Request for Proposals (RFP)
Examining Hormone Concentrations of Interest to Breast Cancer Risk in California's Beef

California Breast Cancer Research Program
California Breast Cancer Prevention Initiatives

Deadline to apply
January 17, 2019

Table of Contents

Published November 8, 2018

About the California Breast Cancer Research Program and the California Breast Cancer Prevention Initiatives

The **California Breast Cancer Research Program (CBCRP)** was established pursuant to passage by the California Legislature of the 1993 Breast Cancer Act (i.e., *AB 2055 (B. Friedman) [Chapter 661, Statutes of 1993]* and *AB 478 (B. Friedman) [AB 478, Statutes of 1993]*). The program is responsible for administering funding for breast cancer research in the State of California.

The mission of CBCRP is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities.

- CBCRP is the largest state-funded breast cancer research effort in the nation and is administered by the University of California, Office of the President.
- CBCRP is funded through the tobacco tax, voluntary tax check-off on personal income tax forms, and individual contributions.
- The tax check-off, included on the personal income tax form since 1993, has drawn over $8.5 million for breast cancer research.
- Ninety-five percent of our revenue goes directly to funding research and education efforts.
- CBCRP supports innovative breast cancer research and new approaches that other agencies may be reluctant to support.
- Since 1994, CBCRP has awarded over $280 million in 1,028 grants to 139 institutions across the state. With continued investment, CBCRP will work to find better ways to prevent, treat and cure breast cancer.

CBCPI Priority Areas

In 2004, CBCRP launched its Special Research Initiatives. The CBCRP's Breast Cancer Research Council devoted 30 percent of CBCRP research funds to support coordinated, directed, and collaborative research strategies that increase knowledge about and create solutions to both the environmental causes of breast cancer and the unequal burden of the disease.

In March 2010, CBCRP's Council decided to build on the existing SRI by devoting 50 percent of CBCRP research funds between 2011 and 2015. This new effort is titled the California Breast Cancer Prevention Initiatives (CBCPI). Approximately $24 million is being dedicated to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to:

1. Identify and eliminate environmental causes of breast cancer.
2. Identify and eliminate disparities/inequities in the burden of breast cancer in California.

3. Population level interventions (including policy research) on known or suspected breast cancer risk factors and protective measures.
4. Targeted interventions for high-risk individuals, including new methods for identifying or assessing risk.

To focus these research efforts, CBCRP issued a Request for Qualifications (RFQ) to fund a team to collaborate with CBCRP to develop and implement the California Breast Cancer Prevention Initiatives planning process. In 2010, the grant was awarded to Tracey Woodruff, PhD, MPH, Professor and Director of the University of California, San Francisco, Program on Reproductive Health and the Environment (PRHE).

In March 2015, CBCRP's Council approved fifteen (15) concept proposals to stimulate compelling and innovative research in all four topical areas of the CBCPI (environmental causes, health disparities, population-level interventions and targeted interventions for high risk individuals). A series of funding opportunities has been released reflecting these concepts.

Examining Hormone Concentrations of Interest to Breast Cancer Risk in California's Beef

A paucity of information is publicly available regarding the human food safety evaluations that form the scientific basis for Food and Drug Administration (FDA) animal drug approvals, especially for hormones. Limitations in industry and federal approaches to evaluation make it difficult to form a comprehensive picture of residues in retail animal products. Insights into cumulative exposure burdens of Californians may be gained from analysis of private well water samples. Further, data documenting drinking water hormone exposure could serve as a first step towards epidemiologic investigations examining the impact of these exposures on subclinical (or clinical) outcomes in follow-up research. *This initiative aims to improve our understanding and quantify exposures to various concentrations of both endogenous and exogenous hormones of interest for breast cancer risk from food animal production.*

Available Funding

This initiative aims to improve our understanding and quantify exposures to various concentrations of both endogenous and exogenous hormones of interest for breast cancer risk from food animal production.

CBCRP intends to fund one pilot project with a maximum direct cost budget of $220,000 and duration of 2 years.

Completed responses to this RFP are due by the deadline: January 17, 2019. Signed face pages of submitted applications must be emailed to RGPOgrants@ucop.edu by **January 24, 2019**. The project start date is June 1, 2019.

For more information and technical assistance, please contact:
Nicholas J. Anthis, DPhil
nicholas.anthis@ucop.edu
CBCRP Phone: (510) 987-0358
CBCRP Toll free: (888) 313-2277

Background/Justification

Toxicological and residue assessment of hormones are supported primarily by industry studies that are not made available to independent scientists for review; as a result, it is impossible to assess the quality and strength of the evidence on which FDA bases its safety decisions. Federal approaches to hormone residue testing are also inadequate for assessment of human exposure. A small, changing number of compounds are inconsistently tested from year to year. The tests rely on potentially outdated methods and do not permit longitudinal evaluation of residue levels in animal products. A search of the open literature indicates that representative studies of residues in retail animal products are lacking.

Limited transparency from the FDA regarding exposures from drug residues and major gaps in the literature provides for novel research opportunities to improve understanding and quantify exposures to various concentrations of both endogenous and exogenous hormones of interest for breast cancer risk from food animal production. Analysis of private well water samples for these compounds will provide a novel portrait of the cumulative exposure burdens faced by California residents who rely on these sources for drinking water. Further, data documenting drinking water hormone exposure could serve as a first step towards epidemiologic investigations examining the impact of these exposures on subclinical or clinical outcomes in follow-up research.

The data from the pilot study could advance, or rule out the need for, larger studies that characterize hormone residue levels in food and water which in turn could inform independent toxicological studies that examine the biological significance (if any) of long-term, low-dose hormone exposures through diet, especially during critical life-stages, and tell us what the use of approved drugs means in terms of subsequent dietary exposure that may have important implications for breast cancer prevention. Thus, this pilot study would serve as a first step towards understanding the potential impacts of these animal production practices on human health.

I. Drug/Hormones Used In Food Animal Production

In recent years, increasing attention has been paid to various sources of hormones that may be involved in breast cancer etiology following reports that heightened levels of endogenous hormones and exposure to exogenous hormones and other endocrine-disrupting chemicals in food are associated with increased breast cancer risk.[1,2,3] In the

U.S., seven pharmaceutical compounds approved by the FDA for use in food animal production are either endogenous hormones (i.e., testosterone propionate [TP], estradiol [E2] and estradiol benzoate, and progesterone) or compounds that display high affinities for human hormone receptors (i.e., trenbolone acetate [TBA], zeranol, and melengestrol acetate [MGA])[4] (Table; NL = non-lactating dairy cattle BS = breeding stock). These drugs are approved for use in cattle and, in the case of zeranol, sheep to increase weight gain and improve feed efficiency (two related indications generally known as "growth promotion"). E2, progesterone, and MGA are also approved to manage estrus in beef cattle and sheep. An additional compound, bovine somatotropin (bST) is approved for use in dairy cattle to increase milk production. bST is known in some cases as recombinant bovine somatotropin [rBST], bovine growth hormone [bGH], or recombinant bovine growth hormone [rBGH]. Hormones are not approved for use in poultry or swine.

Table. FDA-Approved Hormones for Use in Food Animal Production

Active Ingredient	Beef	Dairy	Sheep
Estradiol	x	NL	
Melengestrol acetate	x		
Progesterone	x	BS	x
bST		x	
Testosterone propionate	x		
Trenbolone acetate	x		
Zeranol	x		x

There is concern that the drugs used in cattle and sheep or their biologically active metabolites may accumulate in edible tissues or dairy products from treated animals, potentially exposing consumers of these products.[5] There is also concern that bST use in dairy cattle increases levels of an endogenous hormone, insulin-like growth factor 1 (IGF-1), in milk and dairy products, likewise exposing consumers.[6] As a result, use of these drugs has been controversial. The U.S. and European Union (EU) governments have engaged in a decades-long trade dispute over importation of U.S. beef from cattle that received them.[7] The question of whether or not the use of one or more of these drugs poses a human health risk remains subject to debate.[5,7]

The debate on hormones in food is fueled in part by formidable data gaps in understanding toxicity, exposure and ultimately the potential health risk of hormones in food. The quantitative risk assessment process developed by a National Research Council (NRC) committee in 1983 is the standard approach to estimating human health risks posed by chemical exposures.[8] A variant of this process has been adopted by the FDA for evaluation and approval of new animal drugs for use in food animal production.[9] The NRC process

consists of four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization.[8] The published literature is very limited on each of these factors. However, extensive testing by sponsors is performed and study reports and raw data are submitted to regulatory agencies like the FDA and international bodies like the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Following FDA approvals, however, only brief Freedom of Information (FOI) summaries of the industry-submitted studies may be available, making an independent assessment of the data and conclusions difficult or impossible.

