

**UNLABELED MILK FROM COWS TREATED  
WITH BIOSYNTHETIC GROWTH HORMONES:  
A CASE OF REGULATORY ABDICATION**

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Levels of insulin-like growth factor-1 (IGF-1) are substantially elevated and more bioactive in the milk of cows hyperstimulated with the biosynthetic bovine growth hormones rBGH, and are further increased by pasteurization. IGF-1 is absorbed from the gastrointestinal tract, as evidenced by marked growth-promoting effects even in short-term tests in mature rats, and absorption is likely to be still higher in infants. Converging lines of evidence incriminate IGF-1 in rBGH milk as a potential risk factor for both breast and gastrointestinal cancers.

In 1985, the Food and Drug Administration (FDA) approved the commercial sale of unlabeled milk and meat from large-scale veterinary trials on cows treated with the synthetic bovine growth hormones (rBGH); these hormones are manufactured using recombinant DNA biotechnology by Monsanto, American Cyanamid, Dow Chemical, Upjohn, and Eli Lilly companies. FDA and industry claimed that rBGH had no adverse veterinary effects and that rBGH milk was indistinguishable from natural milk and safe for human consumption.

By 1990, evidence from published and unpublished industry sources had raised a wide range of concerns about the safety of rBGH milk (1-3). These included: contamination of rBGH milk with pus from mastitis and with antibiotics used in its treatment; contamination of milk with rBGH that FDA admitted differed significantly in its molecular structure from the natural growth hormone; and contamination of milk with excess levels of insulin-like growth factor 1 (IGF-1). In spite of these unresolved veterinary and public health concerns, in November 1993 FDA approved large-scale commercial use and sale of rBGH milk, and shortly after issued regulatory guidelines effectively banning the labeling of such milk (4, 5). This article presents an analysis of available information on potential risks of breast and gastrointestinal cancers from IGF-1 in rBGH milk.

Insulin-like growth factor 1 is a potent low molecular weight polypeptide growth factor that mediates the action of the pituitary growth hormone on somatic growth. IGF-1 induces profound metabolic effects through endocrine, paracrine, or autocrine mechanisms (6-10), including regulation of transport processes, macromolecular synthesis, cell growth, replication and differentiation, and milk production. Although the gene encoding IGF-1 is expressed in many tissues, most circulating IGF-1 is produced by liver cells where transcription is regulated by a complex hypothalamic-pituitary-hepatic axis (6, 7). IGF-1 is also synthesized at the local level by both normal and malignant cells (7, 8). It should be further noted that the amino acid sequences of human and bovine IGF-1 are identical (9, 10).

#### ELEVATED IGF-1 LEVELS IN rBGH MILK

In an early report relating IGF-1 milk levels to natural BGH isolated from bovine pituitaries, administration of the hormone increased IGF-1 levels in goat's milk from a mean pretreatment level of 16 ng/ml to 25 ng/ml within four days (11). Normal cow's milk collected just after parturition contained high IGF-1 levels, about 150 ng/ml, which rapidly fell to about 25 ng/ml within one week and then declined to only 1 to 5 ng/ml by 200 days, when levels of IGF-1 induced by rBGH ranged from 6 to 20 ng/ml, up to a 20-fold increase (12). In a subsequent short-term study on 35-47 weeks post-partum cows, a sixfold increase in IGF-1 milk levels was reported as early as 7 days following rBGH treatment (13). Of particular interest was the finding that "a significant proportion [19 percent] of the total IGF-1 was present in the [protein] free unbound form" (13), and was thus probably more bioactive or potent than the protein-bound form (14). Furthermore, pasteurization increases milk IGF-1 levels by some 70 percent, presumably by disrupting protein binding (15). The significance of these findings is emphasized by recent evidence that free IGF-1 levels in human serum are as low as 0.38 percent (16). No data are available, however, on the ratios of free to unbound IGF-1 in the sera and milk of cows treated or untreated with rBGH, and in the sera of humans drinking milk from cows treated or untreated with rBGH.

