UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Washington, DC 20207

Memorandum

Date: January 2, 2008

To: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences (HS)

Through: Lori E. Saltzman, M.S., Division Director, HS

FROM: Sandra E. Inkster, Ph.D., Pharmacologist, HS
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SUBJECT: HS Staff Assessment of the Final Technical Report, *Risks of Hyperthermia Associated with Hot Tub or Spa Use by Pregnant Women* (Christina Chambers, Ph.D., M.P.H., under CPSC Contract No. CPSCS041343), and Staff Recommendations

Purpose

The purpose of this memorandum is to

a) provide the U.S. Consumer Product Safety Commission (CPSC) staff's assessment of the contract report, *Risks of Hyperthermia Associated with Hot Tub or Spa Use by Pregnant Women* (June 2005), authored by Christina Chambers, Ph.D., M.P.H. (Appendix);
b) respond to public comments submitted on this report; and
c) as deemed necessary, recommend changes to appropriate voluntary standards on spas/hot tubs.

This memorandum is organized as follows:

I. Background
II. Contractor's Technical Report
III. Response to Public Comments on the Technical Report
IV. CPSC Staff's Conclusions on the Technical Report and Recommendations Related to Hot Tub/Spa Use and Hyperthermia in Pregnancy
V. Summary of Additional Safety Concerns Related to Spa Water Temperatures
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I. Background

After a discussion with the National Sanitation Foundation (NSF) in November 2003, the CPSC Health Sciences (HS) staff conducted a preliminary review of the potential developmental effects of hyperthermia (elevated body temperature) in

pregnant women resulting from spa/hot tub use. At that time, NSF was interested in developing a protocol for testing spas and hot tubs and requested input from CPSC staff. Pursuant to these discussions, it was apparent that the maximum allowable water temperature for bathing/soaking areas of spas, 40°C (104°F), as specified in the Underwriters Laboratories (UL) standard for spas (UL 1563[1]), might be exceeded unknowingly by consumers during normal operating conditions. This is possible because the standard allows a maximum water temperature tolerance of ± 3°C (± 5°F), so that in fact, the spa water temperature can reach 109°F (43°C) and still meet the standard. Primarily for this reason, CPSC staff decided to revisit the issue of spa water temperature limits[2]. Other factors that also favored a reassessment of the water temperature limits include wider availability and reduced cost of superior electronically-controlled thermostat technology, which can allow tighter tolerance limits, an increase in consumer use of spas, and the 16 year-long interval since the staff's previous assessment of the scientific literature on hyperthermia, during which time there has been a growing awareness among the scientific community of the adverse effects of maternal hyperthermia on embryonic and fetal development.

Subsequent to the NSF discussions, CPSC staff awarded a contract to obtain expert opinion on the effects of maternal hyperthermia on the embryo/fetus. The purpose of the contractor's work was to assist staff in its evaluation of the appropriateness of current performance requirements concerning the water temperature limit and its regulation in hot tub/spa bathing areas, as well as any future proposals concerning these requirements in the appropriate voluntary standards.[3]

The contract (contract number CPSCS041343) was awarded to Christina Chambers, Ph.D., M.P.H. in the Fall of 2004. The objective of the contract was to review relevant scientific and technical literature to assess the likelihood that use of a

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[1] UL 1563 *Standard for Safety for Electric Spas, Equipment Assemblies and Associated Equipment*, 5th Edition, Underwriters Laboratories, Inc., Northbrook, IL 60062-2096, March 8, 2004.

[2] Health Sciences (HS) staff is not clear when UL first applied the ± 3°C (± 5°F) tolerance to CPSC staff's recommended temperature limit of 40°C (104°F). However, it is specifically noted on page 7 of the Engineering Sciences (ES) staff input memo to the petition for Hot Tubs and Spas, CP 90-2 (L. Fansler, memorandum to S. Kyle, dated October 4, 1991) that it was present in the UL 1563 standard and the draft NSPI standard at least 15 years ago. In fact, the same ES staff memo specifically questioned the technical reason for allowing this wide tolerance, noting it allowed water temperature to reach 43°C (109°F), and emphasizing the need for an accurately calibrated thermometer to maintain a temperature of 40°C (104°F). The HS staff input memo for the same Hot Tub and Spa Petition briefing package specifically addressed one of the petitioner's requests, to reduce the recommended maximum spa water temperature to 38.9°C (102°F) (from 40°C (104°F)); it did not address the ± 3°C (± 5°F) tolerance limits allowed in the UL standard (S. Kyle, memorandum to A. Ulsamer, dated May 7, 1991).

[3] HS staff notes that three ANSI/NSPI (National Spa and Pool Institute) standards published in 1999 relate to the temperature limit, and regulation of water temperature, in the bathing area of hot tubs/spas. These standards (ANSI/NSPI 2, *Public Spas*, ANSI/NSPI-3, *Permanently Installed Residential Spas*, and ANSI/NSPI-6, *Portable Spas*) each incorporate harmonized, summary temperature requirements relating to both electric and fossil fuel-heated hot tub/spa units. These requirements are based on the Underwriters Laboratories (UL) standards UL 1563, *Standard for Safety for Electric Spas, Equipment Assemblies and Associated Equipment* and UL 372, *Primary Safety Controls for Gas and Oil-Fired Appliances*, respectively.

spa or hot tub might cause maternal hyperthermia resulting in adverse developmental effects, particularly neural tube defects, in the human embryo/fetus. The contract's Statement of Work (SOW) specified discrete tasks to be accomplished. The contractor was required to:

a) Conduct a comprehensive literature search and a critical review of the literature to independently assess the possible effects of hyperthermia from spa or hot tub use on the pregnancy and pregnancy outcome. Particular attention was to be given to the development of neural tube defects (NTDs) in humans;
b) Recommend to the CPSC staff the maximum temperature and use conditions for a hot tub/spa, considering that pregnant women may use it and may be unaware of the medical recommendations to limit their use of a hot tub/spa, and may be unaware of the temperature of the hot tub/spa;
c) Comment on whether the current UL standard maximum set point temperature of 40°C (104°F) with a tolerance of ± 3°C (± 5°F) is sufficiently protective, i.e., whether a possible maximum temperature of 43°C (109°F) is sufficiently protective for pregnant women and the embryo/fetus; and
d) Comment on whether the UL 1563 /ANSI NSPI-2,3,6 maximum allowable temperature of 40°C (104°F) is sufficient or should be set lower, i.e., to a maximum allowable temperature of 38.9°C (102°F), including tolerance. A maximum allowable temperature of 38.9°C (102°F) is recommended by the Organization of Teratology Information Services (OTIS, 2003).

The final report was received from Dr. Chambers in June 2005. It was posted on the CPSC website for public comment in Spring 2006. The public comments received are listed below in Table 1. They are summarized and discussed in Section III of this memorandum.

Table 1. Public Comments on Chamber's Hyperthermia Contract Report

Comment	Name	Affiliation
1	Anthony Scialli, M.D.	Teratology Society, Public Affairs Committee Chairman
2	Morton Miller, Ph.D.	University of Rochester, School of Medicine and Dentistry
3	Gary Siggins	Underwriters Laboratories

After reviewing the findings and recommendations of Dr. Chambers, considering the public comments received on her report, reviewing the recommendations of prior CPSC staff and other medical and public health organizations and professional societies related to birth defects, and participating in UL Standards Technical Panel (STP) discussions on this topic, HS staff formulated recommendations and suggestions for next steps, which can be found in Section IV of this memorandum.

II. Contractor's Technical Report

The contract report by Dr. Christina Chambers, *Risks of Hyperthermia Associated with Hot Tub or Spa Use by Pregnant Women* (June 2005), is found in the Appendix of this memorandum.

III. Response to Public Comments on the Technical Report

CPSC staff posted the Chambers report on the CPSC website for 45 days of public comment, closing June 1, 2006. The submitted comments are on file in the CPSC Office of the Secretary. A listing of those who commented is found in Table 1. No comments were received that disagreed with the technical review of the teratogenic data or the recommendations of Dr. Chambers. Comments were received from a professional society of physicians and scientists involved with birth defects research and treatment; a medical school professor; and a standards writing and testing organization. The comments and CPSC staff's responses are summarized below.

A. Commenter: Public Affairs Committee of the Teratology Society
Submitted by Anthony R. Scialli, M.D., Committee Chairman

Comment: The commenter considers the Chambers report to be accurate and current with regard to the science of birth defects research. Dr. Scialli and the Public Affairs Committee of the Teratology Society agree with the findings in the Chambers report. The commenter recommends that women of reproductive age not elevate their core body temperatures.

