatory history is a telling example of the problem with false positive results. For decades, scientists have criticized NTP rodent cancer studies for implicating an implausibly large number of chemicals as carcinogenic. The NTP itself has acknowledged that about half the chemicals it has tested have produced evidence of cancer in rodents.^{52,53} A review by cancer researchers at the University of California at Berkeley found that closer to two-thirds of 800 chemicals tested positive in rodent cancer studies.⁵⁴ Other scientists have suggested that the false positive rate could be upwards of 90 percent, meaning that NTP cancer studies are almost completely incapable of correctly identifying chemicals that truly *do not* pose a cancer risk to humans.⁵⁵ This would not be unlike providing traffic police with radar devices calibrated to indicate that 90 percent of drivers are speeding: Most speeders will indeed be caught, but so too will countless nonspeeders. In the context of cancer risk, **such frequent overestimates cost society billions in terms of loss of viable products in commerce, decreased international competitiveness, job loss, litigation, and undue public anxiety.** As past NTP/NIEHS Director Dr. Kenneth Olden acknowledged, “That’s an awful lot of money to be spending to be regulating substances we might not have to be regulating if we had more information.”⁵⁶

IRRELEVANCE OF EXTRAPOLATION TO DIFFERENT SPECIES, STRAINS, AND GENDERS

“A mouse is not a rat is not a human.”⁵⁷
—Dr. Michael Cunningham, NIEHS

“Mice may be between 30,000 and 3,000,000,000 times more cancer prone than humans.”⁵⁸
—Dr. Gio Batta Gori, The Health Policy Center

As stated above, a scientifically valid toxicity study must accurately measure the biological effect in question (e.g., cancer) in the species of interest (e.g., humans).⁵⁹ Genomic research has revealed that rats and mice diverged as separate species 18 to 24 million years ago. Even so, they are much more similar to each other than are rodents to humans, who diverged approximately 80 million years ago.⁶⁰ Thus, not surprisingly, a number of tumor types and mechanisms of cancer development in rodents have been determined by regulatory and other cancer authorities to be of little or no relevance to the human condition (Figure 3).^{61,62,63,64,65,66}

- Male rats produce a protein called “α2u-globulin.” When a chemical binds to this protein, it accumulates in tubule cells in the rats’ kidneys. This leads to cell death and sometimes cancer. This protein is very specific to male rats. There is no similar protein in humans and no evidence that chemicals cause cancer in humans in this way. Unleaded gasoline and d-

limonene, found naturally in fruit juice, are two chemicals that cause kidney tumors in rats by binding to α 2u-globulin but do not cause such tumors in humans.

- High doses of chemicals such as saccharin and sodium ascorbate (vitamin C) produce a calcium-containing buildup in the urine of rats. This irritates the rat's bladder and sometimes leads to cancer. This buildup only occurs in rats and only when very high doses of the chemical are given.
- "Peroxisomes" are microscopic structures found in all animal and plant cells. In rodents, a wide range of chemicals, including cholesterol-lowering drugs, herbicides, and plasticizers, cause an increase in the density and activity of peroxisomes, resulting in the proliferation of liver cells, organ enlargement, and tumor formation. Chemicals that have this effect in rats and mice have been shown to have little, if any, effect on the human liver.
- Elevated levels of "thyroid-stimulating hormone" can lead to thyroid cancer in rats. Chemicals that elevate hormone levels cause cancer in rats, but humans are much less sensitive to this effect. Phenobarbital, an anti-seizure medication that has helped millions of people, causes thyroid tumors in this way *but only in rodents*.