In light of our current knowledge of the association between exposure to endogenous and exogenous hormones and breast cancer risk, widespread exposure to animal food products, and a lack of published, independent research on which to evaluate risk, further characterization of exposure to hormones in food can contribute greatly to advancing prevention-based interventions for breast cancer.

II. Toxicity

Chronic (especially lifetime) bioassays of oral toxicity of the seven compounds (Table) in the published literature are largely lacking. While evaluations of these compounds, sponsored by drug manufacturers, are submitted to the FDA as part of the new animal drug application process, they are not made available to the public for independent evaluation. Thus, they cannot be used to estimate risks and related burdens for people consuming animal products. The extant literature primarily utilizes subcutaneous dose delivery, in which the bioavailability of the administered dose approaches 100%.

This route does not account for variation in toxicological parameters that may result from differences in bioavailability or metabolism of compounds following oral exposure. In addition, the endpoints assessed in the published literature generally do not reflect an emerging understanding of the importance of upstream markers (e.g., circulating hormone levels) on subsequent clinical disease (e.g., breast cancer) nor do they address our current understanding of the importance of whether the exposure occurs during critical or sensitive periods of human development.

III. Exposure

Human exposure to hormones from consumption of animal products is primarily a function of residues present in food in retail markets and consumption of meats, milk and egg products. Available data streams for residue levels include: (1) New Animal Drug Applications (NADA); (2) U.S. National Residue Program; and (3) Published research.

Nationwide dietary intake data for animal products are available through the What We Eat in America (WWEIA) dietary survey of the National Health and Nutrition Examination

Survey (NHANES).[10,11] There are many limitations to these sources of exposure information. Moreover, there appear to be no California-specific data related to hormone residues in animal products and there are no animal product consumption data specific to California. An additional consideration in understanding exposure to hormones used in food animal production is consumption of drinking water from household wells impacted by effluent from meat and dairy production facilities. Each of these aspects of exposure is described below.

III.A. Residues

New Animal Drug Applications. For hormones administered to food animals, data from feeding studies that show the rates of depletion of these compounds in the edible tissues of dosed food animals are required to be generated by drug companies (known as "sponsors") as part of an NADA submitted to the FDA to obtain approval for legal marketing. As part of the drug approval process, the sponsor of a new animal drug is required conduct and submit studies to the FDA that characterize residues that may persist in animal products when the drug is used in accordance with the conditions of use proposed in the NADA. These studies are used to inform recommended dosages and to set withdrawal periods (i.e., the number of days before slaughter that use of the drug must end) that are intended to ensure that remaining residue concentrations have fallen to levels the FDA considers "safe" for human consumption. If properly conducted, these residue studies could be especially helpful in efforts to characterize population exposures to residues through consumption of animal products.

Despite the promise they may hold, the reporting of these studies can be flawed and public accessibility is often limited. The study reports are not released to the public; rather, FOI summaries that contain brief descriptions of the studies submitted have been prepared for approvals granted since 1975. For some hormonal drugs, FOI summaries are not available online. Assuming the approval in question occurred in 1975 or later and a FOI summary was prepared, it must be acquired through a formal Freedom of Information Act request, a process that can be lengthy.

Among synthetic hormones approved for use in food animal production, FOI summaries that include substantive toxicological reviews are not available for zeranol (first approved in 1969) or MGA (first approved in 1968).[12] Melengestrol acetate was introduced as a food additive, just before the process for "new animal drugs" was established in 1968 by amendment to the Federal Food, Drug and Cosmetic Act; thus, no original NADA was identified. It is possible that the drug was "grandfathered" into the system, thus explaining a lack of identifiable toxicological review. Trenbolone acetate was first approved in 1987, and has a FOI summary with a substantive toxicological evaluation that was last updated in 1996.[13] Similarly, a FOI summary (with a toxicological review) is available for rBST, which was last evaluated in 1993.[14]

For externally administered endogenous hormones, researchers at Johns Hopkins were unable to locate FOI summaries with toxicological reviews for progesterone, E2 and testosterone. In some FOI summaries for E2 and testosterone (as they are part of numerous combination approvals and dosage forms), the agency states that it "has concluded that no harmful effects will occur in individuals chronically ingesting animal tissues that contain an incremental increase of endogenous steroid equal to 1% or less of the amount produced daily by the segment of the population with the lowest daily production."[15] No explanation or rationale is provided for the selection of a 1% increase, and the FOI summaries state that if drug sponsors can demonstrate that residues in meat will result in exposures less than the permitted increase, then the drugs are considered safe.

Even for drugs where residue depletion summaries are easily accessible, problems with data design and results reporting limit confidence in any conclusions. An example can be found in the case of NADA 141-043, for a combination implant drug containing TBA and estradiol benzoate.[16] In the FOI summary associated with this approval, serious issues are apparent regarding study design (i.e., data from half [heifers] of the 24 animals tested were dropped, leaving only 12 animals [steers] with unspecified exposure group assignment) and reporting clarity (i.e. number of animals per group is not reported, no control data are reported, urinary and fecal residue measurements are not reported) that would challenge the value of this study for determination of anticipated residues. In this particular case, this study was used to support the decisions to not require marker residue tolerances or withdrawal periods for the drug. Feeding studies conducted outside of the NADA process are not common, but some have found measurable residue concentrations in edible tissues.

U.S. National Residue Program. Another potential source of residue data within the US is the National Residue Program (NRP, which is administered by the Food Safety and Inspection Service of the USDA). The NRP is the only federal effort that routinely examines animal products for residues of administered drugs. An examination of the testing regimens of the NRP from 2002 to 2012 indicates that only three hormones (MGA, TBA and zeranol) have been examined at all during that surveillance period.[17-27] No hormone residue monitoring data were collected under the NRP in 2011 and 2012, though the NRP has noted it has scheduled zeranol and MGA for 2013 sampling efforts[28]; previous years saw variability in which of these three hormones were monitored. For each drug, only a single tissue was tested in the monitoring program. Heifer fat was the tissue analyzed in the case of MGA, whereas livers from formula-fed and non-formula-fed veal calves were the sole tissue examined for both TBA and zeranol. From 2002 – 2012, the greatest number of hormone residue tests was conducted in 2005, and subsequent years saw a steady decline in the number of samples tested.

The NRP does not report hormone residue concentrations as continuous variables. Instead, they are reported as binned categories based on the concentrations detected. Over the period examined, some violations of residue tolerances were observed for zeranol and TBA. In 2002, 16% of samples tested were in violation of residue tolerances. Violations dropped to 5% in the following year (2003), though zeranol was excluded from NRP analysis in 2004.

Challenges exist in utilization of NRP data for the purpose of understanding dietary exposures to hormones in the US population. Testing for hormones is performed in tissues not commonly consumed by people, which would require extrapolations to estimate concentrations in animal products like muscle tissue and milk. Further, residue data reporting is extremely crude and would not allow for the construction of residue concentration distributions or descriptive statistics. Many of these shortcomings are likely a result of the core conflict between the purpose of the NRP and the needs for exposure assessment, as the primary purpose of the NRP – the removal of animal products with residue levels in violation of the regulations from the food supply – may require different data than what is needed to understand residue exposures in people.

Published Literature. While the literature describing various techniques for determination of hormone residues in animal products is expansive, few studies have identified residues in retail animal products. To date, the largest literature is available for hormone residues in dairy products, and studies of E1 and E2 levels in various milk products were most common. The majority of studies identified typically analyzed small numbers of retail samples; single samples per product type were not uncommon, and studies rarely exceeded ten samples per product. Estrogens, particularly forms of E2, were the most frequently examined.[29-34] Looking across studies, some patterns emerge, though it is necessary to acknowledge that the limited number of studies and small sample sizes within those studies do not allow for statements of great certainty.

Research has demonstrated that use of rBST in dairy production has been linked to increases in concentrations of IGF-1 in dairy products from treated animals. Despite this, anecdotal evidence suggests that public concerns related to the use of rBST have prompted dairy producers to abandon the additive, and USDA data suggest that less than a quarter of dairy cows are treated with the drug.[35]

A smaller number of studies have attempted to characterize residues of synthetic hormones in retail beef products.[30,36,37,38] These studies report inconsistent results with some lacking clear descriptions of analytical and/or meat-sourcing methods providing limited confidence in (and relevance of) the findings.

III.B. Consumption

The What We Eat in America (WWEIA) dietary survey analyzed by the EPA and reported by product as per capita or consumers-only intake rates in the 2011 Exposure Factors Handbook (EFH)[39] are the best estimates suited for use in estimation of hormone exposure through foods, as they are derived from the most recent synthesis of NHANES dietary data. In some cases, animal product intake rates are reported by life stage (or age grouping) or by race-ethnicity.