The commenter states that instructions and campaigns aimed at informing women who are pregnant or planning to become pregnant will not be fully effective because almost half of the pregnancies in the U.S. are unplanned. Hyperthermia could occur before a woman knows that she is pregnant, and thus, warnings to avoid spa use during pregnancy would be ineffective. Hyperthermia effects, such as failure of the neural tube to close, occur during these early weeks of pregnancy.

The commenter also notes that studies of hot tub effects on core temperature have not been performed on pregnant women and it may be that physiological changes occurring during pregnancy may influence the susceptibility of women to increases in core temperature.

Response: CPSC staff agrees with the opinion submitted regarding the incomplete effectiveness of public information campaigns.

B. Commenter: Morton W. Miller, Ph.D.
Research Professor in Obstetrics and Gynecology, Department of Obstetrics and Gynecology, University of Rochester, School of Medicine and Dentistry

Comment: The commenter is concerned that the Chambers report does not discuss the literature regarding the mechanisms of hyperthermia-induced birth defects. He states that understanding the mechanism involved will allow a risk calculation, and he provides hypothetical birth defect outcomes for increases in core temperature of 0, 1, 2, 3, or 4°C for a 5-minute exposure.

The commenter notes that two in-depth reviews have been published by the National Council on Radiation Protection and Measurements (NCRP) (1992, 2002) that are relevant to the understanding of the mechanisms involved. He states that the NCRP Report (2002) suggested that it is the temperature elevation *above* core body temperature that is important and not just the core temperature *per se*.

The commenter states the calculation of a "thermal dose," which considers the temperature elevation above core and the duration of this elevation, can be performed. This would allow comparison of inter- and intra-species data collected under various experimental hyperthermic conditions by normalizing them to a constant factor. Further, the commenter indicates that an estimate of the activation energy required for different specific birth defects might also be derived from the data and could be used to estimate the risk of such defects occurring in different species at specific temperature elevations and durations.

The commenter does not differentiate when applying the calculation to core temperature fluctuations during normal pregnancy, maternal fever, or short-term acute insult, such as might occur during spa use. The commenter states that once an activation energy is determined for a specific outcome, the risk can be determined for any combination of timed temperature elevation and the extent of elevation. There would be no threshold, and any temperature elevation for any duration would have some effect. He notes that it might be difficult to observe effects at low temperature elevations due to the large numbers needed to observe an effect. Any effect would be more easily detected at higher temperature elevations. He specifically notes, "Of course, with sauna users and hot tub bathers, the number of pregnant users is potentially large, and thus the number of affected *in utero* embryos/fetuses would not be inconsequential, even at +2°C for 5 minutes."

Response: While the information provided by Dr. Morton may be useful in a risk assessment, specifically in performing a dose-response analysis, this was not the task required in the contract. Dr. Morton agrees with Dr. Chambers that there is no differentiation between the source of maternal hyperthermia (fever, spa use, etc.). His suggestion that there is not a threshold effect for temperature elevation is interpreted by staff to mean that his view is that every increase in core body temperature could be associated with a deleterious effect on the embryo.

3. Commenter: Underwriters Laboratories, Inc.
   Submitted by Gary Siggins, Principal Engineer, Swimming Pool, Spa, and Whirlpool Bath Equipment

Comment: The commenter provides clarification of the spa standard (UL 1563) in the section that discusses the temperature of the water at the inlet. Specifically, he notes that the report inaccurately describes the function of the temperature limiting controls. He states that these controls only function in the event that the temperature-regulating control fails and not under normal use.

The Chambers report states that the maximum allowable water temperature at any inlet jet is 50°C (122°F) with a tolerance of not more than 3°C (5°F). The commenter indicates that the tolerance of 3°C (5°F) is already included in the 50°C (122°F) limit and should not be added to this value.

In addition, the commenter notes that although the Chambers report (Section VII *Conclusions and Recommendations*) recommends that the spa's temperature regulation system should ensure that the maximum water temperature achieved at a given setting is not exceeded due to significant variability in the temperature control mechanism, there will always be some variability in actual spa water temperature above/below the set point.

He further states that the Chambers report neglects to mention the warnings for pregnant women that are contained on the product and in the user safety instructions. These instructions specify that pregnant women should limit their exposure to 10 minutes, keep the water temperature at 38°C (100°F), and check the spa temperature with an accurate thermometer before use.

The commenter specifies that:

a) "UL 1563 recommends that all users measure the water temperature with an accurate thermometer before entering the spa, since the precision of temperature-regulating devices vary,"
b) "Markings and instructions enable informed judgment on individual use of spas," and
c) "Pregnant women and other users with special limitations should always check the actual water temperature before entering the spa to determine whether it is within the guidelines set by their physician."

Response: The commenter indicates that the tolerance of 3°C (5°F) is included in the 50°C (122°F) maximal water temperature at the inlet jets, and should not be added to the limit. The inconsistent treatment of tolerance factors, in different sections of the standard, is confusing. Part 33.1 of Section 33, *Temperature-Regulating Controls*, requires the maximum water temperature-regulating control set point to correspond to a water temperature of 40°C (104°F) in the tub, and part 33.6 provides a tolerance of ±3°C (± 5°F) for the temperature-regulating control. Part 34.1(a) of Section 34, *Temperature-Limiting Controls*, limits the water temperature at the inlet to the tub to a maximum of 50°C (122°F), and part 34.1(d) notes that the maximum temperature limit setting has an identical tolerance of ± 3°C (± 5°F). The performance test requirements for compliance with Section 33.1 are described in Section 49, *Water Temperature Test.* Part 49.1.a) states "the maximum water temperature at any suction fitting or skimmer

does not exceed 43°C (109°F)" indicating that **the tolerance factor ± 3°C (± 5°F) has been added** to the 40°C (104°F) limit specified in 33.1. Part 49.1.b) states "the maximum water temperature at any inlet to the tub does not exceed 50°C (122°F)"; **it is unclear if this includes tolerance.** The performance test requirements for compliance with Section 34 are described in Section 50, *Abnormal Water Temperature Tests.* Part 50.1.1 indicates that when the test is started using the highest water temperature recorded in test 49.1 (up to 43°C (109°F)), the water temperature at any inlet to the tub cannot exceed 50°C (122°F); again, it is **unclear if this includes tolerance.** From further discussions with UL, CPSC staff now understands that the maximum allowable water temperature at any inlet jet is 50°C (122°F) **including 3°C (5°F) tolerance.** However, the discrepant treatment of the tolerance factors within the standard caused confusion for Dr. Chambers and CPSC staff. CPSC staff believes that use of a consistent approach in UL 1563, for either inclusion or exclusion of tolerance for **all** maximum temperature specifications, is warranted.

The staff concurs with the comment on inherent variability of the spa water temperature. CPSC staff understands that there will always be some variability in the water temperature so that it may fall above or below the set point. This variability may be due to thermostatic control (on/off) or heat loss to the environment. However, staff does not believe that this variability should exceed the temperature limits required to ensure that significant health effects will not occur in a sizable percentage of the general population, i.e., pregnant women. Staff does not have data on the number of spa users, but considers it reasonable to assume that more than a trivial number are women of reproductive age (pregnant or able to become pregnant). While some variability in water temperature is acknowledged as the best that the technology can currently offer, staff believes that in the 25 years since UL 1563 was originally approved, design of temperature regulation systems has improved such that a ± 3°C (± 5°F) tolerance is not necessary. Indeed, some industry representatives have indicated to CPSC staff that modern electronic thermostat designs can attain tolerances of 0.5 to1°C (1 to 2°F).