In some six unpublished, confidential industry studies, disclosed by FDA in a highly abbreviated summary form, IGF-1 levels in rBGH milk were consistently increased (15); these increases were statistically significant, ranging from 25 to 70 percent (17). Illustratively, in a 1989 Monsanto trial, milk IGF-1 levels in cows increased from control levels of 3.5 ng/ml to 5.9 ng/ml and 6.1 ng/ml following intramuscular or subcutaneous rBGH injections, respectively; higher levels still, up to 25 ng/ml, were subsequently reported by Monsanto (18). More recently, Lilly Industries, in its application for marketing authorization to the European Community Committee for Veterinary Medicinal Products, has admitted that rBGH milk may contain more than a 10-fold increase in IGF-1 concentrations (19).

A summary report of the 1990 National Institutes of Health Technology Conference noted that IGF-1 levels in unspecified samples of rBGH milk were 3.5 to 13 ng/ml, approximately three to four times the levels in human milk, in contrast to 1.5 to 8 ng/ml in untreated cows (20). This report also noted that IGF-1 levels in meat of rBGH animals were approximately twice as high as in untreated controls.

The results of virtually all these studies are, however, based on flawed analytic techniques that underestimated IGF-1 levels, as recognized by the technique developers and others (17, 21, 22). Problems with these techniques included their inability to separate the IGF-1 molecule from a complex of associated large carrier proteins to which IGF-1 is usually bound. These problems were further extended by the finding that standard IGF-1 analytic techniques underestimate, by a factor of four, levels of a truncated form of IGF-1 (-3N:IGF-1) which is approximately 10 times more potent in stimulating protein and DNA synthesis than normal IGF-1, resulting in a potential 40-fold underestimate of levels in rBGH milk (14, 23). The significance of these considerations was further emphasized: "The presence in colostrum of -3N:IGF-1 and of large amounts of free IGF-1 may be pointers to likely changes occurring in milk in response to bST [rBGH] treatment, since a strong parallel has been suggested between the increased milk secretion which occurs post partum and that following bST treatment" (14).

#### ABSORPTION OF IGF-1 FROM THE GASTROINTESTINAL TRACT

There is unequivocal evidence that a wide range of intact proteins are absorbed across the gut wall in a wide range of species including humans (15, 24). In humans, this evidence is largely based on the detection of serum antibodies to food proteins (25). The infant gut is more permeable to protein than the adult gut, particularly pre-term and prior to "closure" at about 3 months of age (26-28). Infants and young children have higher serum levels of cow's milk protein antibodies than adults (24, 29). These varying lines of evidence on absorption of intact proteins further confirm that smaller molecular weight polypeptides, such as IGF-1, can also be absorbed from the gut. Even more compelling is evidence of marked systemic effects following short-term IGF-1 feeding tests in rats (15).

FDA recently responded to this evidence with a wide range of tenuous and inconsistent claims (30). These include: "There is no evidence that IGF-1 survives digestion in humans," in contrast to FDA's prior publication of Monsanto/Hazleton data on systemic effects of IGF-1 following short-term oral administration (15). And "the IGF-1 content of milk is not altered by BST supplementation" on the basis of "more comprehensive [industry] studies" (31), although these studies in fact conclude that "mean IGF-1 levels in the [rBGH] treated animals are always higher than those found in the controls." Excess IGF-1 milk levels were

trivialized in comparison with endogenous levels in human saliva and blood by FDA's use of highly speculative and misleading calculations (30).

More appropriate calculations should be based on the following considerations and data. Adult humans produce daily about 1.2 liters of saliva containing an IGF-1 level of about 3 ng/ml, equivalent to a daily recycling of some 3 µg of IGF-1 (32); corresponding intake levels in infants are substantially lower. This should be contrasted with an infant's daily consumption of 1 liter of rBGH cow's milk containing the maximum 25 µg level of IGF-1 admitted by Monsanto (18), well over an order of magnitude excess exogenous exposure. While exaggerating endogenous in relation to exogenous exposures from rBGH milk in infants, neither FDA nor industry has presented any data on salivary and blood levels of IGF-1 in infants. A 1990 letter from Monsanto to NIH claimed that plans to obtain the salivary data "will be forthcoming" (33); however, no such data are yet available. FDA's quantitative comparison between IGF-1 levels in bovine milk and human blood is equally misleading (30). Assuming an adult blood volume of 3.5 liters and adult IGF-1 levels of 100 ng/ml, adults have a total circulatory level of 350 µg of IGF-1, rather than the 600 µg calculated by FDA (30). Thus, assuming a neonate blood volume of 0.25 liters, based on a body weight of 3 kg and a volume of 80 ml/kg, this would correspond to a circulatory level of about 25 µg. This should be contrasted with a daily intake of up to 25 µg/l of IGF-1 in rBGH milk, which may be up to 40 times more potent or bioactive than blood IGF-1 (14), constituting a daily intake of 1000 µg blood equivalents.

