Well-done or Over-done?
Questioning Popular Notions About Meat and Cancer

Links between the consumption of red meat and cancer abound in the mass media but are not based on solid scientific fact. New studies of meat safety are bringing good news, based on good science, to the meat industry and the consumers they serve.

“Everybody knows....” “Experts say that....” How many times have we all heard these phrases used as a lead-in to a television news story about diet and health? Picture the anchor saying authoritatively: “Experts have long said that red meat consumption can cause cancer, and a new study affirms that fact....” Unfortunately, the media report is often presented in a definitive, “case-closed” manner.

These stories typically lack the context of the complete body of research, particularly those that find no association between the dietary factor being studied and the health outcome. Often, epidemiological studies that find no association never enjoy the fame of a journal press release and subsequent media coverage.

Let’s face it, null findings seem boring. Or are they? New studies have brought good news—news that is rooted in good science. Regrettably, the “meat causes cancer” bandwagon seems to roll right over these important emerging findings.

Perhaps John Kenneth Galbraith was correct when he said, “The conventional view serves to protect us from the painful job of thinking.” But we must think when it comes to the controversial subject of meat and cancer because unconventional new wisdom is emerging.

WCRF Sounds the Alarm

While the etiology of cancer is complex, multi-factorial and still under debate, in the fall of 2007, the World Cancer Research Fund (WCRF) and its U.S. affiliate the American Institute for Cancer Research (AICR) issued a 517-page report summarizing the opinions and judgments of a WCRF/AICR-appointed panel that declared the de-
Proven Tools, Accurate Results, Faster Decisions

The R.A.P.I.D. LT can quickly and reliably identify food and water pathogens. As the originator of rapid DNA analysis, our technology has become the standard in BioDefense and is now available for food and water testing.

With millions of tests sold and used by government agencies and research laboratories throughout the world, testing for Salmonella, Listeria, E. coli O157, Avian Influenza and other targets has never been easier.

Sensitivity, accuracy, and high speed make the R.A.P.I.D. LT the ideal instrument for rapid pathogen identification.

Check out our AOAC Approved Salmonella LT Test kit!

Visit us online at www.idahotech.com to learn more about this time saving technology and to request a demo.

*See our Web site for a complete list of target assays

Idaho Technology Inc.

Innovative solutions for pathogen identification and DNA research

390 Wakara Way, Salt Lake City, Utah 84108, USA | 1-800-735-6544 | www.idahotech.com
grees to which a food or behavior caused cancer. WCRF/AICR established its own criteria for determining the threshold for causation and primarily relied upon human epidemiological studies, although they state that "evidence of plausible biological mechanisms" is needed to support the epidemiological link. According to the WCRF/AICR summary report, some of the methods used by this panel are "new" and, as such, have not been subjected to broad scientific peer-review and concurrence. The criteria the group established indicate a "convincing" declaration of causation, requiring evidence from two scientifically sound cohort studies along with evidence of dose response and plausible experimental evidence. The other classifications that require less stringent evidence were "probable," "limited-suggestive," "limited-no conclusion" or "substantial effect on risk unlikely."

"But we must think when it comes to the controversial subject of meat and cancer because unconventional new wisdom is emerging."

WCRF/AICR declared that the evidence of a link between red and processed meat and the development of colon cancer was "convincing." The finding was supported primarily by weak to modest associations that may have been influenced by bias or confounding. Still, they recommended a public health goal that no more than 11 oz. of red meat per week be consumed, very little if any of which should be processed meat because they claimed there is no safe level of processed meat. In the discussion, they said nitrite in processed meats or other factors may be to blame.

Studies showing the health benefits of red and processed meat, and studies documenting sodium nitrite's lack of a cancer effect in major rat and mouse lifetime biosays (like those done by the National Toxicology Program) were not considered. In addition, epidemiological studies showing no relationship between meat and cancer—and there are many—were apparently insufficient to sway the panel opinion about their "convincing" judgment.