With regard to the commenter's concern that the Chambers report does not indicate that *"UL 1563 requires on-product warnings and user safety instructions that instruct pregnant women"* about specific temperature and exposure time limits, and their need to check water temperatures with an accurate thermometer, staff believes this wording is misleading. Staff acknowledges that the user manual safety instructions are required to include information that excessive temperatures can cause fetal damage, and advice for pregnant, or possibly pregnant, users to limit water temperature to 38°C (100°F) (section 72.3.11.b). Staff also acknowledges that UL 1563 requires manufacturers to supply, with each spa unit, a separate safety sign, suitable for outdoor use, which includes a specific warning for pregnant users to limit their soak duration to 10 minutes (section 71.9). However, staff notes that this separate sign does not provide any guidance on recommended temperature limits for pregnant women, and though the need to provide visible warnings to occasional spa users is explained in accompanying materials, the actual use and placement of the separate sign is left to the discretion of the owner. Regarding the on-product labels required in UL 1563, staff disagrees that they provide any specific guidance for pregnant women. Staff's reading of UL 1563

finds that there is no required information, relating to safe water temperatures and exposure time limits for pregnant women, in either (1) the temporary, removable, on-product safety warning required on the inside tub surface of new products (UL 1563, section 69) or (2) the additional safety marking, specified in section 70, to be placed adjacent to the permanent, general information markings (manufacturer, model, production date, etc.) required in section 67.1. Furthermore, section 67.1 allows the general information marking, and therefore the additional safety marking, to be positioned either on or ***inside*** the spa's service door. Overall, CPSC staff considers that UL 1563 provides no guarantee, and probably a low likelihood, that pregnant spa users who are not the primary owners, will have access to, or opportunity to read, the important safety information relating to dangers of hyperthermia during pregnancy.

In spa units where water-temperature controls display only the selected temperature and do not provide an actual temperature reading of the water, but allow a tolerance of the magnitude allowed in UL 1563, it is very easy for a woman to find herself in water exceeding the 39°C (102°F) recommendation for pregnant women by as much as 3°C (5°F). Staff does not believe that the onus should be on the consumer to purchase a thermometer to determine whether the temperature of the tub water is within acceptable limits. Further, staff is unaware of any studies that have examined whether spa-users of child-bearing age would understand the reasons for, and appreciate the potentially grave consequences of, not manually checking the spa water with a hand-held thermometer, as opposed to reading the setting on the temperature control and trusting that the device is accurate.

IV. CPSC Staff's Conclusions on the Technical Report and Recommendations Related to Hot Tub/Spa Use and Hyperthermia in Pregnancy

Dr. Chambers' literature review presents conclusive evidence of a teratogenic effect of maternal hyperthermia in multiple, non-human, animal species. Staff concludes that despite some negative research study findings in epidemiology studies, Dr. Chambers' review provides persuasive evidence that the potential for teratogenic effects of maternal hyperthermia due to hot tub/spa use cannot be discounted. These conclusions have been reached by a number of groups and are consistent with the findings of the CPSC staff in its briefing package to the Commission in 1992. In addition, OTIS and the medical community caution pregnant women against the use of hot tubs/spas when water temperature exceeds 39°C (102°F). Since most pregnancies in the United States are unplanned (CDC 2006), women may enter a hot tub without being aware that they are pregnant, thus increasing the likelihood of adverse effects to the embryo.

Staff concurs with Dr. Chambers that the current performance requirements of UL 1563 are misleading. The maximum tub water temperature allowed is suggested by the maximum marked setting of (and the maximum set point for) the adjustable temperature-regulating control, which is 40°C (104°F). This apparently "corresponds to a water temperature of 40°C (104°F) in the tub" (per UL 1563, section 33, *Temperature-Regulating Controls,* 33.1). The requirements in the UL standard do not require that

users be informed that a tolerance of ± 3°C (± 5°F) applies to this maximum setting of the tub water temperature-regulating control. Greater accuracy and precision of temperature regulation are warranted because at, and above, water temperatures of 39°C (102°F) a further temperature elevation of 3°C (5°F) can have a potentially catastrophic impact on a developing embryo.

The current UL 1563 standard provides no level of assurance that the water temperature will be the same as the user-selected temperature setting. There is intrinsic temperature variability within the spa due to differences near the hot water inlet to the tub and constant loss of heat at the water-air interface, as well as gradients due to depth and mixing of the water. As Dr. Chambers reported, there may also be differences between the actual spa water temperature and the user-selected, thermostatically-controlled, temperature set point because of a built in tolerance of up to ± 3°C (± 5°F) that is allowable under UL 1563. Staff believes that public health is not protected when the "set point" already exceeds recommended temperatures for pregnant women due to intrinsic variability of controls.

CPSC technical staff has raised concerns regarding UL 1563 with UL representatives and the members of the UL STP. CPSC staff suggests continued work with UL to tighten the water temperature tolerances in UL 1563, and to ensure a consistent approach is used throughout the standard when referring to tolerance limits associated with any maximum water temperature specification. CPSC staff also suggests that UL consider upgrading UL 1563 to require that an accurate thermometer be incorporated into the spa design to replace the current UL recommendations advising owners to use an accurate hand-held thermometer to check the spa water temperature before entering the tub area. Simply recommending that a consumer purchase a thermometer is not sufficient. For discussion purposes, UL should consider (1) incorporating appropriate physical properties for such a thermometer to ensure accuracy and longevity of performance in the spa environment, and (2) designating the appropriate placement of the thermometer in the tub for the most accurate reading. Finally, staff suggests that UL enhance its requirements for safety messages addressed in on-product markings, to ensure that safety information concerning dangers of hyperthermia in pregnancy will be visible to at-risk users.

V. Summary of Additional Staff Safety Concerns Related to Spa Water Temperatures

In addition to the potentially catastrophic impact of spa-induced hyperthermia on fetal development, CSPC staff has identified other safety concerns related to spa water temperature. Staff believes that further investigation by UL, industry, government, and other interested parties may be warranted to gain greater understanding of, and to ensure adequate information is provided to all users alerting them to, water temperature-safety issues associated with spa products.

Other Hyperthermia-Specific Concerns: Populations known to have an inherent, increased risk of developing hyperthermia in spa environments, due to their

physiological condition, include: children, the elderly, and individuals with certain medical conditions (e.g., cardiovascular disease, hypertension, diabetes, etc.). Others at increased risk include individuals with depressed cognitive function (e.g., from using certain drugs and/or alcohol) and individuals who are dehydrated (e.g., following exercise). Even if the spa water temperature does not reach the current recommended maximum limit of 40°C (104°F), the general population of spa users is also at risk of developing hyperthermia if they remain soaking in spa tubs for excessively long periods. Staff believes it may be appropriate to develop guidance on recommended temperatures and exposure limits for specific at risk groups, as well as the general population of spa users; staff considers such information should be readily available, and clearly conveyed, to all spa users.

Sanitation Issues: The balance between reducing spa users' risk of adverse hyperthermia-related effects versus risk of exposure to harmful microorganisms should be carefully assessed. CPSC staff is aware of the need for minimum temperatures in hot tubs/spas for both the satisfaction of the users and in order to maintain conditions that inhibit the growth of potentially harmful microorganisms in the spa. Infections of the skin and respiratory system, caused by Pseudomonas, Legionella and mycobacterial pathogens have occurred with spa use[4]. One paper notes that *"The high temperature of water in spas makes them particularly vulnerable to depletion of disinfectant, which facilitates pathogen amplification. Pathogens such as Pseudomonas spp. can multiply rapidly when the disinfectant residual falls below 0.5 mg/L or the pH rises above 8.0. Pathogens also can reside in biofilm layers that form in spa pipes and surfaces, where they can be protected from disinfection, which necessitates routine scrubbing and maintenance to decrease biofilm formation"* (CDC-MMWR, 2004). Staff considers that further work may be warranted to determine appropriate minimum average temperature settings for spas in conjunction with disinfectant levels and pH that properly sanitize the water or inhibit growth for harmful microorganisms. It could be helpful for stakeholders to assess whether it is feasible to incorporate a sanitation/sterilizing cycle into the hot tub functions without endangering users.

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[4] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4948a2.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5325a2.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5308a1.htm

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Appendix

Risks of Hyperthermia Associated with Hot Tub or Spa Use by Pregnant Women

by

Christina Chambers, Ph.D., M.P.H

(Contract Report for CPSC Contract No: CPSCS041343)

Risks of Hyperthermia Associated with Hot Tub or Spa Use by Pregnant Women

Technical Report prepared by Christina Chambers, Ph.D., M.P.H.
Under Contract to
U.S. Consumer Product Safety Commission
Contract Number CPSCS041343
June, 2005

Table of Contents

I. Introduction and Purpose of the Report

Birth defects are the leading cause of infant mortality in the United States, accounting for more than 20% of all infant deaths. Of about 120,000 U.S. babies born each year with a birth defect, 5,600 die during their first year of life. In addition, birth defects are the fifth-leading cause of years of potential life lost and contribute substantially to childhood morbidity and long-term disability. Although the cause of about 70% of all birth defects is unknown, some defects are known to be caused by maternal exposures to certain environmental agents during pregnancy (Centers for Disease Control and Prevention, 2005).

