tion. Here is a case of a couture fragrance making a statement which is a good deal more personal than many couture statements. By his use of a model wearing a gown which reflects in its shape the form of the Lalique glass stopper on the perfume bottle, which in turn has a beautiful flowing floral shape, Lagerfeld has unified a number of themes all of which pertain to his fragrance. The fact is that the fragrance itself makes a beautifully wrought floral statement in the area of tuberose and other exotic florals. Again, here is a fragrance which is rich, full bodied, beautifully diffusive, individual, and yet greatly appealing to many people. And, of course, the line "A woman doesn't put on my fragrance, she enters it," certainly ties in well with the promotion.

Other recently launched entries include Faberge's Babe and Lentheric's Je Suis. I am sure we will all be watching their progress with a good deal of interest.

Whatever else we can say about the fragrance and cosmetic industry, it certainly continues to be fascinating. It will never be boring because there is always so much that can be done, so much that is being done, and so much that will be done in the future.

Ms. Fedak: Our next speaker is Dr. Robert L. Henkin, presently the Director of the Center for Molecular Nutrition and Sensory Disorders at the Georgetown University Medical Center in Washington, D.C. After taking a PhD in music at the University of California in Los Angeles, Dr. Henkin went on to earn an MD at the same school. Over the years he has held a number of positions as clinical instructor, assistant professor, and consultant in various medical areas. One of his recent assignments was to the Committee on Biological Effects of Atmospheric Pollutants for the National Research Council in Washington. Dr. Henkin holds membership in over a dozen professional organizations, including the American Federation for Clinical Research and the American Institute of Nutrition. His major fields of research interest encompass the fields of taste and olfaction as well as sensory physiology and biochemistry.

Dr. Henkin continues his early interest in music, having composed original scores for motion pictures and radio and keeping up his membership in the Composers Guild of America and the American Federation of Musicians.

Olfaction and its Relationship to the Sexual Function in Men and Women

Dr. Robert L. Henkin, Center for Molecular Nutrition and Sensory Disorders, Georgetown, University

Olfaction is a neglected sense. Although there are thousands of patients who have experienced smell dysfunction of some sort, the medical profession as a whole and the public at large currently have little interest or knowledge about this important sensory modality and there is little concern with people who develop abnormalities of smell. On the other hand, perfumers and flavorists who depend upon dealing with olfaction as a lifetime work, do not have the knowledge of how this system works or the manner by which this sense changes under the influence of normal and abnormal physiological conditions.

It is almost gratuitous to say that smell is one of the most important aspects of life. However, Aristotle noted many years ago "That which is given to the greatest number has the least care bestowed upon it." Indeed, this most common and fundamental sense is considered such an integral aspect of our sensory function that its presence is not questioned until it is lost. Then, and only then, does the importance of this neglected sense become uppermost in the experience of the losers. For some, the inability to obtain pleasure from a nightly martini is a devastating experience; to others the personal shutting of the door on the smell of freshly cut grass, the odor of a freshly bathed child, the fragrance of flowers at springtime limits personal freedom of expression and produces personal frustrations of an inexpressible type. But there are worries too. If a woman cannot smell, how can she cook? Indeed, many, out of fear of serving spoiled food, abdicate their position in the kitchen to those more sensorily proficient. The inability to smell escaping stove gas, or gasoline, or to detect smoke or other noxious fumes gives people with these defects, at best, an

Table I

TASTE DYSFUNCTION	SMELL DYSFUNCTION
Dysgeusia: a general term describing any distortion of normal taste perception	Dysosmia: a general term describing any distortion of normal smell perception
Cacogeusia: a specific term describing the abhorrent, obnoxious taste produced by the introduction or mastication or both of food in the oral cavity	Cacosmia: a specific term describing the abhorrent, obnoxious smell produced by the inhalation of odorants
Phantogeusia: a specific term describing an intermittent or persistent taste perceived in the oral cavity independent of any external stimulus (This taste may be salty, sweet, sour, bitter, metallic, or obnoxious in such a manner as to present difficulty in description.)	Phantosmia: a specific term describing the intermittent or persistent odor, pleasant or unpleasant, perceived when no apparent odorant is inhaled
Heterogeusia: a specific term describing an inappropriate taste quality of consistent nature associated with the presence or mastication or both of foods and drink (This is unusual and unexpected but not necessarily foul or obnoxious.)	Heterosmia: a specific term describing an inappropriate smell of consistent nature associated with odorants (This smell is unusual and unexpected but not foul or obnoxious.)