Perhaps most critically, one of the largest epidemiological study ever done of the relationship between red and processed meat and colon cancer was not considered. The Pooling Project, led by Harvard University, used a more robust form of meta-analysis called "pooling" whereby source data from international cohort studies are pooled together and re-analyzed using uniform and standardized exposure and analytical methods. This quantitative assessment included 14 cancer centers and involved over 725,000 people.

The study authors concluded that there was no association between red and processed meat consumption and colorectal cancer. Although the results were presented at the 2004 American Association for Cancer Research conference and published in the conference proceedings, the study has never appeared in a journal and, therefore, its landmark findings were not factored into the WCRF report. Had the findings been considered, the WCRF/AICR panel would have had trouble reaching the conclusion that it did.

Key senators have asked the Health and Human Services Secretary for an explanation about why this federally funded study remains unpublished. AICR says that many of the individual publications representing studies that were comprised in The Pooling Project were considered in its analysis. That may be true, but the WCRF report clearly underscores the value of pooled data: "the combination (and re-analysis) of data from multiple studies creates a larger data set and increased statistical power."

An Intellectual Leap over the Facts?

While AICR declared in a press release that the report was "the most comprehensive ever done" and claims to have "convincing the scientific community" about cancer prevention strategies, many scientists are not convinced.

David Klurfeld, Ph.D., national program leader in human nutrition at the USDA Agricultural Research Service, provided an extensive critique of the 2007 report at a 2008 International Association of Food Protection (IAFP) symposium. Despite WCRF/AICR's claims of a "convincing link" between red and processed meat and colorectal cancer, Klurfeld noted that a careful read of the 517-page report and its companion 2,334-page systematic literature review (SLR) on colorectal cancer shows that the SLR's conclusions do not support the warnings issued in the summary report or the press release.

According to Klurfeld, the SLR of colorectal cancer said, "Overall, mechanisms explaining the data linking meat (processed and red) intake and colorectal cancer are far from plausible biological mechanisms." But in stark contrast, the final summary report declared "There is strong evidence for plausible mechanisms operating in humans. Processed meat is a convincing cause of colorectal cancer." The criteria for "convincing" established by the expert panel states that there must be plausible biological mechanisms, but apparently the panel chose to ignore the findings of the research team it had hired to conduct the SLR.

"While few people likely will tackle the 2,334-page literature review after reading a 500-page summary of findings, those who do will find some critical information that was disregarded and contradicted in the report's summary," Klurfeld said. He expressed frustration that the group's press release reflected so poorly what was actually in the report and SLR.

Cancer Research: Approaches, Strengths and Weaknesses

Assessing whether a factor is a "cause" of disease involves a multi-disciplinary approach that involves epidemi-
ological studies, toxicological assays, animal studies, double-blind human trials, meta-analyses, case reports and opinions. Within the field of epidemiology, a variety of approaches can be used, including:

- **Case-control studies.** In this type of study design, retrospective exposure factors are compared between persons with the disease of interest (cases) and persons without the disease of interest (controls). A variety of factors, including environmental exposure, tobacco use, nutrition and exercise level, are analyzed to determine the potential effect on disease development. Isolating one factor’s impact from another can be extremely difficult, especially when it comes to diet, since foods are eaten in combination. A major limitation of this study design is that participants are required to recall their prior history of exposure.

- **Cohort studies.** Cohort studies can be prospective, retrospective or ambispective. Most cohort studies of diet and cancer are prospective in design. In these studies, a very large group of participants with and without the exposure of interest (e.g., high vs. low consumers of processed meat) are followed forward in time, and the rate of disease development is compared between groups of people with and without the exposure(s) of interest. This type of study design theoretically overcomes many of the limitations of a case-control design.

- **Meta-analysis.** A meta-analysis is a statistical technique that combines published results data across studies to produce an overall, or weighted, summary of relative risk. This type of analysis may provide a more accurate reflection of the association across the available literature with enhanced statistical power. The results of a meta-analysis, however, are only as valid as the individual studies included in the assessment. Thus, the “garbage in, garbage out” principle.