The EPA EFH includes some animal product intake data specific to pre-menopausal women. Women between the ages of 13 and 49 consume about 20% less meat on average than the general population, after adjustment for body weight. They also consume just over half of the amount of dairy products that the general population eats. As far as specific meats, women ages 13 - 49 eat about 28% less pork, 22% less beef, and 14% less chicken. While data specific to women ages 50 and over were not available, estimates for people 50+ (for males and females combined) suggest that total meat intake and beef, poultry and dairy product intakes were further reduced below women ages 13-49. Pork intake among persons over 50 was slightly higher than that of women ages 13-49. Data for animal product-specific intake rates for post-menopausal women are needed to estimate dietary hormone exposures in this subpopulation.

Patterns of body-weight adjusted intake of animal products follow a clear pattern. For total meats, and for poultry, dairy products and eggs, per capita body-weight peaks early in life, between ages one and two years. Body weight-adjusted beef and pork consumption peaks between the ages of three and five. Per capita rates of body weight-adjusted intake of dairy products remain elevated until the teenage years at about twice the per capita average.

III.C. Hormones in Well Water Systems in California

In a typical year, California relies on groundwater for approximately forty percent of its water supply, and nearly 16 million California residents use groundwater for their drinking water supply. A sub-set of these residents rely on private wells, which are not subject to federal drinking water regulations. While some states have minimal safety or inspection requirements for private wells, state-level action is usually only triggered during property transfer and rarely requires periodic monitoring of water quality.[40]

A growing body of scientific literature shows that effluent from concentrated animal feeding operations (CAFOs) and manure storage lagoons are capable of contaminating groundwater with a variety of contaminants, including nitrates, pharmaceuticals and hormones.[41-43] California has a sizable dairy industry, with a 2012 inventory of nearly 2 million dairy cattle, that accounts for more than 20% of the US milk production annually. There is also a sizeable beef production industry in the state – California has a

5.2 million head beef cattle inventory. Dairy and beef production occurs primarily in rural settings; thus, waste that is stored in manure lagoons or applied to crop fields as fertilizer may transport manure-borne hormones and other contaminants to groundwater sources used by California residents for drinking water.

Given the size of the dairy and beef industries in California there exists a potential risk for impacting groundwater. In light of the fact that certain regions of California rely on groundwater sources for drinking water, it is important to understand the contribution of dairy and beef (and other animal) production sites to human exposures to hormones.

IV. Health Risk

Key limitations of the currently available data preclude conducting quantitative dose-response and exposure assessments. An early stage of the animal drug approval process is the generation of safety and effectiveness data for a proposed drug by its sponsor. These studies are either conducted or funded by the sponsor, and submitted to the FDA as part of a NADA described above. Included in the data package as part of the NADA submission are toxicological studies to support an assessment of "human food safety" by the FDA's Center for Veterinary Medicine (CVM), which encompasses four main steps: a toxicological evaluation (in which CVM determines an ADI); determination of residues that may result from routine use (in which CVM sets residue tolerances and withdrawal times); a microbiological examination of the impact of the use of the drug on bacteria and resulting resistance; and a determination of the regulatory method, which considers the appropriateness of the testing methods used by the drug sponsor in its human food safety studies.[44]

As above, the studies and primary data submitted to support toxicological evaluations are not available to the public. It is also important to note that in many cases, individual drugs may receive additional approvals for use in new species or in combination with other drugs. While these new uses may serve as an opportunity for CVM to require new toxicological evaluation of specific drug ingredients, it is uncommon for additional testing to be required or submitted. Instead, CVM usually refers to toxicological evaluations conducted as part of earlier approvals for the specific active ingredients, even if these evaluations were conducted decades before.

V. Summary

At present, the available data do not permit an evidence-based quantitative characterization of risks that result from the use of hormonal drugs in food animal production. Thus, despite increased recognition of the role of endogenous and exogenous hormones in breast cancer risk and widespread exposure to food animal products, our

understanding of the role of dietary hormone exposure in the population burden of breast cancer is not possible at this time.

In recognition of this research gap, we propose funding one pilot study to test two hypotheses: 1) that there are FDA-approved food animal production drug residues, including suspected mammary gland toxicants, prevalent in edible portions of beef products as well as in well drinking water systems in California; and 2) there are quantifiable naturally occurring/ endogenous hormone concentrations in edible portions of both retail USDA certified organic and conventional beef that may have implications for breast cancer risk. This second hypothesis, based on the fact that pregnant and lactating food animals have high levels of endogenous hormones, would provide essential complimentary information to our understanding of the contribution of food animal products to exposure to hormonally active compounds of interest to breast cancer risk.

This research would collect the most basic information about hormones in food - whether or not they are even present, and if present, at what levels. There is currently no information concerning hormone residues in meat that can be used to estimate the number of samples needed for a study of hormones in food to have sufficient power to inform conclusions. Specifically, a sense of the variance observed in hormone levels in animal product samples for the various hormones of interest is needed. This pilot project would fill this data gap. This pilot study approach has been successfully employed in studies by researchers at Johns Hopkins of contaminant residues in animal products.

The results provide some insight into expected residues and are used to develop estimates of the number of samples needed to characterize residue occurrence and magnitude with confidence (that will support statistical comparisons). These pilot studies have been especially useful in guiding fuller studies or deciding that a particular project is not worth pursuing on a larger scale.

The results of the pilot study will provide the evidence needed to begin to characterize the nature and extent of FDA-approved food animal production drug/hormone residues in the food and water supply in California as well as of naturally occurring hormones of interest for breast cancer in the food supply. The methods developed for this project can be used in future studies to characterize exposure using more comprehensive testing of food and water. Future studies could utilize raw data from WWEIA (which are publicly accessible) to quantify subsequent dietary exposure for subpopulations of interest for breast cancer, which could elucidate potential disparities in exposure that might contribute to disparities in risk. For example, future studies of levels of hormones in food could be coupled to in-depth analyses of intake rate distributions for subgroups of particular concern in breast cancer prevention efforts. These rates would better support dietary exposure estimation for hormones in vulnerable populations.

Project Guidelines

The main goal of this RFP is to improve our understanding and quantify exposures to various concentrations of both endogenous and exogenous hormones of interest for breast cancer risk from food animal production (beef) and well water.

Proposed budgets should be appropriate to the nature of the proposed work. Total direct costs for one pilot project will be up to $220,000. Length of project: 2 years.

This research study would:

A. Characterize the presence of seven FDA approved drugs for use in food animal products sold in California.

Beef products would be examined for endogenous hormones (testosterone propionate [TP], estradiol [E2] and estradiol benzoate, and progesterone) and synthetic hormones (trenbolone acetate [TBA], zeranol, and melengestrol acetate [MGA]). Samples would be collected from retail stores in the state of California. Beef sampling should evaluate both conventionally produced and USDA-Certified Organic samples for endogenous hormones.

B. Characterize the presence of these same seven FDA approved drugs for use in food animal production in well water.

The research would be conducted in a cross-section of California households at potential risk of contamination due to effluent from large-scale animal production and dairy facilities. Depending on the results, these data could be paired with geo-referenced data on animal production sites, which would allow for analyses of spatial relationships between animal production and groundwater contamination with hormones.

I. Additional Considerations and Requirements for Beef Sampling

The pilot should include beef samples from:

- various brands, as synthetic hormone use practices may vary across producers
- both USDA certified organic and conventional beef products

In developing a sampling strategy consideration must be given to the fact that the FDA does not require producers to report hormone use practices, nor does it report sales data for synthetic hormone products from pharmaceutical manufacturers. Moreover, product labels do not uniformly facilitate identification of animal products derived from treated animals, since producers have no obligation to report hormone treatment. USDA Organic

certification labels, however, are federally regulated, and should only be used on products derived from animals that were not treated with synthetic hormones (MGA, TBA and zeranol in beef). Products that do not bear the USDA Organic certification label do not provide insights as to hormone use – it is possible (but not guaranteed) that one or more hormones could have been employed in the production of those animals.

The use of synthetic hormones is believed to be common in the beef industry. In some cases, conventional producers will label their products as being produced without the use of synthetic hormones. With this in mind, it is possible to target sample analyses to reflect likely usage in the industry.

II. Additional Considerations and Requirements for Water Sampling

It is critical that an understanding of the locations of animal production and manure spreading inform selection of sites/water sources from which samples are acquired, to ensure characterization of hormone contaminant profiles in water can be linked to surface activities.

Sampling of water should include sources of ground or surface waters used as drinking water, preferably from private wells or monitoring wells to which a local or state environmental agency may have access.

The study should include both synthetic and endogenous hormones, depending on the spatial and hydrogeological relationships that exist between animal production sites and sources of water used for human consumption.