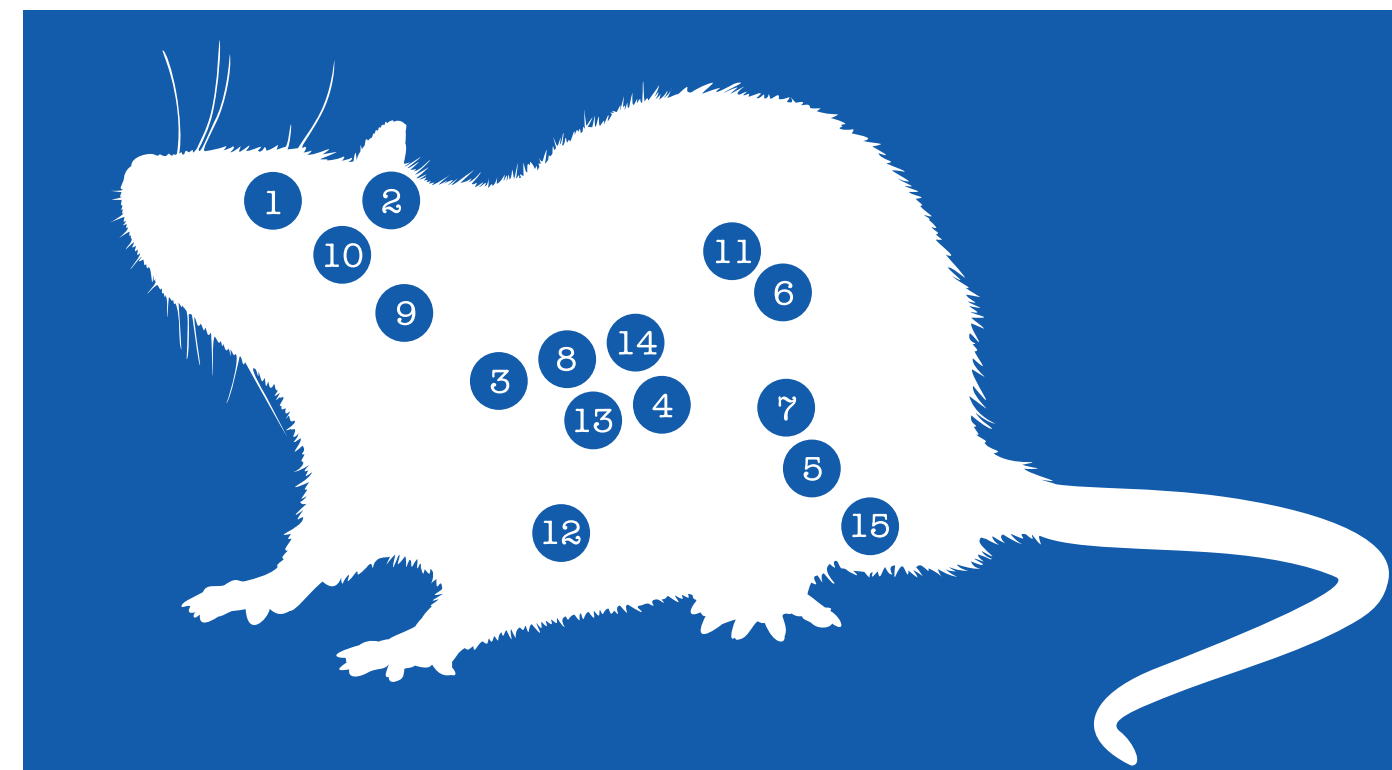
Certain types of tumors have been identified in rodents for which there are no known human equivalents, such as splenic mononuclear cell leukemia in rats and the mouse submucosal mesenchymal lesion of the urinary bladder. In fact, there are entire organs in rodents that have no counterpart in human anatomy, such as the forestomach, Zymbal's gland, and the Harderian gland. In addition, certain tumors of the hormonal and reproductive system (particularly the thyroid, pituitary, adrenal cortex and medulla, parathyroid, pancreatic islets, gastrointestinal endocrine cells, and reproductive organs), while common targets of cancer in rodents, are routinely dismissed as being of little or no relevance to humans.⁶⁷

So lengthy is the list of irrelevant rodent tumors and mechanisms that IARC has published technical reports cautioning scientists and regulators not to rely on the results of rodent studies in which cancers are found in the thyroid, kidney or urinary bladder, forestomach, or gastric neuroendocrine tissues or where the mechanism of action is associated with peroxisome proliferation.^{68,69,70} Similarly, the EPA has issued its own technical reports and risk-assessment guidelines regarding the assessment of thyroid, kidney, and other rodent tumors and has commissioned the International Life Sciences Institute (ILSI) to develop additional "principles for determining when cancer mechanisms of action are relevant to humans."^{71,72}

