Letters

Safety of Bovine Growth Hormone

As a scientist who has expressed concerns about public health hazards of recombinant bovine growth hormone (rbGH) (*1*), I commend the Center for Veterinary Medicine of the Food and Drug Administration (FDA) for its responsible defense of its 1985 decision about the human safety of rbGH-milk (Judith C. Juskevich and C. Greg Guyer, Articles, 24 Aug., p. 875). Given the polarization in the field of rbGH, this demonstration of the regulatory agency's poise and objectivity is most reassuring. The FDA deftly answers two pressing questions, one concerning insulin-like growth factor–1 (IGF-1) in the young, the other about physiologic actions of rbGH in humans. One hopes that equally sound answers can be provided for four other serious concerns.

1) *IGF-1 action on the gut wall of mature or older persons*. The FDA marshals the evidence for IGF-1 acting locally rather than systemically and then presents new data about the lack of systemic effects of oral IGF-1 in young rats. Presumably the high IGF-1 concentrations in cow's milk during the first 2 weeks of lactation and in human milk for a longer period reflect a useful local function in the gut walls of the young. The presumption of usefulness for IGF-1–laden milk in the young need not be extended beyond breast-feeding age. If IGF-1–laden milk helps maturation in the young, will it hasten senescence later?

2) *Immunogenic and allergenic effects of rbGHs*. The FDA marshals the evidence against biologic actions of rbGHs in humans. However, they neglect the possibility of immunogenic and allergenic effects. Such effects served to discriminate between human drugs, Met-rhGH and natural sequence rhGH, when the FDA awarded orphan drug status to the latter in 1987 [despite having awarded orphan drug status to the former in 1985 (*2*)]. In contrast, the FDA has assumed that bacteria-made analogs such as Met-rbGH (Monsanto Agricultural Company), Met-Asp-Gln-rbGH (American Cyanamid), and Met-Phe-Pro-Leu-Asp-Asp-Asp-Asp-Lys-rbGH (Eli Lilly and Company) are identical biologically (if not chemically) with the four natural sequence bGHs. This inconsistency warrants an explanation.

The rbGHs deviate from hGH by 66 or more amino acids. Thus human immune systems might recognize the bovine proteins as foreign. By analogy with the human counterparts (*2*), the rbGHs that retain bacterial links [that is, the Monsanto, American Cyanamid, and Lilly analogs] deserve extra attention and, in my view, should be measured specifically and separately in milk.

The FDA points out that immune responses need to be studied in the species of interest, in this case humans. Some of these responses might occur in the gut walls, that is, they might not require absorption of intact rbGHs.

3) *Nitrogen-retaining action of rbGHs*. The FDA cites studies of pituitary bGH injected into human dwarfs, who were observed for growth, nitrogen retention, and sexual maturation. These clinical studies in the 1950s preceded knowledge of (i) the Laron-type dwarfs, who lack GH receptors; (ii) the importance of androgenic or anabolic steroids for responsiveness to exogenous GHs; and (iii) facilitation by dietary carbohydrate. The most sensitive human subjects for testing the nitrogen-retaining (muscle-building) action of rbGHs arguably would be young athletes taking steroids and carbohydrate loading (*3*). Controlled clinical trials of rbGHs with these subjects would be morally reprehensible, but extra-label abuse of rbGHs by entrepreneurial athletes may be encouraged by the current abuse of rhGHs (*3*) and may not be deterred by fatal responses to another recombinant hormone-drug, erythropoieten (*4*).

4) *Secondary drugs in rbGH-milk*. In the first nine long-term trials of rbGHs, signs of mastitis or infertility were observed in six (*5*). Since then, most if not all trials of rbGHs have been conducted in herds with superior management, including drug-intensive management of mastitis and infertility. A 1987 Monsanto report that was disclosed in a dairy magazine (*6*) listed nine drugs administered to cows given Met-rbGH that are not listed as approved for use in lactating cows. Without prescribed withdrawal times, these drugs could be present in milk used for human food. Thus adverse effects of rbGHs on the cow's health and fertility could indirectly affect human health through secondary drugs entering milk.

The FDA's decision in 1985 to blend rbGH-milk into the public's supply without a withdrawal period was sound scientifically, especially because of massive dilution of rbGH in bulk milk processing. Whether it was wise is a question that turns on public confidence in milk purity and biotechnology.

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Response: Kronfeld raises four considerations regarding the human food safety of recombinant bovine growth hormone (rbGH) use in lactating dairy cattle that we would like to address.

The studies conducted with IGF-1 in rats were done with oral administration because this is the route by which consumers would be exposed to any increased residues of IGF-1 in milk or meat from rbGH-treated animals. Therefore, it is the most appropriate model to use. We believe the presence of IGF-1 in human milk does not necessarily imply that this source of IGF-1 plays a significant physiological role in newborns and young infants. In the oral feeding studies conducted with IGF-1, histopathological examination of different areas of the gastrointestinal tract from treated rats showed no treatment-related effects on the gastrointestinal mucosa. Therefore, we do not believe that IGF-1 in milk will hasten senescence in mature or older persons.

