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October 16, 1989

Ms. Rhoda H. Karpatkin
Executive Director
Consumers Union
256 Washington Street
Mount Vernon, New York 10553

Dear Ms. Karpatkin:

Consumer Reports' attack on my work in your last issue distorts my views and misstates facts. I enclose a rebuttal, which I think you owe it to your readers and to me to print in its entirety. Because of the number of errors in your article, an excerpt would not be satisfactory to me.

Consumer Reports has been noted for its objectivity in the past. I believe that your new activist mode will hurt the reputation of your organization and magazine unless you get advice from the leading experts in the field. It seems that it is reasonable for me to attempt to clarify the relative risks of carcinogens in foods. It also would be reasonable for *Consumer Reports* to educate the public about the comparative importance of the plethora of risks. You have so effectively exposed false claims in other areas, yet you have made no similar attack on people who are talking about millions of cases of cancer due to pesticide residues, or about cancer epidemics that have no scientific justification.

If *Consumer Reports* wishes to be effective in this area, I suggest that they get the best scientists in the country as advisors. You might ask the National Academy of Sciences, the Presidents of the American Association of Cancer Research, Toxicology, Epidemiology, and other societies to recommend people. I think you will get a very different message about what is important. In my view, your article demonstrates that its authors have not taken the time to read or understand the scientific literature adequately.

Yours truly,

Bruce N. Ames
Professor of Biochemistry and Molecular Biology
and Director, NIEHS Environmental Health
Sciences Center

BNA/ssk
Enclosure

cc: Board of Directors, Consumer's Union

October 16, 1989

REBUTTAL TO "TOO MUCH FUSS ABOUT PESTICIDES?"
Consumer Reports (October 1989)

Bruce N. Ames
Professor of Biochemistry and Molecular Biology
and
Director, NIEHS Environmental Health Sciences Center
University of California
Berkeley, California 94720

Consumer Report's four-page attack on my scientific work both distorts my views and misstates the facts on which they are based. Good scientists are committed to rigorously challenging assumptions, and this is particularly important in the prevention of cancer, a murky, complex, multidisciplinary field to which I have devoted much of my scientific career. Sound public policy should be based on sound science, and new data or theory may require altering some prevailing assumptions. In our efforts to prevent human cancer, it makes no sense to apply a double standard for human exposures to natural vs. synthetic chemicals. My colleagues and I have therefore attempted to provide an overview of possible carcinogenic hazards.

The following points clarify my views and their factual and theoretical basis:

(1) *Discovering the causes of cancer.* Epidemiologists are continually coming up with clues about the causes of different types of human cancer, and these hypotheses are then refined by animal and metabolic studies. This approach will, in my view, lead to the understanding of the causal factors for the major human cancers during the next decade. Current epidemiologic data point to the major risk factors for human cancer as cigarette smoking (which is responsible for 30% of cancer), dietary imbalances, hormones, viruses, and lifestyle factors--not to such factors as water pollution or synthetic pesticide residues. For example, epidemiologists in many countries have identified excessive salt as a risk factor for stomach cancer, one of the major types of cancer. Extensive experimental work in rodents on salt as a co-carcinogen supports the epidemiology. I had suggested to the leading Japanese workers on stomach cancer (it is their major type of cancer) that calcium should antagonize the effect of sodium chloride on causing cell proliferation leading to tumors. They have now confirmed this experimentally, and because the Japanese have low calcium and high salt in their diet, this may have a major impact on cancer prevention. Yet you unfairly criticize Edith Efron for saying that salt is a carcinogen.

You have criticized me for calling alcohol a carcinogen, yet alcoholic beverages, of numerous types, are carcinogenic in humans at a level of 5 drinks/day. Alcohol itself was positive in one rat test and also was co-carcinogenic in other tests. Acetaldehyde, the main metabolite of alcohol, is a carcinogen in rodents. Most of the leading scientists in the field believe that the active ingredient in alcoholic beverages is alcohol itself. I think that chronic

high doses of alcohol are active by causing cell proliferation and inflammation and that, therefore, low doses are not of much interest.

(2) *Animal cancer tests.* There are three fundamental problems with the use of animal cancer tests in trying to prevent human cancer from low-dose human exposures.