insecure and fragile existence. The presence of dysosmia (Table I) and dysgeusia further complicates this problem since the appreciation of normally acceptable smells and food tastes is so altered that foods normally accepted are found intolerable; restaurants are shunned, social interactions which commonly occur around meals or sharing food or drink are shunned and a personal withdrawal from much of life occurs. And, as is so important for our immediate interests, about 25% of the people who experience hyposmia (loss of smell acuity) experience a significant loss of libido. The concatenation of these factors are devastating to the patient and can become unbearable, causing depression and withdrawal from normal life patterns.

If these problems were limited to a few people then these symptoms might be treated as medical or physiological oddities. However, these problems are extremely common. Conservative estimates suggest that at least 2 million people in the U.S. suffer from some form of taste and/or smell dysfunction. The magnitude and extent of these disorders and their influence upon appetite and sexual behavior are not yet clearly appreciated.

Nevertheless, in the study of these patients many important physiological phenomena have been uncovered about the sense of smell. The relationships between sexuality and olfaction, particularly between the roles of various hormones and their influence upon olfactory function, and vice versa, have offered a new understanding of olfaction and has allowed us to come to the aid of some of these unfortunate victims.

The importance of smell in daily life can be understood much more clearly if we look at lower species. The first sensory function which was developed among early animal life was probably olfaction. Olfaction is a chemical sense and the ability of unicellular organisms to detect minute changes in pH was probably the forerunner of the important system which we call olfaction today. Thus, it is easy to recognize that changes in the chemistry of the body might easily be interpreted and expressed as dysfunction in the olfactory system since this system is tied in so closely with the metabolic net of the body.

For mammals, higher animals, and man the importance of olfaction may be overshadowed by the admitted usefulness of the senses of vision and audition. However, if we consider the habitat of early animals in the dark primeval seas or in the dense jungles and forests of prehistoric life then the limited usefulness of vision and hearing to recognize friend or foe, to seek and couple with a suitable mate and to find food is readily apparent. In this dark environment olfaction was used as the dominant distance sense to recognize hostile foreigners, to identify the location of important food sources and to identify an appropriate mate at a receptive time that would culminate in maintaining and reproducing the species. Olfactory dysfunction during this period of zoological development would probably result in catastrophe for the affected animal. At present olfactory dysfunction or loss is certainly less catastrophic in regard to preservation of life but it affects the quality of life in a personal and frustrating manner.

First, in order to understand these problems, a few basic physiological and biochemical facts are important. For convenience, olfaction may be divided into two general classes of events—one involving the central nervous system or the neural events of smell, the other involving the periphery, the receptor, or the preneural events of smell. The anatomy of the neural events of smell have not been well studied in man although the connections from the olfactory bulbs to projections in the hippocampus and temporal lobes have been clearly documented. The preneural events of smell have been studied even less. These events involve the interaction between vapor and receptor. The receptors, which probably exist on the cilia of the mitral cells, and are not neural tissue, per se, are imbedded in a thick mucous layer. This mucous layer is critically important, for without it, smell as we know it, does not occur. This has been seen recently among patients who develop dryness of secretions of most mucous glands and develop a profound nasal dryness called xerorhinia. The nature of the proteins in the nasal mucous and their function, which probably is involved in the nourishment and function of these receptors, as with saliva in the maintenance of the taste bud, is not known. However, the odor molecule, in order to be "smelled" must first make con-

tact with the receptor so that an odorant-receptor complex is formed. Olfactory information at this point is maximal and this is the only point in time at which all the olfactory information about the odor is available to the olfactory system. Integration of this information, which occurs as the olfactory message is passed to the neural portion of the sense focusing upon aspects of the vapor that the organism finds useful for preserving life. The neural events, or the coding by which the smell messages are resolved by the brain, are little understood although the general process by which the central nervous system integrates this information and the pathways over which these signals travel have been studied in detail in several species.