Environmental causes of birth defects and other adverse reproductive outcomes (also known as teratogens) are by definition preventable if the environmental cause that confers increased risk for these negative outcomes can be avoided. Maternal hyperthermia or elevated maternal body temperature has been identified in several studies as an environmental cause of major birth defects, as well as a wider pattern of adverse reproductive outcomes. The most commonly reported category of major congenital anomalies linked with elevated maternal body temperature is central nervous system defects that involve improper closure of the neural tube. These defects may be incompatible with fetal or newborn life. If the fetus survives, neural tube defects almost always require surgical correction, and the associated morbidity can represent lifelong disability.

This report was requested by the U.S. Consumer Product Safety Commission staff to provide an overview and critical assessment of the literature with respect to the technical specifications and typical use of hot tubs or spas by women of reproductive age. The specific focus of this review is to assess the evidence for an increased risk of neural tube defects in the offspring of women who use hot tubs or spas while they are pregnant.

II. Exposures and Outcomes – Primary and Secondary

The primary exposure that is the focus of this critical review is hot tub or spa use. However, since there is a paucity of data on this specific exposure in human pregnancy, studies that focus on maternal hyperthermia resulting from fever associated with illness, and to a lesser extent sauna use will be cited and used for extrapolation. Animal studies that involve manipulation of environmental temperatures will also be cited. However, human studies that focus on other potential sources of elevated maternal body temperature, such as electric blanket use, workplace or occupational exposures, exercise-induced hyperthermia, and localized hyperthermia associated with diagnostic ultrasound were not considered as primary to this review – and may be mentioned only secondarily.

The endpoint that is the focus of this critical review is the group of congenital anomalies that comprise neural tube closure defects (NTDs). The number of studies, and to some

extent the most compelling human evidence, exists for this outcome of pregnancy in association with maternal hyperthermia. However, secondary endpoints that will be reviewed to a lesser extent include spontaneous abortion or stillbirth, and other major congenital anomalies such as heart defects.

For purposes of this review, temperatures will be expressed in degrees Celsius (C); however, a Fahrenheit conversion table is provided for reference in the appendices.

III. Principles of Teratology Used for the Review

Established principles of teratology will be utilized as a basis for discussion of findings of published studies cited in this review. These principles as set forth by Wilson and Fraser (1977) include:

1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.

2. Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.

3. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).

4. The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.

5. The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).

6. Manifestations of abnormal development increase in degree as dosage of the teratogenic agent increases from the no-effect to the totally lethal level.

With respect to the primary endpoint for this review, it is relevant to the second principle that the timing of neural tube closure in the human embryo is between the second and fourth week of development following conception. For other major defects, such as heart defects or oral clefts, the critical window for exposure may extend from two weeks post-conception to nine weeks, or near the end of the first trimester.

IV. Approach to the Literature Review

We conducted 12 searches of Medline/PubMed using the National Library of Medicine's MESH terms. All searches were set for Publication Date from 1960 to 2004.

Selected articles were exported in Medline format and imported to an EndNote library with duplicates excluded. The following searches were performed:

1. Abnormalities and Heat/adverse effects and Pregnancy Trimester, First

2. Abnormalities and Fever/complications and Pregnancy Trimester, First

3. Abnormalities and Hyperthermia, Induced/adverse effects and Pregnancy Trimester, First

4. Embryonic and Fetal Development and Heat/adverse effects

5. Embryonic and Fetal Development and Fever/complications

6. Embryonic and Fetal Development and Hyperthermia, Induced/adverse effects

7. Abnormalities and Heat/adverse effects and Pregnancy

8. Abnormalities and Fever/complications and Pregnancy

9. Abnormalities and Hyperthermia, Induced/adverse effects and Pregnancy

10. Abnormalities and Heat/adverse effects and Pregnancy Complications

11. Abnormalities and Fever/complications and Pregnancy Complications

12. Abnormalities and Hyperthermia, Induced/adverse effects and Pregnancy Complications

Additional searches were conducted using key publications to determine if other publications that had included the key paper in citations (Web of Science) were relevant. Research librarian assistance was secured to review alternative databases to determine if relevant publications may have appeared in the literature but were not indexed in Medline/PubMed. References in the English language literature, or with English abstracts, were downloaded into an Endnote library, and all abstracts were reviewed in detail for relevance to the topic. The full text articles for those abstracts selected for retention in the library were then obtained and reviewed in their entirety.

The searches, initially conducted on November 2, 2004, yielded 361 articles (including duplicates) of which 155 were determined to be of interest and are included in the Endnote library. Within the library, 104 articles are labeled "Full Text Review" and were critically reviewed in their entirety; 14 are labeled "Foreign Language" for which only abstracts were reviewed; 36 are labeled "Additional Articles of Interest" for which only abstracts were reviewed, and 1 article is listed as "Unavailable" and could not be obtained in full text form. The subset of articles in this library which have been cited in this technical report are referenced at the end of the report, and hard copies of the full text of these manuscripts are supplied with the report.

V. Summary of Evidence in Key Areas of Research

a. Animal Data

Dating back to the 1960's, Marshall Edwards, an Australian veterinarian, first noted that pregnant guinea pigs that were exposed coincidentally to unusually high environmental temperatures had a remarkably high incidence of adverse pregnancy outcomes. This astute observation led to numerous experimental animal studies designed to confirm the association, and to further define the relationship between the dose or height of maternal temperature elevation and the length of exposure required to induce abnormalities (Edwards et al, 1995; Graham et al, 1998).

As summarized in Table 1 attached, a wide variety of species including guinea pig, rat, rabbit, mouse, hamster, bonnet monkey, and sheep have demonstrated susceptibility to elevated maternal body temperature in the induction of a wide variety of adverse reproductive outcomes. Increased risks for these outcomes noted in animal studies are consistent with each of Wilson's principles of teratology. Of particular importance, susceptibility to specific outcomes with the experimental manipulation of temperature is consistent with the second principle – that susceptibility depends on the developmental stage at the timing of exposure. Thus, for example, the highest risk for neural tube defects in the guinea pig is with exposure at day 13 (Cawdell-Smith et al, 1992).

Also of critical importance is the consistent finding in the animal literature that, above a certain threshold dose, the combination of increasing dose and/or increasing duration of exposure to maternal hyperthermia is related to increased risk for abnormal embryonic development. This is consistent with the sixth principle of teratology – that manifestations of abnormal development increase in degree as dosage of the teratogenic agent increases from the no-effect level to the totally lethal level. Thus, for example, an increased risk for neural tube defects, facial clefting, and other defects is seen in the Sprague-Dawley rat only at core temperature increases above 2.0 degrees C over baseline. Furthermore, an increase in core temperature of 3.0 degrees C above baseline is sufficient for teratogenesis for exposures lasting at least 20 minutes, whereas an increase in core temperature of 4.0 degrees C above baseline is sufficient for teratogenesis after only 5 minutes duration of exposure (Germain et al, 1985).

In addition to the apparent threshold of about 2 degrees C elevation in body temperature across animal species, it is important to note that the increase in core body temperature that is induced by an environmental exposure to a heat source in animal studies is maintained for a period of time beyond removal of the source of heat. Thus repeated exposures with short intervals away from the heat source may not allow the mother to return to normal body temperature and may exacerbate the effects of hyperthermia.

The first principle of teratology indicates that susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors. This principle often is used to explain findings in animal studies that are inconsistent across species and inconsistent with human data regarding the same exposure. However, across species there is remarkable consistency in the animal literature in the spectrum of congenital anomalies that are seen with increased frequency, including neural tube defects, and the magnitude of temperature elevation required to induce a measurable excess of these defects. These findings suggest cross-species similarities with respect to susceptibility, but nevertheless, as the first principle of teratology indicates, human data is required to demonstrate human susceptibility to teratogenesis, and especially to define the dose and duration required to confer increased risk for congenital anomalies.

b. Human Data

i. Maternal fever or febrile illness

The earliest human evidence in support of Edwards' initial animal data was based on a case series published by Smith et al in 1978. The case series identified a pattern of defects associated with exposure between four and six weeks' gestation and another pattern of defects associated with exposure between 7 and 16 weeks' gestation. These patterns included microphthalmia, oral clefts, limb abnormalities, and central nervous system problems. The sources of hyperthermia exposure were primarily high fever – on the order of 38.9 ° C for at least 1-2 days in duration, although there was one case included in the series of hyperthermia exposure in association with sauna use. This series lent compelling support to human susceptibility to the teratogenic effects of maternal hyperthermia because a specific pattern of defects was noted, with specific timing of exposure and an apparent threshold dose – findings consistent with the 2nd, 3rd, 4th and 6th principles of teratology. Of particular significance was that 12 of the 13 cases in the series were associated with maternal febrile illness, while only one case was associated with maternal sauna use.