(a) There are millions of chemicals in the world that we are exposed to in low or moderate doses, 99.9+% of which are natural. To identify significant risks, we need to identify the right chemicals to test in rodents.

(b) About *half* of the chemicals tested in long-term bioassays in both rats and mice have been found to be carcinogens at the high doses administered, the maximum tolerated dose (MTD). Synthetic industrial chemicals account for almost all (82%) of the chemicals (427) tested in both species. However, despite the fact that humans eat vastly more natural than synthetic chemicals, only a small number (75) of *natural* chemicals have been tested in both rats and mice. For the 75 natural chemicals the proportion of positive results (47%) is similar, also about *half*. While some synthetic or natural chemicals were selected for testing precisely because of suspect structures, most chemicals were tested because they were natural or synthetic food additives, colors, high volume industrial compounds, pesticides, or natural or synthetic drugs. Thus, the high proportion of carcinogens among synthetic test agents in rodent studies is not simply due to selection of suspicious chemical structures, and the natural world of chemicals has never been looked at systematically. Recent research into mechanism of carcinogenesis (see below) supports the idea that when tested in rodents at the MTD, a high proportion of all chemicals we test in the future, whether natural or synthetic, will prove to be carcinogenic.

(c) The problem of knowing whether there is any risk at all from the very low doses of human exposure to chemicals causing tumors in rodents at very high doses has been argued by toxicologists and regulators for years, precisely because one cannot measure effects at low doses. Regulators have opted for worst-case estimates, using assumptions that increasing scientific evidence suggests may be incorrect.

Because conventional risk assessment is focused mainly on man-made chemicals and is based on worst-case assumptions that we believe are proving to greatly exaggerate hazard, many leading scientists have argued that it is misleading to the public to try to present estimates of "worst-case risk" from animal studies in terms of expected numbers of human cancers. Our HERP scale uses essentially the same information as that in conventional risk assessment, but is explicitly intended as a relative scale. We have attempted "to achieve some perspective on the plethora of possible hazards to humans from exposure to known rodent carcinogens by establishing a scale of the possible hazards for the amounts of various common carcinogens to which humans might be chronically exposed. We view the value of our calculations not as providing a basis for absolute human risk assessment, but as a guide for priority setting." Carcinogens clearly do not all work in the same way, and as we learn more about mechanisms, HERP comparisons can be refined, as can risk assessments.

Thus, if the public is told that the possible hazard of the UDMH residue in a daily glass of apple juice (about 30 ppb) is 1/18 that of aflatoxin (a mold carcinogen) in a daily peanut butter sandwich (the FDA allows ten times that residue level), or 1/50 that of a daily mushroom, and 1/1000 that of a daily beer, it puts these items in perspective. The possible

relative hazard of a daily apple is at least 10x less than the apple juice. This is quite different from showing a witch's hand holding an apple.

(3) *Pesticides, 99.99% all natural.* All plants produce toxins to protect themselves against fungi, insects, and animal predators such as man. Tens of thousands of these natural pesticides have been discovered, and every species of plant contains its own set of different toxins, usually a few dozen. In addition, when plants are stressed or damaged, such as during a pest attack, they increase their natural pesticide levels manyfold, occasionally to levels that are acutely toxic to humans. We estimate that Americans eat about 1,500 mg/day of natural pesticides, 10,000 times more than man-made pesticide residues, which FDA estimates at a total of 0.15 mg/day. Their concentration is usually measured in parts per thousand or million, rather than parts per billion (ppb), the usual concentration of synthetic pesticide residues and pollutants in water. We estimate that Americans are ingesting 5,000 to 10,000 different natural pesticides and their breakdown products, a subset of the tremendous number of natural chemicals we ingest. For example, there are 49 different natural pesticides (and breakdown products) ingested on eating cabbage.