The interpretation of NTP cancer data is further complicated by the fact that the highly inbred rodent strains most commonly used in these studies—the B6C3F1 mouse and the Fischer 344 rat—have very high "background" tumor rates even when they are not dosed with chemicals.⁷³ For example, the NTP has reported that approximately 96 percent of untreated "control" rats from the Fischer 344 strain developed some type of spontaneous tumor, and 64 percent of the males and 43 percent of the females had at least one cancerous tumor.⁷⁴ The same study similarly reported that more than two-thirds of untreated

B6C3F1 mice developed some type of tumor and that 39 percent of these mice had at least one cancerous tumor. **Such high spontaneous-tumor rates create so much background "noise" that it can be nearly impossible to detect a small rise in chemically induced tumors, thus contributing to the high proportion of inconclusive test results.**

Figure 3
Types of rodent tumors recognized as having little or no relevance to humans



Organs Unique to Rodent Anatomy

- 1 - Harderian Gland
- 2 - Zymbal's Gland
- 3 - Forestomach

Rodent Tumors With No Known Human Equivalent

- 4 - Splenic Mononuclear Cell Leukemia in Rats
- 5 - Submucosal Mesenchymal Lesion of the Urinary Bladder in Mice

Mechanisms of Cancer Causation Irrelevant to Humans

- 6 - Buildup of α 2u-globulin in the Kidneys of Male Rats
- 7 - Calcium Phosphate-Containing Urinary Calculi in Rats

- 8 - Peroxisome Proliferation in Rodent Livers
- 9 - Thyroid Follicular Cell Tumors in Rats

Tumors of the Hormonal and Reproductive Systems to Which Rodents Are Much More Susceptible Than Humans

- 10 - Pituitary Gland
- 11 - Adrenal Gland
- 12 - Luteinizing Hormone-Induced Breast Tumors in Sprague-Dawley Rats
- 13 - Gastric Endocrine Cells
- 14 - Pancreatic Tumors Related to the Use of Corn Oil in Oral Force-Feeding Studies
- 15 - Reproductive Organ Tumors

Chemical	Daily dose fed to rodents	Equivalent human intake
Penicillin	1,000 mg/kg	70 times human daily dose for life
Agar	50,000 ppm	100 times daily human intake for life
Codeine	70 to 80 mg/kg	20 to 80 times the human dose, or 180 Tylenol 3 tablets per day for life
Locust bean gum	50,000 ppm	50 times the level found in most food products
Safrole	5,000 ppm in diet (0.5%)	613 12-oz. bottles of root beer daily
Cyclamates	5% in diet (2.18 g/day)	138 to 522 12-oz. bottles of soda daily for life
Alar	5,000 to 10,000 ppm in diet (0.5 to 1%)	28,000 pounds of apples daily for 10 years

Additionally, cancer studies using rodent strains different from those used by the NTP often produce conflicting results. For example, a chemical that is carcinogenic in Fischer 344 rats may be harmless to rats of the Sprague-Dawley strain or vice versa, which leads to debates over which strain (if either) is most relevant to humans.^{75,76} Moreover, decades of inbreeding have resulted in unintended genetic changes over time in rodent strains commonly used in toxicology studies.⁷⁷ For example, the NTP reports that Sprague-Dawley rats have increased in weight by up to 300 grams over several years, while the Fischer 344 rats (NTP's strain) now weigh 25 percent more than their predecessors. These increased body

weights may result in "decreased lifespan and increased tumor incidences," further complicating the interpretation of NTP cancer study data.⁷⁸ For example, a decade ago, the average two-year survival of untreated male Fischer 344 rats was 66 percent; the survival rate has now fallen to less than 50 percent.⁷⁹

IRRELEVANCE OF NTP MEGA-DOSES TO REAL-WORLD HUMAN EXPOSURES

"Since the standard bioassay cannot adequately distinguish between carcinogens and non-carcinogens tested at the [maximum tolerated dose], it would appear prudent from a public health standpoint to assume that all chemicals may be carcinogenic at the [maximum tolerated dose] in animals."⁸⁰

—Dr. David Gaylor, veteran of the FDA's National Center for Toxicological Research