- **Pooled meta-analysis.** A pooled analysis is similar to a meta-analysis except that in a pooled analysis, individual or primary source data are combined across studies to produce a de novo estimate of relative risk. A pooled assessment may allow for the standardization of exposure categories and analytical proce-

**Epidemiological Findings are Just a Piece of the Puzzle**

Findings from these types of studies must be combined with experimental evidence from animal bioassays and human trials and must fit together like an interlocking puzzle to feel confident in declaring cancer causation.

With respect to the conclusions on meat consumption, WCRF/AICR relied heavily on selected epidemiological studies. Just as in a courtroom, all the evidence must be assessed and persuasive evidence must be presented beyond a reasonable doubt.
Standards of evidence for disease causation are not new. Sir Austin Bradford Hill, a distinguished British biostatistician and epidemiologist, published in 1965 his nine criteria required to establish causation, including:

- Consistency – findings must be observed multiple times with different study participants under different circumstances and with different measurement instruments.
- Biological plausibility – for example, the biological theory of smoking causing tissue damage, which over time results in cancer in the cells, was highly plausible.
- Dose-response – as the dose of a suspected substance increases, the disease risk should increase as well. Unfortunately, many studies with roller-coaster like dose-response curves are often reported as if they clearly show cause and effect.
- Strength of association – for example, a variety of studies show that the lung cancer rate for smokers is about 10–30 times higher than for non-smokers. The strength, or magnitude, of an association is commonly referred to as a point estimate, which usually represents the rate of disease among persons with the exposure of interest compared with the rate of disease among persons without the exposure of interest. This is labeled the rate ratio or relative risk (RR) of disease. A study with an RR of 1 indicates that the outcome was neutral, or null—a factor neither increased nor decreased risk. An RR of 1.2, for example, indicates there is a 20% increase in risk. Generally speaking, associations less than 1.5 may be viewed as weak, while associations between 1.5 and 2.0 may be considered moderate and those above 2.0 are commonly referred to as strong in magnitude. And it is widely accepted that results from a single study are never enough to be considered causal, no matter how large the RR.

While serving as editor of the *New England Journal of Medicine*, Marcia Angell, M.D., told science writer Gary Taubes, “As a general rule of thumb, we are looking for a relative risk of 3.0 or more before accepting a paper for publication, particularly if it is biologically implausible or if it’s a brand-new finding.” Weak and modest associations may contribute to the total picture, but often these associations can be explained by a number of confounders or by issues like inaccurate recall of consumption or behavior (called “recall bias”) and should be evaluated critically.

Cancer epidemiology papers with very small relative risks (well below 2) often are the cause of many of the most frightening health headlines. In the case of the WCRF/AICR report, of the five studies cited as showing a relationship between processed meat and colon cancer, only two were statistically significant. The highest RR was only 1.69 and the summary estimate of relative risk was a mere 1.21.

Klurfeld pointed out that the companion colorectal cancer SLR includes a chart that shows a statistically significant, 26% protective effect against rectal cancer for the highest meat consumption. This, however, was not mentioned in the summary report or in the press release, and it is unclear why that did not deserve to be highlighted in the summary report.

Unfortunately, relative risk and absolute risk are often confused. According to Dr. Klurfeld, WCRF/AICR’s dire warnings about meat failed to put the absolute risk of colorectal cancer in perspective. For instance, a person’s absolute risk of developing colorectal cancer during their lifetime is 5.3%, according to the National Cancer Institute. So, even if you were to accept the WCRF estimate of relative risk of 21% and applied that factor, your lifetime risk of developing colorectal cancer increases by a mere 1.1% from 5.3% percent to 6.4%—a negligible increase.

### Null Findings and Publication Bias

Unfortunately, all too often, “null findings” (those not showing an increased or decreased risk) go either unpublished or publicized. A recent article in the *Journal of the National Cancer Institute* affirmed the importance of publishing null findings: “Caution should be applied in the communication of results to the media and the general public, because ‘positive’ findings tend to attract the media and public attention, whereas findings that do not confirm a previously reported association or do not indicate a new association receive no attention.”