Subsequently, several case control studies appeared in the literature testing the hypothesis that maternal fever is associated with birth defects. Case control studies in birth defects epidemiology are typically constructed with cases that manifest a single major malformation, or category of malformations. Cases are then compared to controls consisting typically of non-malformed infants. The limitations of case control studies in establishing cause and effect are well described and include the possibility of recall bias (that mothers of malformed infants may be motivated to recall differently than mothers of normal infants, and that both case and control mothers may have poor or inaccurate recall about the timing, duration and magnitude of any

temperature elevation that occurred months to years prior to the study interview). These limitations are further amplified with an exposure like hyperthermia which is often difficult or impossible to validate from any source other than maternal report (Christensen, 2002). In observational studies which rely on maternal report of a febrile illness that has already occurred, pregnant women may not have taken and recorded their own temperature, may not have taken and recorded it frequently over the course of an illness, and if they have measured temperature elevations, they may never have reported these values to a health care provider, thereby obstructing possible validation through the medical record. Similarly, with other sources of hyperthermia incurred in a recreational setting, such as hot tub or spa use, in observational studies, it is unlikely that women recalling such exposures would have recorded their body temperature and the duration of the exposure in any manner suitable for validating maternal recall.

As summarized in Table 2 attached, the human data taken as a whole are not comprehensive, consist of observational studies which may or may not be able to appropriately control for confounding, and are limited in ability to tease apart the potential effect of hyperthermia from the potential effect of an underlying disease leading to fever or the medications used to treat it. Furthermore, a major limitation of these retrospective case-control studies is the typical inability to identify the specific timing of the exposure and the specific magnitude and duration of the elevated body temperature.

Nevertheless, several case-control studies demonstrate an association with NTDs and maternal fever, and some well-constructed case-control studies have shown this association with statistical significance (Miller et al, 1978; Layde et al, 1980; Sandford et al, 1992; Lynberg et al, 1994). The fact that these studies are consistent with the animal literature, and that other case-control studies have demonstrated an association with first trimester maternal fever and increased risk for other defects including heart defects, and Hirschprung Disease (Tikkanen et al, 1991; Botto et al, 2001 and 2002; Lipson et al, 1988), all lead to the conclusion that the association in humans between maternal hyperthermia and birth defects is causal.

A very small number of prospective cohort studies have addressed these same hypotheses. Prospective studies generally offer the advantage of more recent and precise maternal recall about exposures, and can avoid to some extent the potential bias of retrospective studies by collecting information about exposure before the known outcome of pregnancy. However, the contribution these kinds of study designs can make to evaluating the effect of hyperthermia on risk for NTDs is usually limited. This is primarily a sample size issue. In a population or clinic based sample, the number of pregnant women who have had a documented elevated body temperature of at least 2 degrees C above baseline that has endured for a documented 24 to 48 hour period, and that has occurred during the very short and early critical period for

neural tube closure is likely to be quite small. Furthermore, even though neural tube defects are one of the most common types of major congenital malformations, a baseline risk of 1 per 1,000 live births translates into a necessary sample size of exposed and unexposed mothers in the thousands in order to have sufficient power to rule out a doubling of risk for that specific defect. Such sample sizes are usually well beyond the bounds of attainability and cost in most cohort study designs.

Nevertheless, four cohort studies bear mentioning. Clarren et al (1979) used the Collaborative Perinatal Project cohort of over 50,000 mother child pairs to identify 178 women who reported a fever of at least 38.9 degrees C or higher on at least one occasion in the first trimester in association with an illness (38.9 degrees C is approximately 1.9 degrees C above the average baseline temperature in humans). No significant associations were found for all major malformations combined or any other adverse outcome. Kleinebrecht et al (1980) looked at any malformation or other developmental problem up to three years of age in a cohort of 7,870 pregnancies. An association between flu in pregnancy and abnormal muscle tone in the offspring was the only significant finding. Little et al (1991) reported on 54 women exposed to a fever of 38.3 degrees C or higher for 24 hours or more in the first trimester, and found significant increased risks for diastasis recti or herniated umbilicus compared to unexposed matched controls.

Finally, Chambers et al (1998) identified 115 women exposed to a fever of 38.9 degrees C or higher for at least 24 hours in the first trimester and found no significant differences in overall proportion of malformed infants compared to controls who reported a lower fever or a fever of shorter duration, and also compared to controls who did not report any fever. However, the authors did note two NTDs among infants of the 34 women who reported a high fever during the critical period for neural tube closure. This finding was not statistically significant but far exceeded the number of expected neural tube defects in a sample of this size. The specific finding of a greater number of NTDs than expected provided not only evidence consistent with previous case-control studies, but also provided some measure of the magnitude of the risk for an NTD with prenatal exposure to a fever of the specified elevation and duration during the critical window of susceptibility. Furthermore, as part of this cohort study design, a subset of live born infants received a specialized dysmorphological examination to evaluate children for minor and major structural defects. In this study an excess of specific minor malformations was noted among infants exposed to high fever, and importantly, these minor malformations were consistent with the spectrum of defects and timing of exposure identified by Smith and others in the previously published case series. Thus, this study was the first prospective evaluation of maternal fever that was able to confirm findings from previous case-control studies and case series with respect to the magnitude and duration of elevated maternal body temperature in relation to an increased risk for NTDs as well as a specific

pattern of malformation. The consistency of findings across these different study designs further lends support to the causal nature of the relationship between maternal fever and specific birth defects.

Other human studies have focused on a range of adverse outcomes. Kline et al (1985) used a case control methodology to show a significant association between late pregnancy spontaneous abortion (<28 weeks gestation) and a maternal fever of 37.8 degrees C or higher. Furthermore, despite the case-control design, Kline and colleagues were able to effectively rule out maternal recall bias by comparing maternal recall of fever in mothers of abortuses with normal karyotype to those with abnormal karyotype, prior to mothers being made aware of the karyotype status of their pregnancy. In the latter situation, there was no excess of maternal fever reported. This is consistent with the presumed cause of the miscarriage as it is expected that a high proportion of fetuses with abnormal chromosomes will spontaneously abort. However, there was an excess of reported maternal fever in mothers whose abortuses had normal karyotype. In contrast, Andersen et al (2002) using the Danish national cohort study consisting of over 24,000 pregnancies, did not find any association between maternal fever in the first 16 weeks of pregnancy and spontaneous abortion or stillbirth. Of note, in this study, more than 18% of the entire sample of women reported a fever occurring sometime in the first 16 weeks of pregnancy, although many did not recall how high the fever was or how long it lasted.

In summary, the consistency of findings across case-control studies taken as a whole supports the conclusion that maternal febrile illness increases the risk for major congenital defects, with most evidence in support of the risk for NTDs. Although cohort studies have produced conflicting results with respect to major defects, typically they have been underpowered to test the hypothesis that maternal fever causes NTDs. The one cohort study that did produce results consistent with both case-control and case series findings had the advantage of a specialized evaluation of a subset of live born infants – therefore improving the sensitivity of the study to detect differences between exposed and unexposed infants, despite relatively small sample size. These data taken as a group support the conclusion that maternal hyperthermia contributes to an increased risk for NTDs as well as other structural defects that represent a characteristic pattern.

ii. Maternal hot tub or sauna use

Few studies have contributed information to knowledge about the risks associated with hot tub or sauna use. Although animal data would suggest that a sufficient increase in core body temperature, regardless of the source, confers risk, evidence supporting that exposure to hot tubs or saunas is teratogenic is sparse.