NTP rodent cancer studies are designed to maximize the likelihood of detecting a statistically significant increase in tumor incidence in chemically exposed animals relative to untreated controls in order to apply observations taken from hundreds of animals in laboratories to millions of people throughout the world. In order to achieve this goal, and cut through the "noise" created by rodents' high spontaneous-tumor rate, animals may be given a nearly toxic overdose of a test substance every day for their entire lives. For example, animals in the highest dose group are given the so-called "maximum tolerated dose"—defined as the highest-dose of a substance that will not shorten the animals' normal

Table 2
Comparative animal/human doses for selected substances⁸²

life span because of noncancer-related toxic effects. Such experimental doses are often many orders of magnitude above the exposure levels encountered by people in daily life (Table 2).^{81,82}

Exposing cells to a nearly toxic dose of any chemical injures and kills some of them. The natural response to cell injury and death is for the remaining cells to divide to replace those cells that have been lost, and increased cell proliferation presents a risk for cancer. Thus, the very conditions of NTP cancer studies may be as much responsible for causing cancer as the chemicals being tested. A review of NTP rodent cancer studies by NIEHS statistician Dr. Joseph Haseman arrived at much the same conclusion, reporting that "two-thirds of the positive bioassays were positive *only* when the [maximum tolerated dose] was employed."⁸³ Similar conclusions have also been reached by regulatory scientists at the EPA and FDA.^{84,85} This partly explains the high rate of "false positive" results described above.

The maximum tolerated dose, by definition, "should be the highest dose that causes no more than a 10 percent weight decrement."⁸⁶ PETA examined study results for the 20 chemicals most recently tested and judged by the NTP to produce clear evidence of carcinogenicity in both genders of rats and mice to determine whether weight loss ever exceeded the 10 percent cutoff, which would mean that the NTP actually used doses above the "maximum tolerated dose." It is recognized that carcinogenic effects produced under such conditions have little or no relevance for humans, who are typically exposed to much lower doses.⁸⁷ We determined that for the 20 most recently tested chemicals, average decreases in body weight among animals in the high-dose group relative to untreated controls did indeed exceed the NTP's 10 percent cutoff, with chemical-specific decreases in body weight as high as 45.8 percent for female mice, 28.5 percent for male mice, 29 percent for female rats, and 34.7 percent for male rats (*see box at right*). The NTP caused great distress to these animals by exposing them to highly toxic doses of chemicals, all for test results that are then by definition useless—a complete waste of taxpayer dollars.

Rather than determining which chemicals in the environment pose real cancer risks to humans, NTP rodent studies simply show that nearly all chemicals cause cancer in rodents at high enough doses. This fact led the NTP's Board of Scientific Counselors to conclude that "the implicit assumptions underlying extrapolation from the [maximum tolerated dose] ... do not appear to be valid. Therefore, both the criteria for selection of the high dose used and the default criteria that are employed for extrapolation from high-dose to low-dose must be reevaluated in a critical manner."⁸⁸

ANIMAL WELFARE FACTS & FIGURES

NTP two-year rat and mouse cancer studies published to date: **502**

Animals used per study: **860**

Proportion of published studies conducted by the following routes of exposure:

- Mixed with food/water 57%
- Daily force-feeding 26%
- Forced inhalation 10%
- Applied to skin 4%

Weight loss in animals in the high-dose relative to control group for 20 chemicals showing "clear evidence" of carcinogenicity:

- Female mice 13.3% - 45.8%
- Male mice 10.8% - 28.5%
- Female rats 7.7% - 29%
- Male rats 10.5% - 34.7%

ANIMAL SUFFERING

“Although some claim that animals used in laboratory experiments are healthier now than in the past, the life of the animal who lives in a barren, sterile environment in which temperature, humidity and lighting are controlled and wall surfaces are disinfected, whose food and bedding are sterilized, and who is subjected to painful and debilitating experiments, is an unhealthy and abnormal one—and one which does not parallel the average human (or animal) condition.”⁸⁹

—Alix Fano, in *Lethal Laws: Animal Testing, Human Health and Environmental Policy*