Second, the preneural events of smell involve a chemical interaction, a binding between an odorant, a molecule of vapor, and a receptor. This interaction generates a small but definable electrical signal which must be amplified in order to produce an electrical event large enough to depolarize the olfactory mitral cell. We have hypothesized that this amplification is carried out by a complex interaction between cyclic AMP and GMP in a carefully integrated trade off. Since many factors influence these substances, including pituitary and gonadal hormones, the influence of physiological changes on gonadal function (e.g., menarche, ovulation, or menopause) or pathological changes in gonadal function (e.g., gonadal tumors, menstrual abnormalities) on olfaction may be readily apparent.

Third, there is a need to quantitate and define normal and abnormal olfactory function in a simple, direct, and quick manner through the use of vapors which will allow reproducible measurement of normality or dysfunction. This need has been met through the use of vapors which will allow reproducible measurement of normality or dysfunction. This need has been met through the development of the three stimulus, forced choice sniff technique whereby reliable estimates of the ability to detect and recognize vapors, as well as the estimation of the number of functioning receptors (by utilizing olfactory scaling, a variation of the method of magnitude estimation) has been carried out. With these tests reliable, quantitative data by which the olfactory status of a subject with normal smell and patients with impaired smell may be obtained.

Fourth, through the use of these tests general categories of normal and abnormal olfactory function have been defined. Anosmia has been defined as the total lack of olfactory sensation. In functional terms, this relates to lack of responsiveness at the primary olfactory area (the anatomical area characterized by the interaction of the olfactory bulb, olfactory nerves, olfactory epithelium, and odorants) and the accessory olfactory areas, (the diffuse anatomical regions at which vapors react with free nerve endings or other more specialized anatomical structures in oral and pharyngeal areas innervated by cranial nerves V, VII, IX, and X (Fig. 1)). This disorder is uncommon but patients who suffer with this problem are at hazard since they have no protective olfactory mechanism against noxious vapors, escaping stove gas, or smoke. Hyposmia has been defined as a relative decrease in olfactory acuity and has been divided functionally into two categories, Type I and Type II hyposmia. Type I hyposmia has been defined as an absence of responsiveness to vapors at the primary olfactory area. These patients can detect vapors in their nasal cavity or throat but are without the normal ability to smell as it is commonly defined. Type II hyposmia has been defined as a relative decrease in the ability to smell at the primary olfactory area. These patients can smell, as is commonly defined, but less acutely than normal.

Figure 1. An artist's representation of the primary and accessory areas of olfaction. O.E. represents the area of olfactory epithelium, an area innervated by the olfactory nerve (I). N.V represents the area of the anterior and lateral portions of the nasal cavity which subserve olfaction, innervated by branches of the trigeminal nerve (V). N.IX represents the area of the upper pharynx which subserves olfaction, innervated by branches of the glossopharyngeal nerve (IX). N.X represents the area of the lower pharynx which subserve olfaction, innervated by branches of the vagus nerve (X). The cross hatched area represents the area of sensory overlap between nerves IX and X.

Relationships Between Olfaction and Gonadal Function. Pheromones have been shown to be important in mutual mate attraction in many lower species although their importance in man has not been clearly demonstrated. Alterations in smell in men and women have been related to alterations in their sexual function, or more commonly, abnormalities of sexual function have been closely related to alterations in olfactory function. Some women who have never had normal menstrual periods and who are not capable of bearing children because they lack the required germ cells in their rudimentary ovaries commonly exhibit decreased smell acuity. Some men who have never reached puberty and

who also lack the required germ cells in their testes to produce children commonly exhibit decreased smell ability.

Men and women with normal sexual and olfactory function may suffer a loss of smell due to a variety of causes. However, regardless of the cause, about 25% of these men and women experience a loss of libido coinciding with their loss of olfactory function. In some men and women the loss of olfactory function and the onset of menopause can occur coincidentally. In the brain the neural pathways over which olfactory information is sent lie in close proximity to those involved in reproductory function. Some of these neural interactions relate to control over the secretion of hormones from the brain and the pituitary gland. In lower animals, interference with the olfactory system, either at the olfactory end organ or in the central nervous system, may produce sexual malfunction. Thus, there are neural, biochemical, and functional interactions which relate olfactory and sexual function in men and women as well as in lower species.