Several relatively small case control-studies have incorporated "other environmental sources of heat" in study questionnaires. Halperin and Wilroy (1978) reported on a small case control study (48 NTD cases and matched controls) and found 3 case mothers who reported an elevated body temperature vs. 1 control. One of the case mothers reported sauna use on four occasions in the fifth week of gestation with a report of one occasion where the temperature was 43 degrees C. Chance et al (1978) in a similarly small case-control study (43 cases of NTD and 63 controls) reported that no case mothers recalled using a very hot sauna for 15 minutes or more during the period of neural tube closure. Lipson et al (1988) found no association between non-fever sources of hyperthermia and Hirschsprung Disease. Similarly, Tikkanen et al (1991) in a case control study in Finland found maternal fever during early pregnancy to be more common among 573 case mothers of infants with heart defects, but found no association with sauna bathing, workplace temperatures, or temperature of the environment. In another Finnish study, Saxen et al (1982) compared sauna bathing habits in the mothers of 100 consecutive cases of infants with defects of the central nervous system and 202 control mothers whose infants had orofacial clefts and found no differences between the groups.

On the other hand, Miller et al (1978) reported on 63 NTD cases and 64 controls, and found that hyperthermia was statistically significantly associated with being a case mother. Of the six instances of hyperthermia, two mothers possibly had experienced hyperthermia related to sauna use near the time of neural tube closure. Fisher and Smith (1981) reported on 17 infants with encephalocele compared to matched children with Down Syndrome and found that maternal fever of at least 1.9 degrees C above baseline was reported at the critical period in four cases and no controls. Two further cases in this series included one child whose source of hyperthermia was a one-hour Japanese bath (not otherwise described). Sandford et al (1992) reported on 44 NTD cases and 44 matched controls and found a statistically significant association with maternal report of "hot baths" in the first gestational month and NTDs.

Li et al (2003a) examined spontaneous abortions in a Kaiser cohort study in which women were interviewed during pregnancy about hot tub use. Although more than half of mothers were interviewed after the spontaneous abortion had already taken place, the authors reported a 2 fold increased risk for spontaneous abortion with hot tub or whirlpool exposure after conception. The authors further noted an increase in risk with increased frequency of use and increasing temperature of the water.

Finally, the single most concerning study regarding hot tub use was published by Milunsky et al in 1992. Based on an ongoing prospective cohort study in which women were recruited primarily through private obstetric offices in New England, 23,491 pregnant women were enrolled almost exclusively between

15 and 20 weeks' gestation at the time of prenatal screening or diagnosis with maternal serum alpha feto protein or amniocentesis. Maternal telephone interviews regarding pregnancy exposures were conducted by trained nurses. Among these women, 737 were excluded due to missing heat exposure information (n=1) or missing outcome information (n=736). Among the remaining subjects, a total of 5,566 women were exposed to at least one heat source including either hot tub, sauna or electric blanket in the first two months of pregnancy or fever greater than or equal to about 38 degrees C in the first three months of pregnancy. There were 1,254 women in the sample who reported using a hot tub or whirlpool in the first two months of pregnancy (for 55 women hot tub exposure was unknown). Forty-nine pregnancies in the entire cohort were identified as involving a fetus with a neural tube defect. In crude analysis, an almost 3 fold, statistically significantly elevated increased risk was found for hot tub or whirlpool use in the first two months of pregnancy and NTDs compared to women with no heat exposure. This relationship held up even after adjustment for maternal age, family history of NTDs, use of folic acid in the first six weeks of pregnancy, and exposure to other heat sources (adjusted relative risk 2.8; 95% confidence interval 1.2-6.5). This translates into a risk of approximately 2-3 per 1,000 NTDs in women who have used hot tubs in the first two months of pregnancy, or an excess of 1-2 NTDs per 1,000 exposed women over the baseline rate of approximately 1 per 1,000 births. In contrast, no statistically significant independent association was found for sauna use, fever, or electric blanket use. Furthermore, the authors found a six fold, statistically significant increased risk for NTDs among women who had at least two heat exposures to any of the following during the first two to three months of pregnancy: hot tub, sauna or fever, compared to those who reported no heat exposure at all.

c. Generalizability of Published Data to Hot Tub or Spa Use in Pregnancy

As indicated above, the only published study that had a reasonable sample size of pregnant women exposed to hot tub use during the approximate critical period for neural tube closure is the Milunsky study. To reiterate, the association in this paper was statistically significant with an adjusted relative risk of 2.8, 95% confidence interval 1.2-6.5. With this study taken on its own merit, there is evidence to suggest based on the lower bound of the confidence interval that there is at least a 20% increased risk for NTDs if a pregnant woman uses a hot tub at least once in the first two months of gestation. One limitation of this study, although described as prospective, is that more than half of all women were interviewed about exposure to hyperthermia after the results of prenatal diagnosis were known, introducing the potential for recall bias. Another important limitation of this study is that details about hot tub use were not collected. Thus, the frequency of use was documented, but not the length of time in the tub, the level of immersion in the water, or the water temperature at the time the hot tub was used. Because a statistically significant association was found, despite the fact that data on dosage and duration of hyperthermia

exposure were missing and the timing of exposure encompassed a broader time period than the short critical window for development of NTDs, it is possible that the association would be stronger (i.e., the relative risk higher) if that information were known. The effect of random misclassification (i.e., some women being classified as "exposed" when their exposure was not during the critical period, or was too brief to confer risk, etc., is thought to erroneously dull the estimate of the relative risk due to "noise" in the data. However, it is not possible to be sure in an observational study such as this. Therefore, even though these specific findings may be valid, it is difficult to apply them to the individual situation, i.e., to suggest that on the average every woman who uses a hot tub for any length of time and at any temperature during the first two months of pregnancy is at increased risk of having a child with an NTD.

Furthermore, with any finding in an observational study such as this, it is difficult to be sure that this association represents a cause and effect relationship. This is true because it is not ethically reasonable to conduct the definitive study which would be a randomized clinical trial that, by design, controls for measured and unmeasured confounding. Furthermore, there is no series of well-designed human studies with varying research designs that have come to the same conclusion as the Milunsky study.

As mentioned above, the only other study with a significantly positive finding for NTDs in association with a perhaps comparable exposure was Sandford et al's 1992 case control study which found a higher frequency of hot baths in the first gestational month reported by mothers of infants with NTDs compared to matched controls. Again, the temperature and duration of exposure was not available in this study.

Similary, the recent cohort study published by Li et al (2003a), showing a doubling of risk for spontaneous abortion with hot tub or whirlpool exposure, included no information on temperature of the water or duration of exposure. This study could also have involved recall bias in that more than half of women who had spontaneous abortions were interviewed about exposures after the event had already occurred.

To summarize, the limited data available that directly bear on the exposure of interest – hot tubs or spas – suggest an association with NTDs. To date, the best estimate of the risk associated with hot tub use during the critical window of NTD closure is a minimum of a 20% increased risk, with a point estimate of a 280% increased risk. This estimate translates to an increase over the baseline risk of 1 per 1000 to a risk of 2-3 per 1000 for an exposed woman to have an NTD-affected pregnancy.

With this limited amount of evidence directly related to hot tub or spa use, it is relevant to view this evidence in the context of data on other sources of hyperthermia.

Some have suggested that the association between fever-related hyperthermia and NTDs could be attributable to the maternal disease and or the medications used to treat the illness. Yet, the association has been noted in studies where the maternal illness has varied from flu to kidney infection, and there is relatively consistent data supporting a dose-response relationship with higher fever, especially fevers resulting in temperature elevations of approximately 2 degrees C above baseline. The consistency of these findings both in terms of the threshold dose, and the effect of temperature elevation in the absence of infection as noted in numerous animal studies, supports the concept that maternal hyperthermia itself is at least in part causally related to the risk for NTDs.

With respect to non-fever related sources of hyperthermia, it has been argued that maternal sauna bathing has been associated with NTDs only in isolated instances (Smith et al, 1978; Halperin et al, 1978), and that in countries where sauna bathing is frequent among pregnant women, the rates of NTDs are not notably higher. For example, Tikkanen et al (1991) reported an association with maternal fever and heart defects in the offspring of Finnish women, but could document no such association with sauna use. In fact, approximately 75% of all cases and controls in this study sauna bathed one or two times per week, and there were no differences between cases and controls on the frequency of use or timing of exposure. In a survey study in the same population, Uhari et al (1979) questioned women about their sauna use during pregnancy and found that 84% of women reported sauna bathing in the first half of pregnancy. It may be that these sauna users are particularly tolerant of the heat exposure, limit their exposure to brief periods, or reduce their core body temperature quickly by taking measures to cool down.