Such calculations not only are based on a wide range of assumptions, but also reflect very substantial data gaps despite over a decade of industry experience with rBGH. What is clear, however, is that simplistic quantitative comparisons by FDA and industry that trivialize milk versus endogenous IGF-1 levels are not meaningful. Alternative calculations raise serious concerns on the potential hazards, particularly to infants, of excess IGF-1 levels in rBGH milk.

#### ORAL ACTIVITY OF IGF-1

There are no published studies, in the scientific literature or in FDA or industry reports, on the oral activity of IGF-1. FDA, however, in 1990 released a highly condensed summary of 1989 toxicity tests by the two major rBGH industries, Eli Lilly & Co. (Elanco) and Monsanto Agricultural Co. (15). The Elanco test was conducted at the company. The Monsanto test was contracted out to Hazleton Laboratories. Apart from a wide range of other flaws, the relevance of both these studies is questionable as they were short rather than long term, were conducted on adult rather than infant rats, and were conducted on rIGF-1 rather than on IGF-1—containing rBGH milk or IGF-1 isolated from rBGH milk.

The FDA report on the Elanco oral toxicity test was cryptic, even more so than that on the Monsanto/Hazleton study (15). The Elanco test used groups of 10 male and female hypophysectomized adult rats, given oral doses of rIGF-1 for two

weeks at 0.01, 0.1, or 1.0 mg/kg/day, with a subcutaneous infusion positive control at 1.0 mg/kg. Gross organ weights were increased in positive control rats but not test rats. No data were presented on epiphyseal width and tibia length. On the basis of these minimal parameters, rIGF-1 was alleged to be devoid of oral toxicity.

In the Monsanto/Hazleton test, groups of 20 male and female 36-day-old rats were dosed orally for two weeks with rIGF-1 at concentrations of 0.02, 0.2, or 2.0 mg/kg/day (15). Two groups of rats served as positive controls. The first was infused subcutaneously with rIGF-1 doses of 0.05 or 0.2 mg/rat/day corresponding to about 1 to 4 mg/kg/day, and the second with porcine growth hormone (pGH) at doses of 4.0 mg/rat/day corresponding to about 80 mg/kg/day, assuming a 36-day-old rat weighs approximately 50 g. Statistically significant increases in body weight were seen with male test rats at 2.0 mg/kg, with a positive linear trend at all dose levels in test females. In addition, statistically significant increases in liver weight and tibia length and decreases in epiphyseal width were seen in test males at doses of 2.0 mg/kg, significant increases in tibia length of test males at 0.02 mg/kg, and significant decreases in epiphyseal width of test females at 2.0 mg/kg. The statistically significant lowest observed effect level (LOEL) of 0.02 mg/kg/day is thus approximately 1/4000 of the positive infusion control pGH dose and approximately 1/50 of the positive infusion control rIGF-1 LOEL.

In spite of the tabulated Monsanto data on the statistically significant sensitivity of rats to oral administration of rIGF-1, FDA asserted "that rIGF-1 is orally inactive at doses up to 2 mg/kg per day" (15). This conclusion conflicts with the cited data and was based on a series of tenuous claims that have been subject to detailed criticism (14, 34). FDA claimed that there were no significant increases in body weight of orally dosed females in contrast to males, even though a similar difference in sensitivity was noted in female rIGF-1 controls injected at 0.05 mg/rat/day. FDA also claimed (a) that the increase in body weight of test males should be discounted as it only occurred in one "block" of half the control rIGF-1 rats, raising questions about the validity of the experimental design of the test on which FDA based its conclusion; (b) that there were no increases in serum IGF-1 of test rats, although no supportive data were cited; and (c) that decreases in epiphyseal width and increases in tibia lengths in test animals should be disregarded as "contradictory [and] sporadic," even though such effects in rIGF-1 control groups were also inconsistent and not even cited at the 0.05 mg/rat dose.