Rats and mice used in NTP cancer studies are treated as little more than test tubes with whiskers. Animals assigned to untreated control groups may suffer less than animals who are dosed with chemicals, but they still spend their lives caged in unnatural and inherently stressful laboratory conditions. Bright lights (which can damage rodents’ sensitive vision), loud noises (including ultrasound), strong odors, and frequent handling and manipulation are but a handful of the routine laboratory procedures that have been proved to cause physiological evidence of stress and distress in captive animals.^{90,91} Rodents are often housed in hanging wire-bottom cages, which can lead to physical injuries, foot ulcers, and related deformities, particularly among animals housed this way chronically, as is the case in NTP cancer studies.^{92,93,94} In addition, it is still common to house rodents individually with no form of behavioral or environmental enrichment, which severely frustrates animals’ complex social and psychological needs and can lead to self-mutilation, incessant biting of cage bars, and other neurotic, anxiety-related behaviors.^{95,96} Laboratory conditions have been found to elevate stress hormones, heart rate, and blood pressure, depress immune function, and induce sleep disorders and gastric ulcers in animals—any and all of which can add to the already substantial variability in these studies and further skew test results and confound data interpretation.⁹⁷



Figure 4
Mouse overcome with massive, painful tumors

The reality for most animals used in NTP cancer studies, however, is even grimmer: Not only are they forced to live in the barren and inherently stressful conditions described above, they are also forced to swallow, inhale, or absorb massive quantities of a test chemical, thus spending their entire existence in varying degrees of sickness and distress (*Figure 4*). Painkillers are rarely, if ever, provided. Animals in the high-dose group are given the



Figure 5
Oral dosing of a mouse with a steel tube measuring the distance to the animal's stomach

maximum tolerated dose of a test substance, which, as previously described, is designed to induce some signs of toxicity, which may include lethargy, anemia, diarrhea, weight loss, fur loss, organ damage, unsteady gait, salivation, tremors, coma, and even death. Those who survive until the end of a two-year study may be riddled with massive, debilitating tumors (*Figure 4*) and suffer other ill effects of cancer.

PETA’s analysis revealed that more than one-quarter (26 percent) of the animals used to date in NTP cancer studies have been exposed to test substances through daily force-feeding (*Figure 5*), a procedure which “involves the physical stresses of handling and restraint, insertion of a rigid metal or flexible plastic tube ... from mouth to stomach (with associated breathing interference), and stomach distention.”⁹⁸ Complications associated with repeated force-feeding can include puncturing of the throat and lungs, aspiration pneumonia, and often death. Such severe damage is particularly common in two-year cancer studies. For example, one study reported that 32 percent of female rats and 6.5 percent of male rats had died within the first year of a cancer study as a result of suffocation related to repeated force-feeding.⁹⁹

Another common route of chemical exposure is forced inhalation, which has been used in roughly 10 percent of NTP cancer studies. In this scenario, animals are either placed in cages that are then sealed inside a large chamber that is filled with gases, or they are squeezed into restraint tubes (*Figure 6*), which are then connected to a tree-like inhalation device, which delivers vapors directly to the animals’ respiratory systems.

Even without the invasive manipulations to which they are subjected in NTP cancer studies, rats and mice of the strains regularly used by the NTP are suffering the effects of decades of inbreeding, as mentioned above. Some of these effects are extremely painful for the animals who experience them. For example, the Fischer 344 strain of rats has inherent problems with debilitating seizures, which have been worsening over time, as well as the potentially lethal accumulation of lymph fluid in the throat.¹⁰¹ Likewise, the B6C3F1 strain of mice has

experienced an inexplicable and scientifically worrisome weight gain over time and, along with it, an increased rate of spontaneous liver tumors (currently upwards of 60 percent).¹⁰²

Given the extreme cruelty inflicted upon animals in these studies, it should come as no surprise that by the NTP's own estimates, between 25 and 70 percent of animals die before the end of a two-year cancer study.¹⁰³ It is disgraceful that techniques causing this level of suffering to sentient animals should ever be tolerated, let alone represent the norm for a government-sanctioned and publicly funded testing program. However, it is not surprising that this has not been previously addressed, given that rats and mice are purposely and unjustifiably exempt from even the minimal protections of the federal Animal Welfare Act.