Budget

CBCRP intends to fund 1 pilot project with a maximum direct cost budget of $220,000 and duration of 2 years. Indirect (F&A) costs are paid at the appropriate federally approved F&A rate for all institutions except for University of California campuses, which receive 25% F&A.

Applicants should consider the following elements when constructing their budgets:

- Expertise: Proposals must involve researchers with appropriate proficiency for the research questions (e.g. epidemiologist, endocrinologist, toxicologist, chemist)
- Capacity: Applicants should demonstrate possession of or access to appropriate tools and technologies (e.g. laboratory facilities and equipment, animal facilities, etc.)

References

[1] Yager JD, Davidson NE: Estrogen carcinogenesis in breast cancer. The New England journal of medicine 2006,354:270-282.

[2] Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Jr., Lee DH, Shioda T,

Soto AM, vom Saal FS, Welshons WV, et al: Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocrine reviews 2012, 33:378-455.

[3] World Health Organization/United Nations Environment Programme. State of the Science of Endocrine Disrupting Chemicals 2012 [Available at: http://www.who.int/ceh/publications/endocrine/en/index.html. Accessed: 29 September 2013].

[4] United States Food and Drug Administration. Animal Drugs @ FDA 2013 [Available at: https://animaldrugsatfda.fda.gov/adafda/views/#/search. Accessed: 25 September 2013].

[5] Galbraith H: Hormones in international meat production: biological, sociological and consumer issues. Nutr Res Rev 2002, 15:293-314.

[6] American Cancer Society. Recombinant Bovine Growth Hormone 2013 [Available at: http://www.cancer.org/cancer/cancercauses/othercarcinogens/athome/recombinant-bovine-growth-hormone. Accessed: 29 September 2013].

[7] Johnson R: The U.S.-EU Beef Hormone Dispute. Washington, DC: Congressional Research Service; 2012.

[8] National Research Council: Risk Assessment in the Federal Government: Managing the Process. Washington, DC:National Academy Press; 1983.

[9] United States Food and Drug Administration. From an Idea to the Marketplace: The Journal of an Animal Drug through the Approval Process 2013 [Available at: https://www.fda.gov/animalveterinary/resourcesforyou/animalhealthliteracy/ucm219207.htm]

[10] United States Department of Agriculture. Food Surveys Products and Services 2013 [Available at: http://www.ars.usda.gov/Services/docs.htm?docid=13793. Accessed: 10 September 2013].

[11] Centers for Disease Control and Prevention. What We Eat in America, DHHS-USDA Dietary Survey Integration 2010 [Available at: http://www.cdc.gov/nchs/nhanes/wweia.htm. Accessed: 10 September 2013].

[12] United States Food and Drug Administration. Freedom of Information Summary, Supplemental New Animal Drug Application, NADA 038-233 Ralgro and Ralgro Magnum (Zeranol) 2005 [Accessed: 25 September 2013].

[13] United States Food and Drug Administration. NADA 138-612 Finaplix® - original approval 1986 [Accessed: 25 September 2013].

[14] United States Food and Drug Administration. FREEDOM OF INFORMATION SUMMARY: POSILAC® (sterile sometribove zinc suspension) 1993 [Accessed: 25 September 2013].

[15] United States Food and Drug Administration. NADA 011-427 Estradiol benzoate and testosterone propionate - supplemental approval (Date of Approval: July 9, 1999) 1999 [Accessed: 25 September 2013].

[16] United States Food and Drug Administration. NADA 141-043 Synovex® Plus - original

approval 1996 [Available at: NADA 141-043 Synovex® Plus - original approval. Accessed: 23 September 2013].

[17] United States Department of Agriculture/Food Safety and Inspection Service. 2002 FSIS NATIONAL RESIDUE PROGRAM DATA 2003 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/73cec9bb-6f41-49f6-9c18-fb0ac45bf542/2002-Red-Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[18] United States Department of Agriculture/Food Safety and Inspection Service. 2003 FSIS NATIONAL RESIDUE PROGRAM DATA 2004 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/f3e4b571-6264-48a2-bda3-6078f8e248e3/2003-Red-Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[19] United States Department of Agriculture/Food Safety and Inspection Service. 2004 FSIS NATIONAL RESIDUE PROGRAM DATA 2005 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/0110d461-c116-4354-a4aa-5cbdb66f561a/2004-Red-Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[20] United States Department of Agriculture/Food Safety and Inspection Service. DOMESTIC SAMPLING RESULTS SCHEDULED SAMPLING – EXPOSURE ASSESSMENTS (CONDENSED AND REFORMATTED RESULTS) 2006 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/547e16bd-7b94-4ebd-a7d9-1d8dc44aa70d/2005_Red_Book_Intro.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[21] United States Department of Agriculture/Food Safety and Inspection Service. 2006 FSIS NATIONAL RESIDUE PROGRAM DATA 2007 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/4460cbe4-2dd7-4946-bea8-29945f21df6a/2006_Red_Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[22] United States Department of Agriculture/Food Safety and Inspection Service. 2007 FSIS NATIONAL RESIDUE PROGRAM DATA 2008 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/3dbe0045-cfab-493d-8617-2c9c36c2464f/2007_Red_Book_Complete.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[23] United States Department of Agriculture/Food Safety and Inspection Service. 2008 FSIS NATIONAL RESIDUE PROGRAM DATA 2009 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/18ee140a-a0b5-418e-a59e-67e92bc4d8a7/2008_Red_Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[24] United States Department of Agriculture/Food Safety and Inspection Service. 2009 RESIDUE SAMPLE RESULTS 2011 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/1d69ab4d-8af2-47ee-9eb9-c4bbe8cfe06e/2009_Red_Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[25] United States Department of Agriculture/Food Safety and Inspection Service. 2010 RESIDUE SAMPLE RESULTS 2012 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/f4c918d8-e175-40fb-a674-bae9598bcbf4/2010_Red_Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[26] United States Department of Agriculture/Food Safety and Inspection Service. 2011 RESIDUE SAMPLE RESULTS 2013 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/f511ad0e-d148-4bec-95c7-22774e731f7c/2011_Red_Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[27] United States Department of Agriculture/Food Safety and Inspection Service. 2012 Residue Sampling Plans 2012 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/48ef8b4a-d8fe-40ab-9483-3eaf5e1fc997/2012_Blue_Book.pdf?MOD=AJPERES. Accessed: 25 September 2013].

[28] United States Department of Agriculture/Food Safety and Inspection Service. 2013 Residue Sampling Plans 2013 [Available at: http://www.fsis.usda.gov/wps/wcm/connect/7fec09dd-3a79-4aa8-8974-97d96bc82ee3/2013-Blue-Book.pdf?MOD=AJPERES. Accessed: 21 September 2013].

[29] Farlow DW, Xu X, Veenstra TD: Quantitative measurement of endogenous estrogen metabolites, risk-factors for development of breast cancer, in commercial milk products by LC–MS/MS. Journal of Chromatography B 2009, 877:1327-1334.

[30] Courant F, Antignac J-P, Laille J, Monteau F, Andre F, Le Bizec B: Exposure assessment of prepubertal children to steroid endocrine disruptors. 2. Determination of steroid hormones in milk, egg, and meat samples. Journal of agricultural and food chemistry 2008, 56:3176-3184.

[31] Courant F, Antignac J-P, Maume D, Monteau F, Andre F, Le Bizec B: Determination of naturally occurring oestrogens and androgens in retail samples of milk and eggs. Food additives and contaminants 2007, 24:1358- 1366.

[32] Farlow D, Xu X, Veenstra T: Comparison of estrone and 17β-estradiol levels in commercial goat and cow milk. Journal of dairy science 2012, 95:1699-1708.

[33] Malekinejad H, Scherpenisse P, Bergwerff AA: Naturally occurring estrogens in processed milk and in raw milk (from gestated cows). Journal of agricultural and food chemistry 2006, 54:9785-9791.

[34] Pape-Zambito D, Roberts R, Kensinger R: Estrone and 17β-estradiol concentrations in pasteurized-homogenized milk and commercial dairy products. Journal of Dairy Science 2010, 93:2533-2540.

[35] US Department of Agriculture, Animal and Plant Health Inspection Service APHIS info sheet: Highlights of dairy 2007 part 1: Reference of dairy cattle health and management practices in the United States. Animal and Plant Health Inspection Service Web site. Published October 2007. [Available at: https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy07/Dairy07_is_PartI_Highlights.pdf. Accessed 9 July 2008]

[36] Hsieh M-K, Chen H, Chang J-L, She W-S, Chou C-C: Electrochemical Detection of Zeranol and Zearalenone Metabolic Analogs in Meats and Grains by Screen-Plated Carbon-Plated Disposable Electrodes. Food and Nutrition 2013, 4:31-38.