FDA's flawed analysis of their cited test data is compounded by a misleading presentation of the data. Notably, in Tables 4 and 5 of the Monsanto/Hazleton report, the dosages of test rats are presented in mg/kg, while those for the positive infused controls are presented in mg/rat, thus using incomparable dose units for test and control animals (15). This resulted in a misleading reduction of oral dose levels in test rats compared with control rats by a factor of some 20, thus substantially underestimating their sensitivity to oral IGF-1 (34). Such data

manipulation is consistent with the documented track record of Hazleton Laboratories (35). Under the circumstances, it is not surprising that FDA and Monsanto refused to comply with a May 1994 Congressional request for an unabridged copy of the 1988 Hazleton report on which FDA bases its near exclusive reliance for the alleged nontoxicity of IGF-1 in rBGH milk (36).

The unpublished Monsanto/Hazleton oral toxicity test was conducted on rIGF-1, rather than more relevantly on IGF-1 in rBGH milk, which may differ from rIGF-1 (14). This study is also seriously flawed as it violated standard protocols on routine lifetime chronic toxicity and carcinogenicity tests based on two species. This study was only two weeks long and included groups of only 20 male and female adult rats. Maximally tolerated doses (MTD) were not determined and test doses were not extended up to this range, nor was testing extended below 0.02 mg/kg in order to determine the no observable effect level (NOEL). No autopsy data were provided, except body and organ weight and epiphyseal width; and no histological data were reported. Moreover, no three-generation and transplacental tests were conducted, nor any tests involving neonatal rodents or neonatal and adult subhuman primates. Finally, no investigations were undertaken on sensitive subcellular effects, including IGF-1 binding and receptor levels in tests and controls.

Of further interest, a recent industry report noted a statistically significant increase in the body weight at weaning of calves from rBGH-treated cows compared with calves from untreated cows (37). While this result suggests that increased IGF-1 milk levels induce growth factor effects, in the absence of paired feeding data it is not possible to exclude the effect of increased availability of milk.

#### ABSENCE OF SAFETY MARGINS FOR IGF-1 FOLLOWING CONSUMPTION OF rBGH MILK

As recently emphasized (14), consumption of rBGH milk would expose infants and young children to IGF-1 levels substantially in excess of the safety margin based on the 0.02 mg/kg (20 µg/kg) LOEL identified in the Monsanto/Hazleton oral toxicity test (15). Assuming a 10 kg child consumes 1 liter daily of rBGH milk with an IGF-1 concentration of 25 ng/ml (25 µg/l), this would then result in an intake of 2.5 µg/kg, one-eighth of the 20 µg/kg LOEL (14). Safety margins for noncarcinogenic toxic effects are conventionally set on the basis of 1/100 of NOELs and 1/1000 of LOELs, which for IGF-1 would thus be 0.02 µg/kg. Thus, an intake of 2.5 µg/kg would actually be 125-fold in excess of the standard safety margin.

Such estimates are conservative for a range of reasons discussed above: pasteurization of rBGH milk increases IGF-1 levels by approximately 70 percent (15); IGF-1 in rBGH milk is more bioactive than IGF-1 in untreated milk; standard analytic techniques underestimate IGF-1 levels by a factor of 4; and

IGF-1 in rBGH milk may well be present, at least in part, in a truncated form that is some 10 times more potent than IGF-1 in untreated milk (14).

#### IGF-1 IN rBGH MILK AS A POTENTIAL RISK FACTOR FOR BREAST CANCER

FDA made its decision on the safety of rBGH milk in 1985 in the absence of data on a wide range of public health concerns, including information about excess IGF-1 levels in rBGH milk, and without consideration of the cellular proliferative effect of IGF-1. Over recent years, several converging lines of evidence have implicated IGF-1 in the initiation or promotion of breast cancer. This evidence raises serious concerns about the potential carcinogenic effects, particularly for female infants, of increased IGF-1 levels in rBGH milk and dairy products.