Figure 6
Rats squeezed into inhalation tubes at NIEHS labs in Research Triangle Park, North Carolina¹⁰⁰

REGULATORY RESPONSE TO RODENT CANCER TEST RESULTS

“We always have a battle on the issue of what to do with the animal data.”¹⁰⁴

—Dr. Edward Stein, health scientist
Occupational Safety and Health Administration

“In the present state of the art, making quantitative assessments of human risk from animal experiments has little scientific merit.”¹⁰⁵

—Statisticians Drs. David Freedman and Hans Zeisel

The purpose of NTP cancer studies is ostensibly to inform government regulators and public health professionals who assess and manage risks and who depend upon empirical data to determine whether or not a chemical causes cancer *in humans*. Yet far from providing a clear and reliable answer to this question, the results of nonvalidated NTP rodent cancer studies are *always* in question. Data from these studies on their own are never enough to classify a chemical as a *known* human carcinogen.¹⁰⁶ At most, rodent cancer data may be used as a basis for classifying a chemical as a *probable* human carcinogen. However, as previously discussed, the great majority of NTP-tested chemicals are not classified in a meaningful or informative way; instead, they are lumped into such noncommittal “catch-all” categories as *possible* human carcinogens or altogether *unclassifiable* as to human cancer risk.

If the NTP does not even classify a chemical as to its cancer risk to humans, then the results of rodent cancer studies are not likely to inspire government agencies to take action to regulate that chemical. PETA's research shows that the NTP classified only 89 of the 476 chemicals it tested in rodents (19 percent) with regard to their cancer-causing potential in humans. Even among the 114 NTP-tested chemicals that caused cancer in both rats and mice (evidence that a chemical hazard is not unique or limited to single species), only 62 (53 percent) have been listed in the *Report on Carcinogens*. Conversely, some of the chemicals that the NTP has classified as *known* or *probable* carcinogens do not produce strong evidence of cancer risk in rodent studies. For example, only three of the nine chemicals that the NTP has classified as *known* human carcinogens caused cancer in both rats and mice. Amazingly, one *known* human carcinogen, an analgesic mixture containing phenacetin, produced only inconclusive evidence of carcinogenicity in female rats and no evidence of carcinogenicity whatsoever in any of the other animals. Of the chemicals classified by the NTP as *probable* human carcinogens, 18 (20 percent) caused cancer in only one species tested, and four chemicals (including the pesticides DDT and lindane) produced no evidence of carcinogenicity in either rats or mice.¹⁰⁷

Even more striking are the discrepancies between NTP cancer study results and classifications by agencies such as IARC and the EPA. For example, of the 114 chemicals that caused cancer in both rats and mice in NTP studies, IARC classifies only eight (7 percent) as *known* or *probable* human carcinogens, and 25 (22 percent) as *unclassifiable* as to human cancer risk. Thus, for a chemical that causes cancer in both rats and mice in NTP studies, it is at least three times more likely that IARC will list it as *unclassifiable* than as a *probable* human carcinogen.¹⁰⁸ Similarly, the EPA classifies just 18 of the 114 chemicals that caused cancer in both rats and mice in NTP tests (15.6 percent) as *known* or *probable* human carcinogens. However, five chemicals that the EPA classified as *probable* human carcinogens (including dioxin and the pesticides DDT and dichlorvos) produced no evidence whatsoever of cancer risk in NTP studies, and two other chemicals produced only inconclusive evidence of cancer risk in one species tested.¹⁰⁹ **These false negative animal test results could lead to dangerous human exposures if government regulators relied on them.**

In the absence of clear and reliable answers from NTP cancer studies, federal agencies and their advisory committees engage in protracted debates with industry and other stakeholders regarding the interpretation of rodent data and their relevance to humans. As former EPA Administrator William Ruckelshaus commented more than 20 years ago: “We should remember that risk assessment data can be like the captured spy: If you torture it long enough, it will tell you anything you want to know.”¹¹⁰ Following are some examples:

- The EPA’s Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel concluded that the pesticide malathion “either is unlikely to cause cancer in humans, or the scientific evidence is insufficient to assess its carcinogenic potential.” The science panel was divided on whether to place malathion in the “suggestive evidence of carcinogenicity” category based on evidence from animal studies or in the “not likely to be carcinogenic to humans” classification. One point of debate was how rare—or relevant—certain tumors in study animals were. One panel member said the pesticide should be classified as a “likely” carcinogen, but most discounted their relevance on the grounds that there is no strong evidence of cancer risk nor any evidence of a mode of action relevant to humans.¹¹¹
- The report of the Chronic Health Advisory Panel of the Consumer Product Safety Commission found that the chemical diisononyl phthalate (DNIP), is “clearly carcinogenic to the rodent” but that DNIP appears to induce liver cancer in rodents by a mechanism not readily induced in humans under real-world exposure conditions involving consumer products. Therefore, the rodent data were disregarded and the human risk has been deemed “negligible” by the panel.¹¹²
- The EPA’s draft characterization of trichloroethylene (TCE) reported that the chemical may be more likely to cause cancer than the EPA had previously recognized based on new scientific data showing that humans retain TCE in their bodies longer than animals do. In addition, human population studies showed an association with prostate and cervical