[37] Kleinova M, Zöllner P, Kahlbacher H, Hochsteiner W, Lindner W: Metabolic profiles of the mycotoxin zearalenone and of the growth promoter zeranol in urine, liver, and muscle of heifers. Journal of agricultural and food chemistry 2002, 50:4769-4776.

[38] Smith G, Heaton K, Sofos J, Tatum J, Aaronson M, Clayton R: Residues of antibiotics, hormones and pesticides in conventional, natural and organic beef. Journal of Muscle Foods 1997, 8:157-172.

[39] United States Environmental Protection Agency. Exposure Factors Handbook: 2011 Edition 2011 [Available at: http://www.ars.usda.gov/Services/docs.htm?docid=13793. Accessed: 10 September 2013].

[40] Rogan WJ, Brady MT, the Committee on Environmental Health, Diseases tCoI. 2009. Drinking Water From Private Wells and Risks to Children. Pediatrics 123(6):e1123-e1137.

[41] Bartelt-Hunt S, Snow DD, Damon-Powell T, Miesbach D. 2011. Occurrence of steroid hormones and antibiotics in shallow groundwater impacted by livestock waste control facilities. Journal of Contaminant Hydrology 123(3–4):94-103.

[42] Arnon S, Dahan O, Elhanany S, Cohen K, Pankratov I, Gross A, et al. 2008. Transport of Testosterone and Estrogen from Dairy-Farm Waste Lagoons to Groundwater. Environmental Science & Technology 42(15):5521-5526.

[43] Lindsey ME, Meyer M, Thurman EM. 2001. Analysis of Trace Levels of Sulfonamide and Tetracycline Antimicrobials in Groundwater and Surface Water Using Solid-Phase Extraction and Liquid Chromatography/Mass Spectrometry. Analytical Chemistry 73(19):4640-4646.

[44] United States Food and Drug Administration. From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process 2013 [Accessed: 25 September 2013].

How We Evaluate RFPs

CBCRP uses a two-tier evaluation process: peer review and programmatic review. It is a combination of (i) the peer review rating, (ii) the programmatic rating, and (iii) available funding that determines a decision to recommend funding.

Peer Review
All applications are evaluated by a peer-review committee of individuals from outside of California. The committee is comprised of scientists from relevant disciplines and breast cancer advocates and other community representatives.

- **Innovation** Extent to which the project explores new and potentially useful information to identify hormones in beef. Are the concepts and hypotheses speculative and exploratory? Are methods novel and original? Has(ve) the investigator(s) thought creatively about how to sample and measure the hormones in beef?

- **Impact:** Potential for the project, if successful, to change policy for or regulation of hormones in beef. Does the research have the ability to translate to population-level change? Will the data yielded by the research be to sufficient to inform policy or future research directions?

- **Approach:** The quality, organization, and presentation of the research plan, including methods and analysis plan. Will the research planned answer the research questions? Are the design, methods and analyses well-developed, integrated and appropriate to the aims and stated milestones of the project? Does the application demonstrate an understanding of the research question and aims?

- **Feasibility:** The extent to which the aims are realistic for the scope and duration of the project; adequacy of investigator's expertise and experience, and institutional resources; and availability of additional expertise and integration of multiple disciplines. Does the investigator (and do co-investigators) have demonstrated expertise and experience working in the topic area? Can the project be completed as proposed given the available funding, time frame and the staff knowledge, skills, experience, and institutional resources?

Programmatic Review
This review is conducted by the Breast Cancer Research Council and involves reviewing and scoring applications with sufficient scores from the peer review process based on the criteria listed below. The individuals on the Council performing this review include advocates, clinicians, and scientists from a variety of disciplines. In performing the Programmatic Review the advisory Council evaluates **only a portion of the application materials** (exact forms are underlined). Pay

careful attention to the instructions for each form. The Programmatic criteria include:

- **Responsiveness.** How responsive are the project and PI to the stated intent of the selected Initiative? Compare the PI's statements on the Other Review Criteria form and the content of the Lay and Scientific Abstracts to the CBCPI topic area. (A score of "0" for Responsiveness is an automatic disqualification.)

- **Dissemination and translation potential.** The degree to which the applicant's statements on the Other Review Criteria form provides a convincing argument that the proposed research has the potential to inform the development and/or implementation of beef production and regulation.

- **Quality of the lay abstract.** Does the Lay Abstract clearly explain in non-technical terms the research background, questions, hypotheses, and goals of the project? Is the relevance to the research initiative understandable?

- **Advocacy Involvement.** Are the named advocate(s) and advocacy organization appropriate for the proposed research project? Were they engaged in the application development process? Are meetings and other communications sufficient for substantive engagement? Are the roles and responsibilities of the PI and the advocate(s) clearly outlined and is the agreement for advocate compensation and reimbursement clear? [The Advisory Council will examine the PI's statements on the Lay and Scientific Abstracts and Advocacy Involvement forms.]

Application Process and Instructions

Submission Deadline: Applications must be submitted through proposalCENTRAL (https://proposalcentral.altum.com/) by Thursday, January 17, 2019 at 12 NOON Pacific Standard Time.

Signed face pages of submitted applications must be emailed to RGPOgrants@ucop.edu by 5pm January 24, 2019.

proposalCENTRAL Online Submission Instructions

Formatting Instructions

All submissions must be in **English**.

Follow these format requirements for written text (consistent with NIH/PHS 398 form):

- The height of the letters must not be smaller than 11 point. Times New Roman or Arial are the suggested fonts.

- Type density must be no more than 15 characters per inch (cpi).
- Page margins, in all directions, must be at least 1/2 inch.
- PI(s) last names and first initials must be in a header, on each page, flush right.

Deviations from the page format, font size, specifications and page limitations are grounds for CBCRP to reject and return the submission without peer review.

Online Application (Proposal) Management

CBCRP requires applications be submitted via an online system: proposalCENTRAL. Following are instructions on how to register and how to submit your response to the RFP. The submission deadline is January 17, 2019. *Note*: the proposalCENTRAL site shows East Coast times. Do NOT wait until the deadline to submit your application; if you miss the deadline, the system will not allow you to submit.

If you have any problems using proposalCENTRAL, please contact the proposalCENTRAL help line at (800) 875-2562.

Online Registration

The PI as well as the institution's signing official, contracts & grants manager and fiscal contact must be registered in proposalCENTRAL: https://proposalcentral.altum.com/. Start with "Click here to register". Fill out all the necessary fields on the registration page: First Name, Last Name, Email Address, User ID (can be your name), Password (case-sensitive), Challenge Question, and Answer.

Click BOTH BOXES on the bottom of the page to confirm your agreement with their "Terms of Service" and "Acceptable Use Policy." Click on the "Register" button. ProposalCENTRAL will send you an email with your username, password and a confirmation number. Once confirmed, you can login and the first time you enter the system, it will ask you to enter the confirmation number. You won't need that number again.

Online Forms and Fields

Once logged on, select the "Grant Opportunities" (gray) tab on the top of the page. Open up the filter and scroll down to California Breast Cancer Research Program. Sort the available funding by CBCRP and all of the funding opportunities for CBCRP will be showing. Choose the Drinking Water Initiative and click on "Apply Now" at the far right of the line.

Portions of the application are prepared using pre-formatted web pages in proposalCENTRAL (Proposal Sections 1 and 3-8). To move from section to section you can click the "Next" button to both save your work and go to the next section, or click "Save" and then click on the next section.

Proposal Section 2 allows you to download the Templates and Instructions for the CBCRP forms. After completing the forms on your computer, Proposal Section 9 allows you upload each one as PDF to attach it to your application.

❒ Section 1: Title Page

The individual being designated as the Applicant/PI should log onto proposalCENTRAL first to begin the submission process.

On the "Title Page" enter the Project Title in the space provided (do not exceed 60 characters). Enter the total budget amount requested for the project, including indirect costs, if eligible. The projected start date for this project is June 1, 2019. Enter the end date of the project (up to 24 mos).

❒ Section 2: Download Templates & Instructions

This section includes these instructions as well as the relevant application forms. You will need these forms in order to respond to this RFP.

❒ Section 3: Enable Other Users to Access this Proposal

Note: A person must be registered in proposalCentral before s/he can be given access.

Click on "Enable Other Users to Access this Proposal" (the left side in the gray box). Read this page thoroughly to understand the different levels of access you can grant others to your application.

At the bottom of that page, in "Proposal Access User Selection," type in the email address of other individuals who will be working on the application (they should all have completed the registration process prior to being enabled) and then click "Find User."

Select "View," "Edit," or "Administrator" for the level of access they will have.

Click "Accept Changes" to save this page.