In the normal lactating bovine mammary gland, IGF-1 is almost exclusively located in intralobular stromal or connective tissue cells with minimal epithelial reactivity (38). In contrast, there is a markedly prominent epithelial uptake of IGF-1 following increased serum levels induced by rBGH (38). Furthermore, IGF-1 binds to specific surface receptors identified in cultured mammary epithelial cells of a wide range of species including pigs, cattle, and humans (39-41). These receptors are proteins in the tyrosine kinase family, to which retrovirus oncogenes also belong (42). IGF-1 receptors have also been identified in normal and malignant human breast tissue (43, 44); levels in malignant tissue are some 10-fold elevated. Related growth factors, such as epidermal growth factor (EGF) and fibroblastic growth factor (FGF), also bind to receptors of breast cancer cells (43). Of further interest, estradiol and progesterone regulate IGF-1 receptors in cultured normal and neoplastic human uterine endometrial cells (45).

More direct evidence on the role of elevated levels of IGF-1 in rBGH milk as a potential risk factor for breast cancer is based on the following considerations. IGF-1 induces highly potent mitogenic effects in a variety of cell types (46), including normal human breast cells maintained in long-term tissue culture (39). IGF-1 is also a potent regulator of cultured human breast cancer cells (47, 48) and is more mitogenic than the potent estradiol (49). While distinct from carcinogenesis, mitogenesis is likely to promote malignant transformation induced by estradiol in breast epithelium (43). Furthermore, estrogens induce IGF-1 synthesis in both normal and malignant breast epithelia (50, 51). Accordingly, it is now recognized that growth factors such as IGF-1 "are responsible at least in part for the evolution of normal breast epithelia to breast cancer" (52). IGF-1 and related growth factors are critically involved in the aberrant growth of human breast cancer cells, and maintain their invasive or metastatic phenotype (43, 53). Of further interest is the fact that IGF-1 plasma concentrations are higher in breast cancer patients than healthy controls: "even if there is no direct evidence that elevated plasma levels of IGF-1 reflect elevated levels of the growth factor at the

tumor level, the possibility exists that increased levels of circulating IGF-1 may contribute to breast tumor growth" (44). Relevant in this connection is the suggestion that tamoxifen used in the chemotherapy of breast cancer acts by reducing blood IGF-1 levels (49).

These unresolved concerns about the potential carcinogenicity of IGF-1 in rBGH milk are heightened by evidence that the undifferentiated prenatal and infant breasts are particularly susceptible to "imprinting" by hormonal influences (54). This may implicate IGF-1 itself as a direct breast cancer risk factor. It may also act indirectly by sensitizing the breast to subsequent unrelated risk factors, such as carcinogenic and estrogenic pesticide contaminants in food, and radiation, particularly mammography in premenopausal women (55, 56).

#### IGF-1 IN rBGH MILK AS A POTENTIAL RISK FACTOR FOR GASTROINTESTINAL CANCER

IGF-1 stimulates proliferation of intestinal epithelial cells in culture (57). Such mitogenic effects are induced at concentrations equivalent to those occurring in mature bovine milk. Furthermore, a related growth factor with similar biological effects on the human gut, epidermal growth factor, passes undigested through the stomach to the small intestine from where it is rapidly absorbed into the blood stream, suggesting the likelihood that IGF-1 is similarly absorbed (57). Subsequent studies have demonstrated that EGF-1 is protected from digestion by casein, a protein in milk (58). Reflecting these considerations, the 1990 NIH Technology Conference concluded: "Whether the additional amounts of IGF-1 in milk from [rBGH-treated] cows has a local effect in the esophagus, stomach or intestines is unknown." It was accordingly recommended: "Determine the acute and chronic action of IGF-1 if any, in the upper gastrointestinal tract" (20). However, no information is yet available on the local effects of IGF-1, particularly increased levels of the probably more bioactive IGF-1 in rBGH milk, on the gastrointestinal tract of infants and adults.