The authors concluded that epidemiology is particularly prone to generating false-positive results and noted that epidemiology has been increasingly criticized for producing findings that are often sensationalized in the media and fail to be upheld in subsequent studies. They urged their epidemiology colleagues to have increased humility regarding their findings, concluding this “…would go a long way to diminishing the detrimental effects of false-positive results on the allocation of limited research resources, on the advancement of knowledge of the causes and prevention of cancer, and on the scientific reputation of epidemiology and would help to prevent oversimplified interpretations of results by the media and the public.”

### The Media Factor

Today, embargoed press releases from journals announcing “landmark” findings are provided in advance to news media. Because these stories are often written during an embargo, they rely heavily—and sometimes exclusively—on press releases and comments from the researchers themselves. Certainly, both scientists and journals benefit from publicity, especially if findings are cast as dramatic or landmark.

Even Walter Willett, M.D. of Harvard’s School of Public Health, who has
long been an advocate of reducing red meat consumption, acknowledges the issue. "Part of the problem is that the public is interested in nutrition... Very often science is presented to the public in a way that is conclusive when in fact the science behind it is often very preliminary, very inconclusive," Willett told PBS’ "Frontline."

But just as the public is bombarded with this news, researchers are not immune either and their attitudes and opinions can be impacted by the media “buzz” — and sometimes steeled against new findings that are so important to consider.

So What Does All the Evidence Show?

Were a panel to analyze all the research—epidemiological and experimental—and consider the number of studies that have shown that red meat’s nutrition benefits, the conclusions surely would be far different compared with those of WCRF/AICR.

As Klurfeld points out, “The trouble is, we don’t eat nutrients, we eat foods, and we don’t eat them in isolation, we eat them as a dietary pattern.”

Recent studies published in the *Journal of the American Medical Association* and the *New England Journal of Medicine* that have looked at dietary patterns both found that low-carbohydrate and Mediterranean diets caused more weight loss than low-fat diets. It has been documented that meat can contribute to a sense of satiation that can control hunger. Emerging research on the role of protein and satiety is promising and positive. Therefore, meat protein in the diet may play an important role in weight management.

The fact that the National Cancer Institute has estimated that 25 to 30% of seven major cancers are linked to obesity would suggest that meat can be a very important part of a weight reduction program and potentially reduce cancer risk.

Sodium Nitrite and Cured Meats: The Facts

Similarly, evidence of sodium nitrite’s safety and benefits also is emerging in a way that is turning scientific heads—and evoking skepticism from some corners.

When WCRF/AIRC declared in 2007 that there was no safe level of processed meat consumption—a statement that defies logic given that there are safe levels of everything—especially nutritious foods—they cited sodium nitrite in cured, processed meats as a potential reason to support their hypothesis.

In the same 2008 IAFP symposium where Klurfeld challenged WCRF, Nathan Bryan, Ph.D., of the Institute of Molecular Medicine at the University of Texas Health Science Center at Houston said many people have outdated notions about sodium nitrite’s safety.

“The public perception is that nitrite and nitrate are carcinogens but they are not,” Bryan said. “If nitrite and nitrate were harmful to us, then we would not be advised to
eat green leafy vegetables or swallow our own saliva, which is enriched in nitrate and nitrite.” According to Bryan, fruits and vegetables contribute far more nitrite and nitrate to human daily intake than cured meats. For example, a person would derive 100 times as much nitrite from the modern elixir pomegranate juice than from a hot dog.

While much attention is focused on epidemiological studies, critical findings from the U.S. National Toxicology Program (NTP) seem forgotten just eight years after they were published. An NTP review panel found that sodium nitrite, even when fed to rats and mice at levels well beyond that used in cured meats, is not a carcinogen. Interestingly, a careful analysis of NTP’s data also showed that nitrite protected against some of the very cancers that epidemiologists had earlier suggested it caused, like brain cancer and leukemia.