❒ Section 4: Applicant/PI

Click on "Applicant/PI" and make sure that all required fields (identified with a red asterisk) are complete. Click "Edit Professional Profile" to enter any missing data. **A required field entitled "ORCID ID" has been added to Professional Profile Page, at the bottom of Section 4: Personal Data for Applications.** ORCID provides a persistent digital identifier that distinguishes you from every other researcher and, through integration in key research workflows such as manuscript and grant submission, supports automated linkages between you and your professional activities ensuring that your work is recognized. If you have not already obtained an ORCID ID number, you may do so here: http://orcid.org/. Once you have done so, please enter your 16-digit identifier in the space provided on your profile page in the following format: xxxx-xxxx-xxxx-xxxx.

Click “Return to Proposal” after entering missing data. Enter the % effort that the PI will devote to this project. The minimum effort is 10% FTE. Click “Save.”

❒ Section 5: Institution & Contacts

On the “Institution & Contacts” page, make sure that all required fields (identified with a red asterisk) are complete, including the Signing Official, Contracts and Grants Official, and Fiscal (Accounting) Contact for the applicant institution. To complete these fields select the name or enter the email address of the individual in each of those roles and click “Add.”

If you add someone, the “Contact Screen - Applicant Institution” screen will open. Make sure that all required fields (identified with a red asterisk) are completed. Click “Save”, then click “Close Window.” Then click “Save” on the Institution & Contacts page.

❒ Section 6: CSO Codes and Keywords

On this page you should select and add CSO codes. There are seven major CSO categories, and each of these is divided into 4-9 sub-categories. The CSO coding scheme is presented in the Web site https://www.icrpartnership.org/cso in the downloads section in the upper right hand corner. Choose a major heading for your research and read the subcategory description. Choose the one that most closely fits. If your project fits under more than one CSO category, add a second code. The second code should represent a different, but integral, part of the research and about half of the total effort.

In addition, add three key words (1-3 words) that describe your project’s main topic, technology, or methods. This helps to place it in the appropriate review committee and assign reviewers. Please use words not in the title.

❒ Section 7: Budget

Provide the total costs for the entire funding request for the grant year on this page. Make sure the budget numbers are exactly the same as those in the provided Excel Budget Summary form that you upload.

❒ Section 8: Organization Assurances

Provide any required information for Human Subjects. If assurances will be required and have not yet been received, mark “pending” and enter the (proposed) date of submission in the “Approved or Pending Date”.

❒ Section 9: Upload RESEARCH PLAN and Other Attachments

This page contains a duplicate list of the forms and instructions that are in Download Templates and Instructions (above and Proposal Section 2). This is where you will upload the CBCRP forms and any other attachments to your proposal; the required items are listed.

To upload attachments, fill in the fields at the top of the page:

- **Describe Attachment:** Provide a meaningful description, such as Jones CV.

- **Select Attachment Type:** From the drop down menu, select the type of form that is being attached.
- **Allowable File Type:** Only an Adobe PDF document may be uploaded. Do not password protect your documents. Help on converting files to PDF can be found on the proposalCentral site at https://proposalcentral.altum.com/FAQ/FrequentlyAskedQuestions.asp.
- **Select File From Your Computer to attach:** The Browse button allows you to search for the PDF on your computer; click Open to select the file.

Note: Explicit instructions on the content of the documents to be uploaded follow in the "Instructions for CBCRP Forms" section.

❒ **Section 10: PI ORCID ID**

This section is a reminder to returning investigators to obtain and enter an ORCID ID number by editing your professional profile using the link that appears here. At the bottom of Section 4 in your profile (Personal Data for Applications), you will find the space to enter your 16 digit ORCID ID number and a link to obtain one if necessary. Please enter the information in the following format: xxxx-xxxx-xxxx-xxxx.

❒ **Section 11: Validate**

This function allows you to check whether all required items have been completed and attached. Don't wait until the last minute to check! Validate often during the course of completing your application so you have time to address missing items. Clicking the "Validate" button will either result in a link to missing items so you can easily go to the page and complete them, or a message at the top of the page "Has been validated and is ready to submit."

❒ **Section 12: Print Face Page When Application Complete**

Applicants must print application's Face Page and obtain the necessary PI and institutional signing official signatures within a week of the electronic submission (see below).

❒ **Section 13: Submit**

Submission is only possible when all required items have been completed and all required forms have been attached. Once an applicant hits "Submit," the application cannot be recalled.

❒ **Outside of proposalCENTRAL: Email Face Page Submission**

The PI, institution's signing official, Contract and Grants official and Fiscal (or Accounting) official all must sign the printed Face Page. Scan the signed form as a PDF and email to RGPOGrants@ucop.edu before 5 pm (Pacific Time) by January 24, 2019.

CBCRP Uploaded Form Instructions

Lay Abstract (REQUIRED)

This item is evaluated mainly in the programmatic review. The Lay Abstract is limited to one page and must include the following sections:

- A non-technical introduction to the research topics
- The question(s) or central hypotheses of the research in lay terms
- The general methodology in lay terms
- Innovative elements of the project in lay terms

The abstract should be written using a style and language comprehensible to the general public. Avoid the use of acronyms and technical terms. The scientific level should be comparable to either a local newspaper or magazine article. Avoid the use of technical terms and jargon not a part of general usage. Place much less emphasis on the technical aspects of the background, approach, and methodology. Ask you advocate partner to read this abstract and provide feedback.

Scientific Abstract (REQUIRED)

This item is evaluated mainly in the peer review. The Scientific Abstract is limited to one page and should include:

- A short introductory paragraph indicating the background and overall topic(s) addressed by the research project
- The central hypothesis or questions to be addressed in the project.
- A listing of the objectives or specific aims in the research plan
- The major research methods and approaches used to address the specific aims
- A brief statement of the impact that the project will have on breast cancer.

Provide the critical information that will integrate the research topic, its relevance to breast cancer, the specific aims, the methodology, and the direction of the research in a manner that will allow a scientist to extract the maximum level of information. Make the abstract understandable without a need to reference the detailed research plan.

Other Review Criteria (REQUIRED)

This item is evaluated in the programmatic review. Limit the text to two pages. The CBCRP Council (who conducts the programmatic review) will NOT see your Research Plan. The information on this template allows the CBCRP Research Council to rate the application for adherence to the objectives of the CBCPI research area as outlined in the specific RFP.

CBCPI Focus (Responsiveness): Provide a clear, brief summary for the CBCRP Council (1 or 2 paragraphs) of how your proposed research addresses the specific RFP topic area, by increasing or building on specific scientific knowledge; by pointing to additional solutions to identify and eliminate environmental causes, and or disparities in, breast cancer; and/or, by helping identify or translate into potential prevention strategies.

Dissemination and Translation Potential: Describe how research findings will be shared with various stakeholder audiences (i.e., policymakers, community members, breast cancer advocates, other researchers/agencies, health care providers, funders etc.). Describe the potential for how the research findings will be translated into policy and/or other practice.

Advocacy Involvement (REQUIRED)

Follow the instructions on the form, and be sure to address the requested three items (Advocacy Organization/Advocate(s) Selection and Engagement to Date, Advocate(s) Role in Proposed Research and Meeting and Payment Plans). Limit the text to one page.

Discuss what involvement, if any, advocates had in the development of this proposal and will have in the project, if funded. Explain how this proposal shows awareness and inclusion of breast cancer advocacy concerns involved in the proposed research.

Letter(s) of Commitment (REQUIRED)

Please use the template as a basis for commitment letters from the advocate, scientific and/or subcontracting individuals/institutions. Limit the text to two pages.

Budget Summary (REQUIRED)

Please enter the budget for the presented categories by year into the summary sheet (Excel format). Additional instructions are presented on the form.

The maximum duration and direct costs may not exceed the following for the RFP *Quantifying Exposures to Hormones of Interest for Breast Cancer Risk in Beef and Drinking Water in California*.

Pilot Project (1 project):	2 years & $220,000

Note: The amount of the subcontracted partner's F&A costs can be added to the direct costs cap. Thus, the direct costs portion of the grant to the recipient institution may exceed the award cap by the amount of the F&A costs to the subcontracted partner's institution.

Personnel. List the PI for the application and "individuals who contribute in a substantive way to the scientific development or execution of the project, whether or not salaries are requested." (NIH definition). Include those at the level of postdoctoral

fellow and higher. Upload a NIH "Biographical Sketch and Other Support" form for each individual listed. The minimum "Months Devoted to Project" required for the PI is 1.2 months (= 10% FTE).

Other Project Expenses. Enter the costs associated with each category presented on the template (description to be provided in Budget Justification).

Advocate(s) Expenses. Include any travel, meeting, and consultation costs/fees associated with advocate engagement.