More recent studies have demonstrated that following consumption of rBGH milk, IGF-1 in the gastrointestinal lumen, unlike serum IGF-1, is not protein bound and thus more likely to "exert biological activity" (59). Intraluminal infusion of IGF-1 in rats at concentrations equivalent to those in bovine milk has been found to increase the cellularity of the intestinal mucosa (60). In one study, rIGF-1 at concentrations of 100 ng/ml induced statistically highly significant mitogenic effects in crypt epithelial cells of cultured human duodenal explants (61). The authors concluded: "The combination of IGF-1 in BST-milk and IGF-1 normally secreted into the human gastrointestinal lumen would augment intraluminal concentrations of this hormone, increasing the possibility of local mitogenic effects on gut tissues" (61), and expressed concerns about local carcinogenic effects (62). Research has also shown that human colorectal cancer cell lines are responsive to IGF-1 (63), and that IGF-1 is mitogenic to five of eight carcinoma cell lines and

synergizes the effects of another growth factor, transforming growth factor (TGF). The authors concluded that their results illustrated the importance of IGF-1 as "stimulators of growth of colorectal carcinoma." There is also evidence that human gastric cancer cells have IGF-1 receptors (64).

These results raise questions about IGF-1 residues in rBGH milk posing potential risks for the initiation or promotion of gastrointestinal cancer. An extensive recent review of rBGH milk further emphasized these concerns (65): "It could be considered an oversight for [the FDA] to suggest that ingested IGF-1 is inactive. . . . Many more potential effects of ingested IGF-1 on the gastrointestinal tract and the local immune system of the gut need to be explored."

#### DISCUSSION

Critical information on a wide range of potentially adverse health effects of IGF-1 is still unavailable (e.g., 14, 17, 19, 63, 65, 66). This is particularly disturbing because FDA made its decision on the safety of rBGH milk in 1985, when there had been no consideration of the effect of IGF-1 on cell proliferation. Needed studies include (a) determination of free versus protein-bound IGF-1 in sera of cows treated with rBGH and of untreated cows; (b) study of the lifelong, three-generation, and subcellular effects in rodents and subhuman primates of rBGH milk and derived IGF-1; (c) chemical characterization of IGF-1 in rBGH milk; (d) radioactive label studies on gastrointestinal absorption of IGF-1 in rBGH milk; (e) pharmacological studies on binding to receptor sites; and (f) even more critically, extensive studies on humans who drink rBGH milk, with particular reference to absorption and characterization of serum IGF-1, determination of free versus bound forms, and subcellular binding. The significance of such data gaps is compounded by converging lines of evidence implicating IGF-1 in rBGH milk as a potential risk factor for breast and gastrointestinal cancers. Nevertheless, FDA has dismissed these concerns without investigation and on the basis of unpublished "confidential" short-term toxicity data, primarily from an industry consulting firm with a tainted track record. Furthermore, contrary to FDA and industry claims and in spite of misleading data, the results of this test revealed statistically significant growth-promoting effects.

In spite of these serious and still unresolved public health concerns, in November 1993 FDA approved commercial sale of rBGH milk, some eight years after the agency approved the sale of unlabeled rBGH milk from large-scale veterinary trials. This was soon followed by regulatory guidelines effectively banning the labeling of such milk (4, 5). The rationale for this continued denial of consumers' right to know was developed by Michael Taylor, then Deputy FDA Commissioner and formerly chief counsel for the International Food Biotechnology Council and Monsanto (5). This ban has since been challenged by nationwide grassroots consumer groups and by two milk suppliers, both of whom have been sued by Monsanto.

In short, with the active complicity of the FDA, the entire nation is currently being subjected to an experiment involving large-scale adulteration of an age-old dietary staple by a poorly characterized and unlabeled biotechnology product. Disturbingly, this experiment benefits only a very small segment of the agricultural industry while providing no matching benefits to consumers. Even more disturbingly, it poses major potential public health risks for the entire U.S. population.

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**Note added in proof**

The potential carcinogenicity of incremental IGF-1 in rBGH milk is confirmed by studies on acromegaly, in which levels of total and free serum IGF-1 are significantly elevated (Juul, A., et al. The ratio between serum levels of IGF-1 and the IGF binding proteins decreases with age in healthy patients and is increased in acromegalic patients. *Clin. Endocrinol.* 41: 85-93, 1994). A recent review has reported increased rates of pre-malignant polyps and colon cancer and also of overall cancers in acromegalics (Tremble, J. M., and McGregor, A. M. Epidemiology, complications and mortality. In *Treating Acromegaly*, edited by J. A. H. Wass, pp. 5-12. Journal of Endocrinology Ltd, Bristol, England, 1994).

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