Surprisingly few plant pesticides have been tested in animal cancer bioassays, but among those tested, again about *half* (25/47) are carcinogenic. A search for the presence of just these 25 carcinogens in foods indicates that they occur naturally in the following (those at levels over 50,000 ppb are listed in parentheses): anise, apples (50,000+ ppb), bananas, basil (4 million ppb), broccoli, Brussels sprouts (500,000 ppb), cabbage (100,000 ppb), cantaloupe, carrots (50,000+ ppb), cauliflower, celery (50,000+ ppb), cinnamon, cloves, cocoa, coffee (brewed) (90,000 ppb), comfrey tea, fennel (3 million ppb), grapefruit juice, honeydew melon, horseradish (4 million ppb), kale, lettuce (300,000 ppb), mushrooms, mustard (black) (40 million ppb), nutmeg (5 million ppb), orange juice (30,000 ppb), parsley, parsnips (30,000 ppb), peaches, black pepper (100,000 ppb), pineapples, potatoes (50,000+ ppb), radishes, raspberries, strawberries, tarragon (1 million ppb), and turnips.

There is every reason to expect that we will continue to find mutagens and carcinogens among nature's pesticides if we ever test them systematically. In short-term tests for detecting mutagens, the proportion of natural pesticides that turn up positive is just as high as for synthetic industrial chemicals. In a compendium on the ability of 950 chemicals to break chromosomes in animal tests, there were 62 natural pesticides: half of them were positive. Thus, it seems highly probable that almost every plant product in the supermarket will contain natural carcinogens at much higher levels than those of man-made pesticides. We have suggested that many more natural pesticides (and chemicals from cooking of food) be tested in long-term bioassays.

Additionally, there is a fundamental trade-off between nature's pesticides and man-made pesticides. We can easily breed out many of nature's pesticides, but then we will need more man-made pesticides to protect our crops from being eaten by insects. In contrast, growers are currently breeding some plants for insect resistance and unwittingly raising the levels of natural pesticides. A new variety of insect-resistant celery that is being widely sold is almost 10x higher in carcinogens (6,200 ppb) than standard celery.

(4) *Mechanisms of carcinogenesis.* In the rapidly advancing field of mechanisms of carcinogenesis, there is now evidence to suggest that cell proliferation is extremely important. A large number of the major human carcinogens such as hormones, chronic viral infection,

salt, asbestos, and alcohol are likely to be primarily active through causing cell proliferation. A cell is at considerably greater genetic risk during division, so chronic cell proliferation in itself is a mutagenic and carcinogenic stress. Cancers induced in animal cancer tests done at high doses seem to be primarily caused by cell proliferation, in part due to chronic cell killing, and inflammation that results from high toxic doses. This would be in agreement with the high proportion of all chemicals that are turning out to be carcinogens at high doses and the relation of toxicity to carcinogenic potency. The induction of cell proliferation is restricted to high doses, and this strongly suggests that low doses of carcinogens are of no risk, or are very much less hazardous than has been assumed.

In addition, humans, who live in a world of natural toxins, are well protected by many layers of inducible general defenses against low doses of toxins--defenses that do not distinguish between synthetic and natural toxins. Therefore, even the high levels of natural plant pesticides may not be of much concern in a balanced diet.

(5) *Trade-offs.* Identifying and controlling the major causes of human cancer are not a matter of blame. We have tried in our scientific work to put into perspective the tiny exposures to pesticide residues by comparing them to the enormous background of natural substances. Minimizing pollution is a separate issue, and is clearly desirable, aside from any effect on public health, but it involves economic trade-offs. As a society, efforts to regulate pesticides or other synthetic rodent carcinogens down to the ppb level inevitably involve understanding these trade-offs. Synthetic pesticides (and chemicals such as Alar) have markedly lowered the cost of our food, a major advance in nutrition and, thus, health. Every complex mixture from gasoline to cooked food to orange juice contains rodent carcinogens. When people drive to work, put logs on a fire, or make a barbecue they are putting carcinogens into the air. There are costs and benefits to all of these. Exaggerating the risks from man-made substances, ignoring the natural world, and converting the issue to one of blaming U.S. industry does not advance our public health efforts. If we spend all of our efforts on minimal, rather than important, hazards, we hurt public health. EPA is trying to prevent hypothetical risks of 1 in a million at enormous economic cost. Yet the leading scientists trying to prevent cancer are working on numerous possible carcinogenic risks in the 1 in a 100 to 1 in 10 range: my lab is working on 4 that we think are in this range.