In the initial evaluation of rbGH for use in dairy cattle, the potential for allergenic and immunogenic effects in humans was examined and determined to be insignificant. When this drug's potential for an increased incidence of allergenicity is evaluated, it is important to remember that the consumer is exposed to a wide variety of foreign proteins every time any meat, milk, fish, egg, or plant product is ingested. Specifically, there is no reason to suspect that bGH is more allergenic than other milk proteins and thereby provides a case for a specific allergic reaction to bGH. Bovine GH is an extremely minor component of milk protein [less than 5 nanograms per milliliter or 5×10^{-6} milligrams per milliliter (mg/ml)], whereas the concentration of major milk proteins is 25 to 28 mg/ml for caseins, 3.5 to 6.5 mg/ml for whey proteins, and 0.5 to 1 mg/ml for immunoglobulins. On the basis of the amino acid sequence of rbGH compared with that of bGH and the route of exposure of humans to these proteins, we believe the potential for an increased incidence of allergenicity resulting from rbGH over what may naturally exist from bGH is insignificant. With regard to Kronfeld's point concerning a perceived inconsistency between how recombinant human growth hormone (rhGH) and rbGH are being regulated, one does not exist. Both

pharmaceutical companies developing rhGH products, Met-rhGH and natural sequence rhGH, were required to conduct the same studies independently before these products received approval. Although the rbGH products may be biologically indistinguishable from each other, they are being evaluated as separate products.

It is generally accepted that bGH is biologically inactive in humans when administered parenterally, and the lack of effects has been documented. We share Kronfeld's concern regarding the extra-label abuse of any animal drug by young athletes. With regard to this potential for abuse, if rbGH is approved, the label will contain information stating that the product is for use in animals only. Although there is no warning label for any over-the-counter veterinary drug that can ensure that human use will not occur, the warning label serves as a deterrent for such illegal use. We believe that the extra-label abuse of rbGH is unlikely because of its lack of activity in humans.

The extensive review of the multilactational target animal safety studies has not been completed by the FDA, so we cannot comment on whether or not an increase in mastitis or infertility will occur. These conditions are being monitored in all animal safety and effectiveness studies and will influence the agency's final decision concerning rbGH. Moreover, the use of antibiotics in lactating dairy cattle is regulated by having specific milk discard periods follow the use of approved antibiotics. State and federal regulatory systems monitor milk for drug residues and remove adulterated sources from commercial sale. As with all unapproved animal drugs, the use of unapproved antibiotics in lactating dairy cattle is illegal unless the drug is given under strict supervision by a veterinarian or authorization has been provided for such use under an investigational new animal drug or new animal drug application by the FDA. This authorization includes an appropriate milk discard period to ensure that the use of such products will not present an increased risk to consumers of milk products from treated dairy cattle.

We appreciate comments from the scientific community concerning our review of the human food safety of rbGH. We have always believed that all products regulated by the FDA should be evaluated strictly on the basis of their scientific merit and that FDA scientists should maintain a high level of objectivity in reviewing studies submitted by pharmaceutical companies.

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Interpreting Cancer Tests

Jean Marx's 9 November News & Comment article (p. 743) about the controversy engendered by Bruce Ames' criticism of the maximum tolerated dose (MTD) bioassay points out the broad range of agreement that now exists concerning testing for carcinogenicity and how the results of these tests should be interpreted. Ames criticizes an obsolete status quo, and his critics defend an abandoned practice. Thus they obscure the significant changes that have occurred in the science of carcinogenicity and the lessons learned from those 1000-plus bioassays.

As Samuel Cohen observes, the practices under attack were based on a previous generation's theories of carcinogenesis. Those led to two precepts now found wanting: (i) exposure to any "animal carcinogen" in any amount will increase cancer risk in humans; and (ii) the dose-response curve for carcinogens is best represented by a straight line from the highest response to zero. From these came, in the 1970s, the regulatory procedures Ames criticizes, procedures now beginning to change in the wake of scientific advances. Several examples of compounds are now recognized where a "threshold" dose response appears to exist (all of these either mimic or alter the physiology of endogenous hormones). Morever, there are now several well-studied examples where an animal cancer model is considered not to predict human response: Marx's article refers to two of these, D-limonene and saccharin. As William Farland observed during the recent National Academy of Sciences workshop on "two-stage models," substances can be "situational carcinogens," causing cancer under some circumstances of exposure but not under others. Science is outstripping the legal framework in which it is applied: neither the Environmental Protection Agency's (EPA's) Guidelines for Carcinogen Risk Assessment nor the Food and Drug Administration's (FDA's) basic law (the Delaney clause of the Food, Drug and Cosmetic Act) recognize this reality. The dissonance between these laws and scientific reality causes much distress to scientists in these two agencies; they appear to be doing their best to circumvent the most absurd consequences.

Also obscured by the controversy is the change that has occurred in the strategies for testing chemicals. Our understanding of the impact of mitotic rate on cancer risk (most prominently evident from the work of Cohen and Leon Ellwein) implies that chronic toxicity testing needs to include tests that gather information about this response to exposure. Identification of instances where critical metabolic pathways differ strongly among species implies inclusion of metabo-