With respect to self-modulation of maternal exposure to hyperthermia, it has been suggested that sauna bathers in Finland may reduce body temperature between sauna sessions by immersion in snow or cold water (Lipson et al, 1993). Unlike fever-related hyperthermia that may not be under the control of the pregnant woman, hot tub or sauna bathing may pose less of a risk because the pregnant woman can self-limit her exposure, especially if the temperature becomes uncomfortable or unbearable. Furthermore, women who use hot tubs can control the level of immersion and the temperature of the water, although it is important to recognize that one of the normal mechanisms for body temperature regulation, i.e., perspiration, is limited in the hot tub setting (Edwards et al, 1995).

Relevant to the possible differences in tolerance to heat exposures with hot tub or sauna use, a study conducted by Harvey et al (1981) examined the effect of various hot tub water temperatures and sauna temperatures on increasing core body temperature and ability to tolerate these temperature elevations in non-pregnant women. In this study, 20 healthy non-pregnant volunteers immersed in hot tubs heated to 39 to 41 degrees C. At 39 degrees subjects began to leave

the tub because of discomfort after 10 minutes, and only five women could remain in the tub long enough to reach a core body temperature of 38.9 degrees C. These women could remain in the tub for 15 to 25 minutes. At 41.1 degrees C, subjects began to leave in discomfort after 5 minutes. However, six women remained in the tub until their body temperatures reached 38.9 degrees and these women stayed in for 10 to 30 minutes. Following the hot tub experiment, these same 20 subjects were exposed to sauna bathing on a different experimental day. None of the subjects who entered a sauna with an average temperature of 81.4 degrees C could remain in the heated environment long enough to reach a core body temperature of 38.9 degrees C. Of interest, some women in each condition (hot tub or sauna) whose temperatures were measured 10 minutes after the heat exposure showed an increase in core temperature above the final reading in the heated environment. This could suggest that women who leave and re-enter a hot tub with only a short interval in-between (less than 10 minutes) may achieve the same maximum elevated body temperature that would have been achieved by remaining in the heated environment the entire time, i.e., that short intervals between exposures may not be sufficient to reduce body temperature to normal.

Based on this study in non-pregnant women, the authors concluded that it was unlikely that typical recreational exposures to hot tubs or saunas would present a significant risk for NTDs or other hyperthermia-related adverse outcomes because women would self-limit their exposures to a level below the threshold of effect. The authors further suggested that prolonged exposures might pose a risk even when interrupted by short cooling off periods. The guidelines suggested by the authors of this study for maximum temperature and duration of exposure (no more than 15 minutes at a water temperature of 39 degrees C) are aimed at keeping maximum body core temperature below 38.9 degrees C and would be conservative estimates of the limits of safety for pregnant women.

However, there are of course a number of limitations to these conclusions – first, these women were not pregnant – and ability to modulate temperatures effectively may differ during pregnancy. Secondly, some women may be naturally more or less tolerant of heat than the average person, and Harvey et al did note that there was large inter-individual variation in their sample. Therefore, some women may be more or less susceptible or resistant to the effects of environmental sources of hyperthermia. Third, the perception of discomfort may be modulated by other factors commonly associated with a social setting but not involved in an experimental setting. For example, social interactions surrounding hot tub use may distract from or moderate perceptions of discomfort, or may influence the perception of elapsed time; and the use of alcohol before or while immersed in a hot tub may also modulate body temperature, affect perception of discomfort, passage of time, and/or impair decision-making ability. Finally, other pre-existing conditions or events may affect risk. For example, if a woman enters a hot tub after vigorous exercise, or with a mild fever, she may already have an

elevated body temperature that is further aggravated by the hot tub exposure leading her to reach a higher core temperature with a shorter duration of time.

In summary, there is limited specific information linking hot tub or spa use to increased risk for NTDs. However, taken in the context of a relatively large volume of animal data and the association between high maternal fever and NTDs in humans, the potential for hot tub or spa exposure to increase the risk for neural tube defects is likely. It may be that the risks of exposure are limited to the most extreme patterns of use – high temperature and frequent and repeated immersion for lengthy periods of time – analogous to some of the human data on dose and duration of fever.

d. Potential Risk Modifiers

As noted in the first principle of teratology, susceptibility to teratogenesis can be species specific. Within species, genetic susceptibility to an environmental teratogen is suggested due to the fact that not all embryos with a similar exposure are similarly affected by the teratogenic insult. Thus, it is hypothesized that one or more genetic factors may put the embryo at risk of an NTD, and a hyperthermic insult of a certain magnitude and duration is sufficient to push that embryo over the threshold of effect. Genetic susceptibility to environmentally induced neural tube defects has been demonstrated in animal models (Finnell et al, 1986).

Other non-genetic risk factors may be involved; e.g., nutritional deficiencies or excesses may play a role (Ferm and Ferm, 1979; Shin and Shiota, 1999; Li et al, 2003b), and alcohol may act synergistically with hyperthermia to induce NTDs (Shiota et al, 1988). Botto et al, (2002) has shown in a case-control study that the association between maternal febrile illness and one of seven major congenital anomalies is modified by multivitamin use.

In addition, susceptibility to hot tub or spa-induced hyperthermia may be modified by a previous history of having a child with an NTD, maternal age, and other conditions or medications that are associated with increased risk of NTDs, including maternal diabetes, and use of some folate-antagonist drugs such as carbamezapine and valproic acid.

Thus women, who fall into an elevated risk category, or who are already ill with a fever, or have an elevated body temperature from another source, may consider carefully the use of hot tubs or spas in pregnancy, especially during the critical period for neural tube closure.

VI. Relevance of Data to Technical Specifications for Hot Tub or Spa Construction

UL 1563 Electric Spas, Equipment Assemblies, and Associated Equipment, Section 33 (p. 57) indicates that the maximum set point water temperature in the tub is 40 degrees C and that the temperature regulating controls must be adjustable to temperatures below that level. This section also sets tolerance requirements for temperature regulation and control and calibration verification. The temperature regulation control at the maximum setting is required to have a tolerance of no more than plus or minus 3 degrees C. This means that at the maximum level of tolerance in a hot tub or spa that meets specifications, the maximum temperature could reach 43 degrees C.

A backup system consisting of a capillary tube or sensing circuit is required to reduce the risk of loss of temperature control in the event of damage; should this backup system malfunction, there is the potential for temperatures higher than 43 degrees C to be achieved.

In Section 34, (p. 58) it is specified that the temperature limiting controls at the water inlet limit the maximum temperature to 50 degrees C with a tolerance of not more than 3 degrees C. This suggests that under normal conditions, the water at the inlet could reach temperatures as high as 53.0 degrees C and areas surrounding the inlet would be expected to reach relatively higher temperatures than the remaining areas of the hot tub or spa.

These maximum temperature levels, overall and at the inlet, are at or substantially above levels that would be considered at the limits of safety for women in early pregnancy who are immersed in a hot tub or spa for more than a few minutes.

VII. Conclusions and Recommendations

It is widely recognized that in the human embryo the developing central nervous system is exquisitely sensitive to environmental insults. As environmental causes of birth defects are potentially preventable, measures to avoid potentially harmful exposures or minimize risks should be taken. Women of reproductive age are advised by the Centers for Disease Control and Prevention (2005) to take 400 mcg. of supplemental folic acid daily in order to reduce the risk of NTDs should they become pregnant. In addition to following this advice, women who choose to use hot tubs or spas should consider the possibility that they might unknowingly be pregnant. Approximately 50% of pregnancies in the U.S. are unplanned, and the majority of these pregnancies are not recognized until the period of neural tube closure has already passed (Floyd et al, 1999). Therefore, women who are of reproductive age and have a possibility of being pregnant, based on the findings in non-pregnant women reported by Harvey et al (1981) might limit exposure in the hot tub to less than 15 minutes in 39 degree C water and less than 10 minutes in 40 degree C water. This recommended maximum time would be reduced if there are other risk factors present, e.g., the woman is not in good health, already has

an elevated body temperature from previously being in the hot tub or spa, fever, exercise, or another source of hyperthermia, or begins to feel uncomfortable.

The female consumer who may be pregnant and uses a hot tub or spa should be aware of these possible risks (Rogers and Davis, 1995). However, the current requirements for hot tub temperature control are not, in my judgement, sufficiently protective for use of these products by women who might be pregnant.