Equipment. Purchases up to $10,000 are allowed. Only include individual items >$5,000. Any items less than $5,000 must be purchased under the "supplies" budget category above.

Travel Expenses. Requested travel costs must be broken down and justified as Project-related, Annual meeting (third year only) or Scientific meeting (PI only capped at $2,000 per year).

Subcontracts. In the case of University of California applicants, subcontracts need to be categorized and broken out as one of two types, University of California-to-University of California (UC to UC) sub agreements or transfers; or, Other. Both categories require additional description (Budget Justification) and documentation (Appendix).

Service Agreements and Consultants. Both categories require additional description (Budget Justification) and documentation (Appendix).

Pooled Expenses. The RGPO takes a conservative budgeting approach to the allocation of pooled expenses. Pooled expenses such as insurance surcharges, system wide networking surcharges, and other pooled training and facilities expenses are generally disallowed as direct costs. Pooled expenses may be allowed at the discretion of the RGPO Program Director if the grantee can show that: 1) the project to be funded will be directly supported by the pooled expenses, 2) the pooled expenses have been specifically excluded from the indirect cost rate negotiation, and 3) the pooled expenses have been allocated consistently over time within the organization (e.g. it is not allowable to charge a new indirect expense such as "facilities" as a direct line item in order to recoup funds lost due a poorly negotiated rate agreement). No indirect cost recovery will be allowed on pooled expenses.

Indirect (F&A) costs. Non-UC institutions are entitled to full F&A of the Modified Total Direct Cost base (MTDC); UC institutional F&A is capped at 25% MTDC*

> **Allowable expenditures in the MTDC base calculation include salaries, fringe benefits, materials and supplies, services, travel, and up to the first $25,000 of each subgrant or subcontract (regardless of the period covered by the subgrant*

or subcontract). Equipment, capital expenditures, charges for patient care and tuition remission, rental costs, scholarships, and fellowships as well as the portion of each subgrant and subcontract in excess of $25,000 shall be excluded from the modified total direct cost base calculation.

Please see the RFP under **Allowable Indirect (F&A) Costs** for more information.

Budget Justification & Facilities (REQUIRED)

This item is evaluated in the peer review. Limit the text to two pages. Follow the instructions on the template. The minimum "Months Devoted to Project" required for each PI is 1.2 months (= 10% FTE).

Key Personnel (REQUIRED)

This item is evaluated in the peer review. Limit the text to one page. Follow the instructions on the template.

Biographical Sketch & Other Support (REQUIRED)

This item is evaluated in the peer review. Use the NIH form. Limit the length of each biosketch to *no more than* five (5) pages.

Research Plan (REQUIRED)

This section is the **most important** for the peer review. Note carefully the page limits, format requirements, and suggested format.

Page limit: 12 pages

An additional 3 pages is allowed for References.

Format issues: Begin this section of the application using the template. Subsequent pages of the Research Plan and References should include the principal investigator's name (last, first, middle initial) placed in the upper right corner of each continuation page.

The Research Plan and all continuation pages must conform to the following four format requirements:

1. The height of the letters must not be smaller than 11 point; Times New Roman or Arial are the suggested fonts.
2. Type density, including characters and spaces, must be no more than 15 characters per inch (cpi).
3. No more than 6 lines of type within a vertical inch;
4. Page margins, in all directions, must be at least ½ inch.

Use the appendix to supplement information in the Research Plan, not as a way to circumvent the page limit.

Suggested outline:

Introduction and Hypotheses: Provide a brief introduction to the topic of the research and the hypotheses/questions to be addressed by the specific aims and research plan. The relationship of the project to the specific CBCPI Project Type and expectations outlined within the RFP should be clear.

Specific Aims: List the specific aims, which are the steps or increments deemed necessary to address the central hypothesis of the research. The subsequent research plan will detail and provide the approach to achieving each of these aims.

Background and Significance: Make a case for your project in the context of the current body of relevant knowledge and the potential contribution of the research.

Preliminary Results: Describe the recent work relevant to the proposed project. Emphasize work by the PI and data specific to breast cancer, water and non-targeted mass spectrometry.

Research Design and Methods: Provide an overview of the experimental design, the methods to be used, and how data is to be collected and analyzed. Describe the exact tasks related to the Specific Aims above. Provide a description of the work to be conducted during the award period, exactly how it will be done, and by whom. Include a letter of commitment if the applicant PI will be using a data set that they do not control/own. Recognition of potential pitfalls and possible alternative approaches is recommended. How will technical problems be overcome or mitigated? Cover all the specific aims of the project in sufficient detail. Identify the portions of the project to be performed by any collaborators. Match the amount of work to be performed with the budget/duration requested. A timeline at the end will demonstrate how the aims are interrelated, prioritized, and feasible. Explain the use of human subjects and vertebrate animals and show their relationship to the specific aims.

Resources and Facilities: Describe the resources and facilities to be used (e.g., laboratory space, core facilities, major equipment, access to populations, statistical resources, animal care, and clinical resources) and indicate their capacities, relative proximity and extent of availability. Include an explanation of any consortium/ contractual arrangements with other organizations regarding use of these resources or facilities. Describe resources supplied by subcontractors and those that are external to the institution. Make sure all of the research needs described in the research plan are addressed in this section.

Human Subjects (OPTIONAL)

This item is evaluated in the peer review. **This form is required only for applications that use Human Subjects, including those in the "Exempt" category. Use additional pages, if necessary. For applications requesting "Exemption"** from regular IRB review and approval please provide sufficient information in response to item #1 below to confirm there has been a determination that the designated exemptions are appropriate. **The final approval of exemption from DHHS regulations must be made by an approved Institutional Review Board (IRB).**

Documentation must be provided before an award is made. Research designated exempt is discussed in the NIH PHS application: https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general/g.500-phs-human-subjects-and-clinical-trials-information.htm#1.2. The categories of research that qualify for exemption are defined in the Common Rule for the Protection of Human Subjects. These regulations can be found at 45 CFR 46. Many research projects funded by CBCRP fall into Exemption category #4. Even if a grant application is exempt from these regulations, it must, nevertheless, *indicate the parameters of the subject population* as requested on the form.

For applications needing full IRB approval: If you have answered **"YES"** on the Organization Assurances section of the CBCPI Application Face Page and designated no exemptions from the regulations, the following **seven points** must be addressed. In addition, when research involving human subjects will take place at collaborating site(s) or other performance site(s), provide this information before discussing the seven points. Although no specific page limitation applies to this section, be succinct.

1. Provide a detailed description of the proposed involvement of human subjects in the project.
2. Describe the characteristics of the subject population, including its anticipated number, age range, and health status. It is the policy of the State of California, the University of California, and CBCRP that research involving human subjects must include members of underserved groups in study populations. Applicants must describe how minorities will be included and define the criteria for inclusion or exclusion of any sub-population. If this requirement is not satisfied, the rationale must be clearly explained and justified. Also explain the rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, prisoners, other institutionalized individuals, or others who are likely to be vulnerable. Applications without such documentation are ineligible for funding and will not be evaluated.
3. Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.
4. Describe the plans for recruiting subjects and the consent procedures to be followed, including: the circumstances under which consent will be sought and obtained, who will

seek it; the nature of the information to be provided to the prospective subjects; and the method of documenting consent.

5. Describe any potential risks —physical, psychological, social, legal, or other. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.
6. Describe the procedures for protecting against, or minimizing, any potential risks (including risks to confidentiality), and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects on the subjects. Also, where appropriate, describe the provision for monitoring the data collected to ensure the safety of subjects.
7. Discuss why the risks are reasonable in relation to the anticipated benefits to subjects, and in relation to the importance of knowledge that may be reasonably expected to result.

Documentation of Assurances for Human Subjects

In the appendix, if available at the time of submission, include official documentation of the approval by the IRB, showing the title of this application, the principal investigator's name, and the approval date. Do not include supporting protocols. Approvals obtained under a different title, investigator or organization are *not* acceptable, unless they cross-reference the proposed project. Even if there is no applicant institution (i.e., an individual PI is the responsible applicant) and there is no institutional performance site, an USPHS-approved IRB must provide the assurance. If review is pending, final assurance should be forwarded to CBCRP as soon as possible**.** Funds will not be released until all assurances are received by CBCRP. If the research organization(s) where the work with human subjects will take place is different than the applicant organization, then approvals from the boards of each will be required.

Data and Safety Monitoring Boards (DSMB)

Applications that include Phase I-III clinical trials may be required to provide a data and safety monitoring board (DSMB) as described in the NIH policy release, http://grants.nih.gov/grants/guide/notice-files/not98-084.html. This ensures patient safety, confidentiality, and guidelines for continuing or canceling a clinical trial based on data collected in the course of the studies. CBCRP may require documentation that a DSMB is in place or planned prior to the onset of the trial.