I take issue below with a number of other statements about which I believe *Consumer Reports* is mistaken:

(a) Allyl isothiocyanate is ingested from a variety of foods; its precursor is in cabbage at a level of over 100,000 ppb and in mustard, horseradish, and Brussels sprouts at a level of millions of ppb. *Consumer Reports* questions my calling it a carcinogen. The National Toxicology Program evaluated its bioassay in male rats as having "clear" evidence of carcinogenicity because the induced transitional-cell papillomas are practically never seen in controls and "are considered to represent a stage in the biologic continuum to malignancy." Allyl isothiocyanate has also been shown to break chromosomes in animal cells in tissue culture, to mutate animal cells, and to transform animal cells to tumor cells at concentrations tens of thousands of times below the concentration in cabbage.

(b) You say that no mushroom hydrazine has been clearly shown to be an animal carcinogen, yet Bela Toth, who did the UDMH (from Alar) study, also has shown that 7 different hydrazines present in mushrooms induce tumors in mice--3 of these occur in the

common commercial mushroom (their total is greater than 50,000 ppb).

(c) We believe that there are many flaws in the work of Perera and Boffetta, on which you base numerous criticisms of our paper. This is not the place to discuss their paper in detail, but I will point out a few examples. In calculating what turned out to be their most hazardous estimate from a man-made substance, they overestimated by a factor of 1,000. We called this mistake to their attention, and they concurred with us. We disagree with some of their other numbers as well. We believe that those that are correct support our argument despite their own interpretation. For example, we pointed out that squid cooked in a gas oven contained significant levels of nitrosamines (potent carcinogens). This was support for our argument that *anything* cooked in a gas oven is likely to be high in carcinogenic nitrosamines and nitropyrenes as a consequence of the NO_2 released from gas flames. For them and *Consumer Reports* to indicate that we were calling attention to squid, a rarely eaten food, as a hazard completely misses the whole point. It is already clear that cooking our food makes a zoo of interesting rodent carcinogens.

(d) You assert that we looked at only two examples of synthetic pesticides, both of which had previously been banned. We, in fact, quoted the FDA numbers on total pesticide residues in foods. FDA selected 70 compounds they thought most important, and we pointed out that the 0.05 milligram of pesticide residues that potentially could be rodent carcinogens ingested per person per day in the U.S. (about 45 ppb in plant food) is about 10,000 times less than the natural pesticides we ingest and already thousands of times less than the amounts of natural carcinogens already turned up with minimal, and no systematic, testing. *Consumer Reports* is in error when it says our figures for the residue level of EDB in food was low because they were done after its ban. We indicated levels before the ban to illustrate that the EPA banned EDB, the main fumigant used in U.S. agriculture, for levels of less than 1 ppb, despite the enormous economic costs, lack of a suitable substitute, and inevitable trade-offs of increased mold carcinogens, such as aflatoxin, in grain.

(e) You say that I do not adequately discuss anticarcinogens, yet I am a leader in that field and have discussed at length why anticarcinogens protect us against all carcinogens, both man-made and natural. You mention broccoli as an anticarcinogen, yet when we eat broccoli or cabbage we ingest large amounts of a natural chemical, indole carbinol, that forms breakdown products in the stomach that have the same properties as dioxin (TCDD). When given to rodents before some carcinogens (e.g. aflatoxin), both dioxin and indole carbinol provide protection from carcinogenesis, yet administering either of these chemicals (or cabbage) after carcinogens results in many more tumors. This shows the complexity of "risk assessment." To look at only the good effects of the broccoli compound and the bad effects of the dioxin is a double standard. Based on comparative receptor binding, the compound in a portion of broccoli would be millions of times worse than the levels of dioxin that the EPA is trying to regulate.