Olfactory Changes During the Menstrual Cycle. It has been commonly observed that women experience changes in olfactory perception during the menstrual cycle. These observations were initially considered specific for musk-like compounds but later studies showed that there was a midcycle peak for olfactory acuity which was independent of the olfactory stimulus used (see Fig. 2). Increased olfactory detection acuity, as measured by the three sniff, forced choice technique previously mentioned, occurred in the follicular phase of the menstrual cycle prior to the midcycle increase in basal body temperature or in plasma luteotrophic hormone

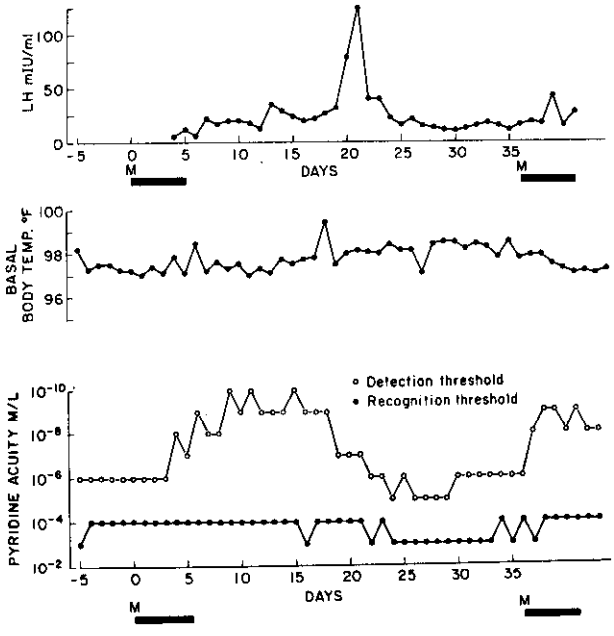

Figure 2. Daily changes in sensory function, basal body temperature, and plasma LH concentration in one woman studied throughout 1 complete menstrual cycle. The abscissa of each panel is plotted in days. The onset of menses is indicated by M, the length of the menses by a solid black line. Detection and recognition thresholds for the smell of the vapor of pyridine in water (in M/l) is shown on the lowest panel. The normal range of detection is from 10^{-5} to 10^{-9} M/l, for recognition from 10^{-2} to 10^{-4} M/l.

(LH) secretion. This increased olfactory acuity is in contrast to the relative decrease in olfactory detection acuity which occurred during the luteal phase of the cycle.

These changes in olfactory acuity were observed whether the menstrual cycle was "short," that is, less than 28 days in length, or "long," greater than 28 days in length. These changes also occurred for taste, touch, and hearing but were more apparent for olfactory acuity. These changes in detection acuity were relative; although the changes observed were more apparent during the follicular or preovulatory phase of the menstrual cycle, the smell changes were generally within normal limits. In this sense, in order for these changes to be apparent, relatively frequent testing of sensory acuity had to be carried out in order for the trends within the normal ranges to become apparent. It is of interest that those studies in which no change in sensory acuity within the menstrual cycle was reported were those in which the least frequent testing of sensory acuity was undertaken.

The relative increase in sensory detection acuity during the follicular phase of the menstrual cycle may be related to the effects of estrogen or progesterone on either receptor, nerve, or central nervous system activity. On the one hand there may be positive effects of estrogen producing increases in detection acuity during the follicular phase although these changes have not been isolated in any systematic manner. The increase in detection acuity to levels above the upper limits of normal for smell during this phase tends to support this concept. On the other hand, the increase of progesterone which occurs during the luteal phase coupled with the decrease in estrogen concentration may be related to the decreased detection acuity observed. Although specific sensory data are not readily available, depression, accidents, admission to hospital, and suicide are more frequent during the luteal phase than during the follicular phase of the cycle.

It has also been recently demonstrated that administration of progesterone to rats was associated with decreased plasma zinc concentration and that this relationship also was apparent during the estrus cycle. Since loss of zinc has been associated with decreased taste and smell acuity, this relationship could provide another possible link between progesterone secretion and decreased sensory acuity.

These observations suggest that behavior in several systems may be worsened during the luteal phase of the cycle in relationship to the hormonal changes that occur during this phase. Thus the changes in sensory acuity that occur during the menstrual cycle may be a sum of the actions of both estrogen and progesterone although other factors not yet recognized may also play significant roles.

It is tempting to speculate on the meaning of the changes in sensory acuity that occur during the menstrual cycle. As noted earlier, the changes in hormonal concentration observed during the two phases of the cycle may exert specific effects on receptor, nerve, or central nervous system function which could relate to the sensory changes observed.