NTP’s findings don’t surprise Bryan. His studies have uncovered nitrite’s cardiovascular and other health benefits. According to Bryan, nitrite can prevent injury from a heart attack and can also act as an active source of nitric oxide within the body. Bryan said that preliminary research at his university is showing that when nitrite has been applied directly to tumor cell lines, it does not promote tumor growth. And when ascorbate (vitamin C) is added along with the nitrite, cell growth is inhibited (ascorbate is routinely added along with nitrite in cured meats).

Bryan’s encouraging research mirrors findings at the National Institutes of Health where Dr. Mark Gladwin has also published studies about nitrite’s value as a medical treatment. “The idea it’s bad for you has not played out,” Gladwin told USA Today.

As nitrite’s human health benefits are uncovered, Bryan and others say it’s critical to remember why nitrite is added to cured meats in the first place: food safety. Nitrite prevents the growth of Clostridium botulinum and its subsequent toxin formation, which can cause the deadly foodborne disease botulism. Nitrite also inhibits the growth of Listeria monocytogenes if it is present in ready-to-eat meats.

**PAHs and HCAs**

Polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) are chemicals that can be formed in meat when proteins are heated to high temperatures. Certain HCAs and PAHs have been shown to be carcinogenic in lab animals. However, the outstanding issue is the following: how much exposure do meats cooked to high temperatures provide to the average consumer? And, how much exposure is needed to cause an increase in risk to humans?

During an IAFP presentation in August 2008, Arthur Miller, Ph.D., senior managing scientist of the food and chemicals practices at Exponent, a nutrition consulting and research firm, said “Information to date indicates that HCAs/PAHs are found in parts per billion levels in some cooked muscle foods, but present a very low cancer risk for U.S. consumers.” He cautioned that any risk cannot be viewed in isolation: proper cooking is vital to food safety and the acute risk posed by potential bacterial pathogens in food.

Miller also noted that in August 2008, the European Food Safety Agency (EFSA) found after extensive review that there is a low risk to consumers from PAHs in foods based on average dietary exposure. The EFSA report also highlights a long list of commonly consumed food that contain significant levels of PAHs, including cereals, vegetable oils, coffee and certain seafood and smoked or cooked meat products.

**So What is the Best Advice?**

In the face of the diet and cancer debate, it’s instructive to refer to the U.S. Dietary Guidelines for Americans that recommend, “Consume a variety of nutrient-dense foods and beverages within and among the basic food groups while choosing foods that limit the intake of saturated and trans fats, cholesterol, added sugars, salt and alcohol. Meet recommended intakes within energy needs by adopting a balanced eating pattern.” The Guidelines also stress the importance of physical activity.

Just last year, the American Dietetic Association echoed this message in a statement about fat weight loss diets. “Countless reputable studies over many years have shown balance and variety are needed for good health. Any diet that requires you to give up whole categories of foods...is by definition, unbalanced.”

When it comes to cancer, there clearly is no clear and singular cause and, tragically, there is no easy prevention or treatment. These basic facts understandably drive us to seek a factor to blame and meat has become a target for many. This singular focus on limited studies showing theoretical risk may ultimately lead to public policies and practices that shun a food that clearly has much to offer in terms of valuable nutrition, satiety and weight control, delivering important nutrients including vitamin B12, iron, zinc and vitamin D and, in the case of one of our common ingredients—sodium nitrite—even promoting wellness.

It’s time to confront the facts fearlessly lest we run fearfully, and dangerously, in the wrong direction.

**Randall D. Huffman, Ph.D.,** joined the American Meat Institute (AMI) Foundation in January 2000 as Vice President of Scientific Affairs and was promoted to President of the AMI Foundation in April of 2008. Prior to joining AMI, Huffman was director of technical services at Koch Industries, Inc. Huffman received a B.Sc. in animal science from Auburn University; an M.S. and Ph.D. in animal sciences, with specialization in meat science from the University of Florida.