cancers, an effect not previously detected because “there is no good mouse or rat model that can be used to determine whether chemicals cause prostate or cervical cancer.” On the other hand, some scientists have argued that people may be less susceptible to TCE’s cancer-causing properties because of differences between rodents and humans. For example, liver tumors in mice resulting from peroxisome buildup are considered to be irrelevant to people. Likewise, people may be less susceptible than mice to TCE-induced lung cancers seen in laboratory studies.¹¹³

- A manufacturer of pyrethrin pesticides sued the EPA for its classification of pyrethrins as “likely to be a human carcinogen if ingested orally.”¹¹⁴ The EPA’s Cancer Assessment Review Committee reportedly “decided on the classification because of studies indicating tumors in the rat, the relevance of [which] could not be discounted in humans.” However, the pyrethrin manufacturers have argued that the EPA’s “assessment overestimated the significance of tumors and did not weigh the scientific evidence properly.”¹¹⁵

Debates such as these can rage on for years or decades, impeding acceptance of beneficial compounds and misdirecting attention and resources away from substances that pose a real and present danger to human health and the environment. At the same time, many substances determined to be rodent carcinogens are still widely used in human drugs, pesticides, and food additives.^{116,117,118,119}

SUMMARY AND RECOMMENDATIONS

“In the face of these shortcomings, many experts believe the scientific value of the 2-year bioassay is highly limited—barely worth the investments in personnel, animals, money, and time.”¹²⁰
—Charles W. Schmidt, MPH

“I have to say we don’t serve the American people very well right now.”¹²¹
—Dr. Kenneth Olden, director, NTP & NIEHS (1991-2005)

As we have documented, rodent cancer studies, such as those conducted for more than 25 years by the NTP, have never been properly validated and have proved to be highly imperfect predictors of cancer risk in humans. Numerous genetic, physiological, biochemical, and metabolic differences between and among species, together with irrelevantly high doses and physiologically stressful laboratory conditions, make extrapolations of rodent data to humans all but meaningless. While these facts may explain the profound disarray and discord among regulatory classifications and decisions regarding chemical cancer risk to humans, they do not excuse the years of political and scientific complacency that have led to the present situation.

On the whole, we estimate that **the great majority of the U.S. government’s more than \$1 billion investment in the NTP/NCI rodent cancer-testing program has been wasted** on studies that:

- are judged to be “inadequate” or to produce “equivocal” (ambiguous) results, which are disregarded by health authorities (\$121 million).
- produce such dubious and conflicting results that more than 75 percent of NTP-tested chemicals are never ultimately categorized as to their cancer risk to humans or are lumped into such meaningless categories as “possible” human carcinogens or “unclassifiable” as to human cancer risk—designations which do nothing to inform or enhance public health or worker protection measures (\$460 to \$720 million).
- have been shown by other scientists to produce consistent and reproducible results only 57 percent of the time when the same chemicals are tested more than once using the same method—a result that could be achieved by simply tossing a coin.

In addition, society has paid untold billions responding to “false alarms” on the one hand, while at the same time, providing for costly treatment of cancer-related illnesses such as smoking- and asbestos-induced lung cancers that could have been prevented through earlier—and accurate—recognition of true human carcinogens.