However, the changes that are most apparent relate to increased acuity and appear to occur prior to ovulation. Whether or not this increased acuity has any biological meaning related to increasing fertility is not known. Although there is disagreement about the level of sexual receptivity or desire prior to ovulation, there is a large body of observations suggesting that increased sexual activity occurs during the follicular phase, prior to ovulation when estrogen levels are elevated. Teleologically this activity would increase the odds of ultimate fertility. If this were the case, then any increase in sensory acuity on the part of the female might be helpful particularly in relationship to mutual mate finding behavior. Certainly the presence of pheromones in insects appears consistent with this hypothesis with respect to females attracting males of the species, and mate finding does have certain mutual attraction processes. Indeed, recent work suggests male insects also secrete olfactory recognizable signals which influence female mating behavior. Thus, the increased sensory acuity observed during the follicular phase of the cycle in man may relate in some ultimate context to fertility.

Olfactory Acuity and Abnormal Sexual Function in Women and Men. Hyposmia (decreased olfactory acuity) is an important and generally unrecognized concomitant of women with menstrual abnormalities occurring in 8%-33% of women with these problems (Table II). Type I hyposmia occurs with increased frequency only in women with primary amenorrhea who have potentially functional ovaries in that oocytes or functional germ cells are present in their ovaries.

In contrast, Type II hyposmia occurs with increased frequency in all categories except that of

secondary amenorrhea, without oocytes (menopause) and is strikingly increased in women with primary amenorrhea without ooctyes. Women with primary amenorrhea who do not have oocytes will most frequently have Type II hyposmia. In contrast, all other women with menstrual abnormalities will almost always have normal olfactory acuity, but when these women do have hyposmia it will also most likely be Type II. Next to women with primary amenorrhea without oocytes, women with primary amenorrhea with oocytes have the highest prevalence of hyposmia.

Table II

Menstrual History and Oocyte and Olfactory Status

		Olfactory Status					
				Hyposmia			
		Normal		Type I		Type II	
Menstrual History	Oocytes	No	%	No	%	No	%
Normal	Present	493	98.6	5	1	2	0.4
Oligomenorrhea	Present	11	73	1	7	3	20*
Secondary amenorrhea	Present	12	80	11	7	2	13*
Secondary amenorrhea	Absent	25	92	1	4	1	4
Primary amenhorrhea	Present	9	60	3	20*	3	20*
Primary amenhorrhea	Absent	3	13	1	4	20	83*

*Chi-square P value, with respect to normal, <0.005.

The prevalence of hyposmia in women with oocytes is significantly greater in those having menstrual abnormalities than in women with normal menses. Again, although both Types I and II achieve statistical significance, Type II occurs more frequently.

Women with secondary amenorrhea without oocytes (natural, premature, or surgical menopause) have no increase in the occurrence of either Type I or Type II hyposmia. In contrast, those with primary amenorrhea have a significantly increased prevalence of Type II hyposmia.

The olfactory abnormality most frequently present in the patients we studied is Type II hyposmia, and most patients with this defect are unaware of their quantitative decrease in olfactory acuity. Therefore, it is necessary that each patient with a menstrual abnormality be tested in order to determine olfactory acuity. Since measurements of olfactory threshold can be performed relatively easily and early in the life-span of the patient, they should be included in the medical evaluation of any such patient.

These tests are of particular importance in the evaluation of young women with primary amenorrhea because they can provide information of critical diagnostic and prognostic importance. If the patient has primary amenorrhea and Type II hyposmia there is an 83% likelihood that oocytes are absent and therefore the patient will not be fertile. In this sense knowing the status of the olfactory sense is useful to an understanding of ultimate fertility. On the other hand, in patients with primary amenorrhea and either normal olfactory acuity or Type I hyposmia there is a 75% likelihood that oocytes are present: this, particularly if associated with some evidence of endogenous estrogen production, would suggest probable ultimate fertility.

In men, in contrast to women, Type II hyposmia has been associated with the presence of sperm or the ultimate ability to produce sperm whereas Type I hyposmia or anosmia has been associated with the inability to produce offspring. These differences between men and women with respect to their olfactory-gonadal function is at present unexplained.