Although, in my judgement, the maximum allowable temperature that a hot tub can achieve need not be set below 38.9 degrees C, the female consumer should be able to monitor maximum water temperature to a level at or below a specified degree so that she can be assured that she will maintain her body temperature below 38.9 degrees C. Therefore, the product's temperature regulation system should ensure that the maximum water temperature achieved at a given setting is not exceeded due to significant variability in the mechanism that controls this level. The mechanism should be precise enough to ensure that a setting of 38.9 degrees C does not result in variability in the true temperature, i.e., that true temperature can be reliably and validly maintained. The current best recommendations are for women who might be pregnant to limit exposure to less than 15 minutes if the water temperature is at 38.9 degrees C. However, with the current standards for hot tub temperature regulation, a woman could limit her hot tub exposure according to these guidelines, but due to variability in the accuracy of the temperature regulation system, she could in reality be exposed to a true temperature of up to 41.9 degrees C.

And finally, the variability in water temperature within the tank should be taken into consideration, in that an individual who is positioned in the hot tub or spa near the inlet for newly heated water can be exposed to a much higher water temperature than that measured in other parts of the hot tub and reflected in the overall temperature gauge. Therefore, temperature gauges should be placed near the water inlet; and women who use hot tubs should be advised not to place themselves near the water inlet while using the hot tub so as to avoid exposure to water temperatures that exceed the overall recommended maximum.

VIII. References

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Table 1. Selected Animal Studies

	Author	Year	Species	Temperature and Conditions	Findings
1.	Edwards	1970	Guinea pig	Lowest mean temp association with malformation +3.4 ° C In egg incubator x 1 hour, 1-8 occasions between GD 4 and 67	arthrogryposis
2.	Kilham	1976	Hamster	+3.0 - +4.0 ° C egg incubator X 1 – 1.25 hours on GD 8	Resorption Exencephaly encephalocele
3.	Hartley	1974	Sheep	+ 3.0 - +4.1° C x 9 hours daily during last 1/3- 2/3 gestation In controlled temperature room	Cavitation of cerebral matter microcephaly
4.	Hellman	1979	Rabbit	+2.3 - +2.8 ° C 2 periods of 1 hour – one group incubator; One group heat inactivated mixovirus GD 11	Hyperthermia – NTD Fever – dysplastic vertebrae
5.	Hendrickx	1979	Bonnet monkey	+ 2.4 – + 5.4 ° C for 1 – 8 days x 1 hour in incubator GD 23-30 Lowest dose at which malformations occurred + 2.4 ° C	No distinct pattern of malformations
6.	Edwards	1984	Guinea pig	+ 5.5 - + 6.0 ° C x 6 minutes to 1 hour at inteverals 6-20 hrs. GD 20-23	Microcephaly and reduced brain Weights; interaction between interval And temperature elevation
7.	Germain	1985	Rat	+ 2.0 - + 5.0 ° C with various durations in water bath at 9-12 hours gestation – low dose not teratogenic After 8 hours, highest dose teratogenic after only a single spike	Microphthalmia, maxillary hypoplasia Encephalocele, facial clefting
8.	Webster	1985	Rat	+ 5 ° C spike x 2 doses partially immersed in water bath 6 hrs apart GD 8-10	Microphthalmia, encephalocele, Maxillary hypoplasia
9.	Shiota	1988	Mouse	42.0 -43.0 ° C x 7.5-15 minutes in hot water bath at GD 8.5	Exencephaly, encephalocele, anencephaly, cranial NTD with facial clefting, skeletal malformations
10.	Cawdell-Smith	1992	Guinea pig	+ 3.2 ° C lowest dose associated with defects in incubator x 1 hr 1-2 times on GD 11-14	Exencephaly, encephalocele, microphthalmia
11.	Sasaki	1995	Rat	Exercise/heat – force swim in 40.5 ° C water vs. restrained in hot water, exercise in cool water, and restrained in cool water at GD 9; All effects seen in exercise + heat group	Anophthalmia, microphthalmia, encephalocele, gastroschisis, mandibular And maxillary hypoplasia
12.	Aoyama	2002	Rat	+ 6 ° C x 15 minutes in water bath at GD 9	NTD, facial cleft, heart defects

- GD – gestational days

Table 2. Selected Human Studies

	Author	Year	Design	Sample Size	Temperature and Source	Findings
1.	Smith	1978	Case series	13 cases	Various high temps – 1 sauna bather x 15 minutes "very hot"; Critical periods 4-6 wks gestation and 7-16 wks gestation	Malformation syndrome
2.	Clarren	1979	Prospective Cohort – CPP	178 exposed 178 matched controls	Fever temperature elevation 38.9 ° C or higher with illness on at least one occasion in first trimester	No consistent pattern
3.	Chance	1978	Case-control	43 NTD 63 control	Febrile illness 38.9 – 40.0 ° C	3 cases associated with febrile illness; none sauna
4.	Halperin	1978	Case-control	45 NTD 48 controls	Febrile illness and sauna	2 cases associated with febrile illness (1 with 40 ° C peak) and 1 with sauna use at 5 weeks x 4
5.	Miller	1978	Case-control	63 NTD 64 controls	Fever 38.9 – 40.0 ° C maximum temperature with fever all different illnesses , sauna	5 cases of fever and 2 possible cases of sauna use near time of neural tube closure
6.	Kleinebrecht	1979	Cohort	7870 pregnancies	Flu and fever	Flu associated with decreased muscle tone
7.	Layde	1980	Case-control	229 NTD 173 Down Syndrome controls 285 oral cleft controls	Fever	Fever associated with NTD's vs. Down Syndrome controls only
8.	Fisher	1981	Case-control	17 cases encephalocele 17 Down Syndrome controls	Fever of at least 1.5 ° C above baseline	Four cases reported fever and no controls
9.	Saxen	1982	Case-control	100 cases CNS 202 controls oral clefts	Sauna use	98.5% of cases and controls used sauna early in pregnancy; no differences in reported rates between cases and controls
10.	Kline	1985	Case-control	703 cases SAB 1057 controls	Fever 37.8 ° C or higher	Fever significantly associated with late spontaneous abortion
11.	Lipson	1988	Case-control	40 cases Hirschprung Disease 41 controls	Fever, infection, occupational and other environmental sources of heat	Fever only significantly associated with Hirschprung Disease
12.	Tikkanen	1991	Case-control	573 cases heart defects	38.0 ° C or higher fever, sauna, workplace temperature, temperature of environment	Fever associated with atrial septal defects – hypolastic left heart;

				1054 controls		No association with sauna bathing or other
13.	Little	1991	Cohort	54 exposed 54 unexposed	Defined exposed as first trimester fever of 38.3 ° C or higher for 24 hours or more	No significant overall increase in major malformations; increase in diastasis recti, and herniated umbilicus
14.	Sandford	1992	Case-control	44 cases NTD 44 controls	Fever and hot baths	Hot baths associated with NTD
15.	Milunsky	1992	Cohort	23,491 women 49 NTDs	Fever 37.7 ° C or higher , sauna, hot tub, electric blanket	Hot tub in first two months associated with NTD, or multiple heat exposure
16.	Lynberg	1994	Case-control	385 cases NTD 3647 malformed controls 2676 non-malformed controls	Flu and fever in the periconceptional period	Increased risk of NTD with flu with fever lasting 2 or more days, especially if medication used to treat; no association of fever if mothers reported without flu
17.	Chambers	1998	Cohort	115 exposed high fever 147 exposed low fever 298 unexposed	Fever from variety of illnesses classified as high if 38.9 ° C or higher for 48 hours or more in the first trimester; low fever < 38.9 ° C or <48 hours	2/34 high fever exposed during critical period had NTD No controls
18.	Botto	2001	Case-control	905 cases heart defects 3029 controls	Febrile illness and vitamins in periconceptional period	Febrile illness associated with heart defects and vitamins modify effect
19.	Botto	2002	Case-control	548 cases – 7 defects 1540 controls	Febrile illness and vitamins in periconceptional period	Febrile illness associated with defects and vitamins modify effect
20.	Andersen	2002	Cohort	24,040 women	Fever 1st 16 weeks	No increased risk for spontaneous abortion or stillbirth
21.	Li	2003a	Cohort	1,063 women	Hot tub or whirlpool after conception	Increased risk of spontaneous abortion

Conversion Table for Degrees Celsius to Degrees Fahrenheit

Degrees Celsius	Degrees Fahrenheit
1.0	33.8
1.9	35.4
2.0	35.6
3.0	37.4
37.0	98.6
37.8	100.0
38.0	100.4
38.3	100.9
38.4	101.1
38.9	102.0
39.0	102.2
40.0	104.0
41.0	105.8
42.0	107.6
43.0	109.4
51.7	125.1
59.0	138.2
81.4	178.5