CURRICULUM VITAE

NAME:	BRUCE N. AMES	
DATE OF BIRTH:	16 December 1928	
PLACE OF BIRTH:	New York, New York	
MARITAL STATUS:	Married to Professor Giovanna Ferro-Luzzi Ames Two children	
EDUCATION:	Cornell University, B.A. Chemistry Major, Biology Minor	1946-1950
	California Institute of Technology, Ph.D. Biochemistry Major with Prof. H.K. Mitchell; Chemistry and Genetics Minors	1950-1953
PROFESSIONAL EXPERIENCE:	Postdoctoral Fellow (U.S.P.H.S.) at N.I.H. with Dr. B.L. Horecker	1953-1954
	Biochemist at the National Institutes of Health	1954-1960
	Sabbatical year as N.S.F. Senior Fellow in Laboratories of F.H.C. Crick in Cambridge, England, and F. Jacob in Paris, France	1961
	Chief, Section of Microbial Genetics, Lab. of Molecular Biology, N.I.A.M.D., N.I.H.	1962-1967
	Professor of Biochemistry, Dept. of Biochemistry, University of California, Berkeley, CA 94720 (415) 642-5165	1968-present
	(Chairman: 1983-1989)	
	Director, National Institute of Environmental Health Sciences Center, U.C. Berkeley	1979-present
PROFESSIONAL SOCIETIES:	American Society of Biological Chemists Genetics Society of America American Society for Microbiology Environmental Mutagen Society American Association for Cancer Research American Chemical Society Society of Toxicology	
HONORS:	American Academy of Arts and Sciences	1970
	National Academy of Sciences	1972
	Fellow of the American Association for the Advancement of Science	1980
	IBM-Princess Takamatsu Cancer Research Fund Lectureship (Japan)	1984
	Honorary Doctor of Science Degree, Tufts Univ.	1987
	Honorary Pharmacology Degree, University of Bologna	1989
	Elected Honorary Foreign Member, Japan Cancer Association	1987
	Elected Foreign Member, The Royal Swedish Academy of Sciences	1989

AWARDS:	Eli Lilly Award of the American Chemical Society	1964
	Arthur Flemming Award (as Outstanding Young Government Employee)	1966
	Lewis Rosenstiel Award	1976
	FASEB/3M Award for Research in Life Sciences	1976
	E.R.D.A. Distinguished Associate Award	1976
	Environmental Mutagen Society Award	1977
	Cal. Tech. Distinguished Alumni Award	1977
	Simon Shubitz Cancer Prize	1978
	Felix Wankel Research Award	1978
	John Scott Medal	1979
	Bolton L. Corson Medal	1980
	New Brunswick Lectureship Award of A.S.M.	1980
	Wadsworth Award	1981
	Charles S. Mott Prize, GM Cancer Research Fdn.	1983
	Gairdner Foundation Award (Canada)	1983
	Tyler Prize	1985
	Spencer Award	1986
	Roger J. Williams Award in Preventive Nutrition	1989
SERVICE ON BOARDS AND COMMITTEES:	Program Committee of the Am. Soc. Biol. Chem.	1963-1967
	Editorial Board, Arch. of Biochem. and Biophys.	1964-1969
	Member of National Research Council (representative of Genetics Society)	1964-1969
	Editorial Board, Journal of Biological Chemistry	1965-1971
	Nominating Committee of the American Society of Biological Chemists	1967-1969
	Governing Council, Environmental Mutagen Society	1971-1975
	Advisory Committee, Earl Warren Legal Institute	1971-1975
	Nominating Committee of the Genetics Society	1971
	Organizer, 1st International Conference on Environmental Mutagens, Asilomar, California	1973
	Consultative Panel on Hazards of Chemical Pesticides, Natl. Res. Council, Natl. Acad. Sci.	1974
	Subcluster on Environmental Health and Toxicology of President's Biomedical Research Panel	1975
	National Cancer Advisory Board (Presidential appointment)	1976-1982
	Search Committee for Director of N.C.I.	1977
	Scientific Advisory Panel, California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)	1977-1979
	Member, Commission on Life Sciences, National Research Council	1989-
RESEARCH INTERESTS:	Identifying agents damaging human DNA and the consequences for aging and cancer; endogenous oxidants and defenses against them; mutagenesis and carcinogenesis.	
PUBLICATIONS:	Over 200 scientific publications: 7 of these are among the 1000 most-cited scientific papers (in all fields) in the last 30 years, and 2 are among the 100 most cited.	