Importance of the Perfume and Flavor Industry. Knowledge of the existence of changes in olfactory acuity throughout the menstrual cycle may be of great importance in the designing of new fragrances. Some vapors may be more preferred prior to ovulation, some after ovulation. Changes in olfactory acuity occur with age, during the 24 hour period of the day, between men and women. Knowledge of the existence of these changes and the manner by which these differences can be applied may make the development of physiologically precise fragrances possible in ways never before conceived. Fragrances may be tailor-made based upon physiological considerations, for the mature woman, for evening, for morning, or for men, in which the complex factors shared by personal preference and individual physiology may be combined for maximal esthetic and physiological impact. The factors relating changes in human physiology to human preference are admittedly complex and still not well understood. However, with our present tools it is possible not only to begin to understand the complex interrelationships between olfactory and gonadal function but also to harness these relationships in order to create a more harmonious blend of esthetics and physiology by which the quality and odor of life may be enhanced for us all.

Ms. Fedak: We will hear next from Dr. Richard B. Ward, a native of England and a research associate for E. I. du Pont de Nemours & Co. After taking a BSc degree and a PhD at the University of Birmingham, Dr. Ward studied as a fellow at Ohio State University, then joined du Pont in 1959. Currently, as technical consultant for liaison on toxicology and environmental effects, he works in research and development of fluorocarbon aerosol propellants. His previous assignments have included research in carbohydrates, radiation chemistry, fluorocarbon synthesis, fluorinated polymers, permeation, and dye production.

The Future of Fluorocarbons, Status Report

Dr. Richard B. Ward, E. I. duPont de Nemours & Co.

During the period between 1970 and 1974, a program to determine the environmental impact of fluorocarbons was initiated and funded by industry. Dr. J. E. Lovelock, at the University of Reading, England, developed an extremely sensitive analytical device called an electron capture gas chromatograph. This device is capable of measuring a few parts per trillion of compounds such as the common fluorocarbon propellants, FC-11 and FC-12. Dr. Lovelock found these fluorocarbons in the "background atmosphere," away from sources of release. Measurements showed the background concentrations were increasing and were comparable to, but less than, the estimates of total release to date. The first conclusion was that these fluorocarbons have a long lifetime in the atmosphere.

Dr. Taylor and Dr. Pitts, at the University of California, Riverside, showed that fluorocarbons had no effect on smog formation and were not destroyed by smog reactions in the atmosphere. Dr. Sandorfy, at the University of Montreal, Canada, showed that very energetic ultraviolet light could break down fluorocarbons. This light is absorbed in the stratosphere, and does not reach ground level. Given enough time, long-lived compounds can diffuse high enough to encounter the energetic radiation. At high altitudes, the fluorocarbons would be dissociated to give chlorine atoms. It was expected, early in 1974, that the chlorine atoms would be converted to chloride ion and eventually return harmlessly to the oceans. The environmental impact appeared negligible.

Ozone depletion hypothesis

Coincident with this environmental study was a major research program, the federally supported Climatic Impact Assessment Program (CIAP), which attempted to define the effect of supersonic transports on the upper atmosphere. Important developments in our understanding of the stratosphere emerged, including speculation that chlorine atoms may catalytically react with ozone. In June of 1974, Dr. Molina and Dr. Rowland, at the University of California, Irvine, postulated that fluorocarbons could provide the chlorine and, thus, the catalyst to convert ozone to ordinary oxygen. A computer program was used to "model" atmospheric processes and hence to calculate ozone depletion. Such depletion might cause serious biological effects since ozone filters out some of the ultraviolet light from the sun. Among these potential effects is the incidence of certain types of nonmalignant skin tumors in light-skinned people (Caucasians), which appears to be correlated to the amount of ultraviolet exposure (e.g., in sunbathing and other outdoor activities).

The issue became news immediately and has resulted in extensive technical, legislative, environmental, and political activity.

The key questions were rather promptly defined. What additional information is needed to determine whether the theory is quantitatively correct? Who can get this data? How long will it take?

The questions were resolved rapidly in 1974, resulting in a substantial expansion of the industry program under the auspices of the Manufacturing Chemists Association. Federal recommendations made in 1975 were in close agreement with industry recommendations. The time period for the work was estimated at about three years, with frequent reassessent during that period. Over $1.5 million was funded in 1975 by the fluorocarbon industry, and estimates for the three-year period now exceed $5 million.

At the Federal level, an analysis report of the Federal Task Force on Inadvertent Modification of the Stratosphere (IMOS) concluded that the question was a legitimate cause for concern, and