These findings call into question the wisdom of continued federal appropriations to the NTP’s rodent cancer-testing program—especially if federal policymakers wish to have any hope of determining the cancer risk to humans of the more than 80,000 environmental chemicals that have not been specifically tested for carcinogenicity, a process which would require more than 32,000 years, 68 million animals, and \$160 billion at the current rate of progress using current methods.¹²² As Dr. Joshua Lederberg, Nobel laureate in medicine, stated in 1981: “It is simply not possible with all the animals in the world to go through chemicals in the blind way we have at the present time, and reach credible conclusions about the hazards to human health.”¹²³ **Clearly, the time has come for fundamental changes to the NTP’s testing paradigm and for the archaic NTP rodent cancer study to be relegated to the history books.**

There have been many proposals for refining rodent cancer studies as a short-term animal reduction measure while better, more human-relevant test methods are developed. For example, one short-term option proposed by a panel of pesticide regulators and industry convened by the International Life Sciences Institute is simply to conduct carcinogenicity studies in only one species of rodent instead of both rats and mice.¹²⁴ This would reduce costs and animal use by 50 percent. A similar proposal has called for development of a “reduced protocol,” using one or the other gender of rats and mice. For example, NTP scientists have reported that a reduced protocol “using male rat and female mouse would have identified correctly 95 percent of the positive or no evidence chemical carcinogenicity results obtained using the more extensive protocol.”¹²⁵

Another alternative accepted by pharmaceutical regulators at the International Conference on Harmonization (ICH) is to conduct a full two-year cancer study only in rats and to obtain second-species information from shorter-term studies using genetically modified mice.¹²⁶ The NIEHS has invested considerable resources in the evaluation and use of various strains of transgenic mice, only to conclude that “important issues of validation and standardization need further attention to permit their regulatory acceptance and use in human health risk assessment.”¹²⁷ However, U.S. agency representatives on the NTP’s Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) have been considerably less enthusiastic in their assessment of transgenic mouse studies. As documented in the summary minutes of the March 10-11, 2004, SACATM meeting:

- Dr. Calvin Willhite of the California Environmental Protection Agency concluded that “1) the use of transgenics may not decrease total animal use for carcinogenicity testing, 2) these models are not ready for validation, and 3) they are not sufficiently robust for human health assessment.”
- Dr. Alan Poland of the National Cancer Institute “also did not think the transgenic models are appropriate in the current context.”
- Dr. Marilyn Wind of the Consumer Product Safety Commission “did not support having ICCVAM validate these studies. She said since NTP made it very clear that they do not

believe the mouse model should be replaced by transgenics, there would be no point for ICCVAM to spend money to validate a model that is not going to replace, refine, or reduce the use of animals.”

As the above examples clearly demonstrate, the critical scientific and ethical limitations associated with the NTP’s rodent cancer studies cannot be remedied simply by using fewer test groups or genetically engineered animals. Senior FDA officials have stated that what is needed are “better methods that have such desirable characteristics as being cheaper, faster, using fewer animals, and providing the appropriate sensitivity and specificity desired of a screen for carcinogenic potential.”¹²⁸ This is largely true, but rather than use fewer animals, it would be scientifically best to use none at all. In 2003, the NTP articulated its “vision” for toxicology in the 21st century, which proposes to move toxicology from an observational to a predictive science, with markedly reduced reliance on animal testing.¹²⁹ Among the methods that the NTP has identified for further development are “high throughput” screens, which combine robotics and *in vitro* (cell-based) toxicology to create a system capable of rapidly and inexpensively screening tens of thousands of substances per year at multiple concentrations relevant to real-world human exposure levels. PETA believes that a “battery” of several *in vitro* tests—based on human tissues and mechanisms of cancer induction that are relevant to humans (e.g., genetic damage, cell transformation, depression of the immune system, hormone imbalance, etc.) represents the best approach for accurately identifying chemicals that pose a cancer risk to humans.^{130,131,132}

RECOMMENDATIONS

1. **Federal appropriations to the rodent cancer-testing program at the NTP/NIEHS should cease.**
2. **Funding that would otherwise have been spent on animal-based cancer studies should be redirected to the following two areas:**
 - **The NTP “21st Century Vision” program, with a specific proviso that funds be spent on the development and validation of *non-animal* methods and testing strategies for the detection of human carcinogens.**
 - **Human epidemiology (population) studies to identify additional human carcinogens as well as human noncarcinogens.**
3. **The U.S. Environmental Protection Agency, Food and Drug Administration, and other agencies that continue to require or recommend long-term cancer studies should limit this requirement to a single species or a “reduced protocol,” described above, and commit to replacing this requirement with a battery of non-animal methods as soon as practicable.**

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