Vertebrate Animals (OPTIONAL)

This item is evaluated in the peer review. *This form is required only for applications that use Vertebrate Animals. Limit the text to two pages.*

If you have answered *"YES"* to the Vertebrate Animals item on the Organizations Assurances section of the CBCPI Application Face Page, then following *five points* must be addressed. When

research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Plan. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic and tranquilizing drugs, and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any methods of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If it is not, present a justification for not following the recommendations.

Documentation of Assurances for Vertebrate Animals. Grants will not be awarded for research involving vertebrate animals unless the program for animal care and welfare meets the standards of the AAALAC or the institution has a U.S. Public Health Service assurance. In the appendix, if available at the time of submission, include official documentation of institutional review committee approval showing the title of this application, the principal investigator's name, and the inclusive approval dates. Do not include supporting protocols. Approvals obtained under a different title, investigator or institutions are not acceptable unless they cross-reference the proposed project. If review is pending, final assurances should be forwarded to CBCRP as soon as possible, but no later than June 1, 2019. Funds will not be released until all assurances are received by CBCRP.

Appendix List (OPTIONAL)

Follow the instructions and items list on the template. **The appendix may not be more than 30 pages in length.**

Note that the *research plan must be self-contained* and understandable without having to refer to the appendix. Only those materials necessary to facilitate the evaluation of the research plan or renewal report may be included.

General Funding Policies

Eligibility and Award Limits

1. Any individual or organization in California may submit an application. The research must be conducted primarily in California. We welcome investigators from community organizations, public or privately owned corporations and other businesses, volunteer health organizations, health maintenance organizations, hospitals, laboratories, research institutions, colleges, and universities.
2. We encourage researchers new to breast cancer to apply. Applicants who have limited experience in breast cancer research should collaborate with established breast cancer researchers.
3. PIs who have previously been funded by CBCRP are welcome to apply, but the research aims must be distinct from their previous CBCRP grants.
4. Multiple applications and grant limits for PIs. A PI may submit more than one application, but each must have unique specific aims. For Cycle 25 applicants are limited to a maximum of two (2) grants either as PI or co-PI, and these must be in different award types. The Research Initiative grants are not included in this limit. A PI may have more than one Research Initiative grant in a year.

Policy on Applications from PIs with Delinquent CBCRP Grant Reports

PIs with current CBCRP grant support will not be eligible to apply for additional funding unless the required scientific and fiscal reports on their existing grants are up-to-date. This means that Progress/Final Scientific Reports or Fiscal Reports that are more than one month overdue may subject a Cycle 25 application to possible disqualification unless the issue is either, (i) addressed by the PI and Institution within one month of notification, or (ii) the PI and Institution have received written permission from CBCRP to allow an extension of any report deadlines.

Application Revision Guidelines

A revised application must have the same principal investigator as the original application. When possible it should have the same title as the original application. However, if the specific aims of the project have changed sufficiently, then a modified title may be chosen. A revision submission for all eligible award types (except CRCs) must include a section of not more than 2 pages uploaded as a part of the Research Plan. This section is a summary of the substantial additions, deletions, and changes that have been made. It must also include responses to criticisms in the previous Review Committee evaluation. This material does not count towards the normal page limit for the Research Plan. We also recommend emphasizing in the Research Plan any relevant work done since the previous application. CRC applicants should follow the directions in the CRC application materials regarding resubmissions.

Confidentiality

CBCRP maintains confidentiality for all submitted applications with respect to the identity of applicants and applicant organizations, all contents of every application, and the outcome of

reviews. For those applications that are funded CBCRP makes public, (i) the title, principal investigator(s), the name of the organization, and award amount in a "Compendium of Awards" for each funding cycle, (ii) the costs (both direct and indirect) in CBCRP's annual report, (iii) the project abstract and progress report abstracts on the CBCRP Web site. If the Program receives a request for additional information on a funded grant, the principal investigator and institution will be notified prior to the Program's response to the request. Any sensitive or proprietary intellectual property in a grant will be edited and approved by the PI(s) and institution prior to release of the requested information.

No information will be released without prior approval from the PI for any application that is not funded.

Human Subjects and Vertebrate Animal Use

If a project proposes activities that pose unacceptable potential for human and animal subject risks, then a recommendation either not to fund or to delay funding until the issue is resolved may result.

IRB approval, human subject "exemption" approval, or animal assurance documentation must be provided prior to funding, but is not needed for application review. Applicants are encouraged to apply to the appropriate board or committee as soon as possible in order to expedite the start of the project, and you must do so before or within 21 days of notification that an award has been offered. If all reasonable efforts are not made to obtain appropriate approvals in a timely fashion, funds may be reallocated to other potential grantees' proposed research projects.

Award Decisions

Applicants will be notified of their funding status by April 1, 2019. The written application critique from the review committee, the merit score average, component scores, percentile ranking, and programmatic evaluation are provided at a later time. Some applications could be placed on a 'waiting list' for possible later funding.

Appeals of Funding Decisions

An appeal regarding the funding decision of a grant application may be made only on the basis of an alleged error in or deviation from, a stated procedure (e.g., undeclared reviewer conflict of interest or mishandling of an application). Details concerning the appeals procedure may be obtained from the appropriate Research Administrator (with whom the applicant is encouraged to discuss his/her concerns), the CBCRP Director, or by contacting us through the CBCRP Web site: www.cabreastcancer.org/. The period open for the appeal process is within 30 days of receipt of the application evaluation from the Program office. Contact CBCRP to obtain full information on the appeals process.

Final decisions on application funding appeals will be made by the UCOP Research Grant Program Office (RGPO) Interim Executive Director Julia Arno. Applicants who disagree with the

scientific review evaluation are invited to submit revised applications in a subsequent grant cycle with a detailed response to the review.

Pre-funding Requirements

Following notification by CBCRP of an offer of funding, the PI and applicant organization must accept and satisfy normal funding requirements in a timely manner. Common pre-funding items include:

- Verification of Principal Investigator status from an appropriate institutional official.
- Documentation of 501(c)(3) non-profit organization status for the organizations.
- Documentation of the DHHS-negotiated (or equivalent) indirect cost rate for non-U.C. institutions.
- Supply up-to-date documentation for approved indirect rate (F&A costs) agreements as of the grant's start date and any derived calculations, if applicable.
- Supply any missing application forms or materials, including detailed budgets and justifications for any subcontract(s).
- IRB applications or approvals pertaining to the award.
- Resolution of any scientific overlap issues with other grants or pending applications.
- Resolution of any Review Committee and Program recommendations, including specific aims, award budget, or duration.
- Modify the title and lay abstract, if requested.

Open Access Policy

As a recipient of a California Breast Cancer Research Program (CBCRP) grant award, you will be required to make all resulting research findings publicly available in accordance with the terms of the Open Access Policy of the Research Grants Program Office (RGPO) of the University of California, Office of the President (UCOP). This policy, which went into effect on April 22, 2014, is available below:

RGPO Open Access Policy

The UCOP Research Grants Program Office (RGPO) is committed to disseminating research as widely as possible to promote the public benefit. To that end, all RGPO grantee institutions and researchers grant RGPO a nonexclusive, irrevocable, worldwide license to exercise any and all rights under copyright and in any medium for all scholarly articles and similar works generated as a result of an RGPO grant award, and agree to authorize others to do the same, for the purpose of making their articles widely and freely available in an open access repository. This policy does not transfer copyright ownership, which remains with the author(s) or copyright owners.

Scope and Waiver (Opt-Out)

The policy applies to all scholarly articles and similar works authored or co-authored as a result of research sponsored by an RGPO grant, except for any articles published before the adoption of this policy and any articles for which the grantee institution and/or researchers entered into an incompatible licensing or assignment agreement before the adoption of this policy. Upon

express written request of the institutional grantee and/or researcher, RGPO will waive the license for a particular article or delay "open access" to the article for a specified period of time.

Deposit of Articles

To assist the RGPO in disseminating and archiving the articles, the grantee institution and all researchers to the grant award will commit to helping the RGPO to obtain copies of the articles that are published as a result of an RGPO sponsored grant award. Specifically, each author will provide an electronic copy of his or her final version of the article to the RGPO by the date of its publication for inclusion in an open access repository, subject to any applicable waiver or delay referenced above. Notwithstanding the above, this policy does not in any way prescribe or limit the venue of publication.

Grant Management Procedures and Policies

Details concerning the requirements for grant recipients are available in a separate publication, the University of California, Office of the President, "RGPO Grant Administration Manual." The latest version of the Manual and programmatic updates can be obtained from the Program's office or viewed on our Web site: http://www.ucop.edu/research-grants-program/grant-administration/index.html.