Letters

Lars Mølhave Responds to "TVOC: Is It Dead?"

*In Vol. 3, No. 8 of the **BULLETIN**, p. 10-14, we discussed the TVOC construct and its lengthy historical discussions within the IAQ community. We recently received an "answer/comment" from Lars Mølhave whose work on the TVOC concept is probably the most extensive and best known in the world. Many of his publications on the subject were cited in the article on VOC health effects published in the last **BULLETIN**, Vol. 3, No. 9. Dr. Mølhave offered his comments for publication in the **BULLETIN**, and encouraged editorial corrections, a few of which have been made. We have attempted to preserve the intent of his submitted comment, and he has reviewed and approved the text that appears below. Readers may want to read articles by Mølhave on the approach being used by WG13 (referred to below) in the Proceedings from Indoor Air '96, from Healthy Buildings '95, or from "Indoor Air Quality, Ventilation, and Energy Conservation in Buildings" (held in Montreal, Canada, May 9-12, 1995).*

We asked Alfred Hodgson, Lance Wallace, and Michael Hodgson to comment on Mølhave's remarks. Their comments follow Mølhave's. Note that Alfred Hodgson and Michael Hodgson are not related.

In Vol. 3, No. 8 (pages 10-14) of the ***BULLETIN***, several pages were used to address the TVOC construct and its use in the IAQ context. The heading was "TVOC: Is It Dead?" The author summarizes the ongoing discussion on TVOC and makes several references to statements made by me. The article as a whole carries the answer: "Yes" to the question, "TVOC: Is It Dead?" as most of the citations seem to object to the only logical alternative which is "Yes - It is Alive."

Several years ago, a working group (EU-ECA WG13) consisting of 15 European scientists was established with the "European Concerted Action on Indoor Climate and Its Impact on Man." The group discussed the use of the TVOC measure for evaluation of the importance of volatile organic compounds (VOC) for the indoor climate of non-industrial buildings and will publish its report in the Spring of 1997. In its report, the working group will deal with the questions raised in the ***BULLETIN*** and I recommend that the readers abstain from jumping to any final conclusions regarding TVOC until the report has been published *and read.* [emphasis in original]

The following are my personal comments to the notes in the ***BULLETIN***, and they should be looked upon in that light. To me, it is an unacceptable oversimplification only to discuss whether TVOC is "dead" or "alive." The question instead should be "under what circumstances can useful information be extracted from TVOC measurements?" The following summarizes my interpretation of the TVOC, an interpretation which has not fundamentally changed during the last 10 years.

Dose response data (DR) are well known for many individual VOCs. They describe the relation between the air concentration of a substance and the prevalence or risk of a specified health effect, for example. For each individual VOC, a set of such DR relations exists, one for each type of health or comfort effect.

It is generally expected that for any VOC mixture with a constant composition, such DR-functions also exist for each of the health effects of this specific mixture. However, at present, this relation cannot be established from knowledge of the components, their individual concentrations, and DR relations, etc.

Most researchers agree that in principle, sometime in the future, it may be possible to construct a set of such mathematical functions (one for each type of health effect) which, for a known composition of air polluted with any mixture of VOC, may be used to calculate the expected effects. This development, however, may take decades, but VOCs already have been demonstrated to be important for IAQ. Therefore, we cannot wait for the researchers to establish these dose-response relations. So, what do we do until then?

TVOC is the simplest first approximation to the unknown general DR-relationship. The TVOC measure assumes an equal relative weight of each type of VOC in relation to health. This, in practice, corresponds to saying that less VOC is better than more. (In many ways this is the same as the procedure used in interpretation of such indices as TSP (total suspended particles) or total PAN. As such, the accuracy cannot be expected to be high. Further, this approximation should not be used for general health, but only for sensory irritation, etc. and can only cover the effects on IAQ of a limited range of indoor air pollutants.

This approximation to the DR-relation needs to be standardized and documented before it can be generally used. It should be modified and refined as soon as

more knowledge accumulates. Until then, the TVOC, at best, should be considered to be a screening tool.

In contrast to the view of TVOC described above, some practitioners have developed a practice of using a few measurements of TVOC (often without specifying the measuring procedure) to classify buildings as acceptable/unacceptable. This is often done with great personal or financial consequences for the building occupants and owners. These practitioners are using TVOC as an exposure measure in a hypothetical, generalized DR relation covering all VOCs and all VOC mixtures and for all types of health effects. Clearly, the scientific literature does not support this. Therefore, this practice is a misuse of TVOC, and I agree with the Nordic Committee and EU-ECA WG13 that this use of TVOC must stop.

However, we still have the problem of VOC indoors. The reporting of long lists of compounds and concentrations is impressive and may be scientifically useful, but it does not help the practitioner. The practitioners have for years and will probably continue to report VOC, and we still have to tell them how much (or how little) health information they can extract from their lists. If they decide to use TVOC, then at best TVOC can be used to indicate that the probability of effects is high at high TVOC and low at very low TVOC levels. This is the approach used by the ECA working group WG13. I support this interpretation.

Therefore, the essence of my message to the practitioner has been that in doing IAQ evaluations they should do the following:

a) Not only focus on VOC. There are other physical, chemical, and biological factors to consider in relation to IAQ. TVOC does not cover these factors and TVOC is not a measure of general IAQ, but rather of the possible contribution of VOC to IAQ problems.

b) Not only focus on sensory irritation. There are other health and comfort effects to consider in relation to IAQ. TVOC does not cover these effects.

c) If more accurate evaluation procedures are developed in the future, then use them instead of TVOC if you expect VOC to be a major exposure factor.

d) If such methods do not exist, then as a fallback solution, measure TVOC in a standardized way (*e.g.*, according to EU-ECA WG-13).

e) The practitioner may then use TVOC to extract a minimum of health information from the lists of measured compounds. This can only be made in relation to discomfort, for screening purposes, and never for a sharp Yes/No decision. This means that only very small TVOC values are of no concern and only very large values can be classified as unacceptable. In between, the practitioner has to do something else to demonstrate that VOC is part of the problem.

f) My approximately 10-year-old summary and conclusions about TVOC levels (Mølhave, 1986) found in field investigations was already then, when published, described as being based on an incomplete review of publications using measurements which were not standardized. As concluded both by EU-ECA WG13 and by the Nordic group, little additional information has been made available since then, and there is still no scientific basis for setting official limit values. The use of the values 0.2 and 3-5 mg/m^3 in this context as recommended definitive guideline values is not advisable.

However, the data mentioned above are those which are available, and nobody can object if the practitioner, in the absence of official guidelines, uses these estimates of the low and high values as discussed under point e). This, of course, has to be done with many precautions. These precautions have, among other things, been the target for discussions of the EU-ECA WG13.

In conclusion, for years I have wanted to stop the ongoing, fruitless discussion and speculation pro or con TVOC as illustrated in the article in the ***BULLETIN***. A more constructive approach would be to develop guidance for practitioners on how to measure and report VOC and how to avoid misusing the TVOC. This is the aim of both the EU-ECA WG13 and the Nordic IAQ Working Group.

If we, in relation to an IAQ guideline, need a simple measure such as TVOC for VOC exposure, then we must establish an acceptable scientific basis for accepting or rejecting the scientific hypothesis that TVOC is an acceptable guideline. If not, then we must develop a better approximation than TVOC as an exposure measure in the general DR-relation for VOC mixtures. (Members of the scientific community already are discussing such models.)

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References

Bornehag *et al.*, 1996. Report from a Nordic Scientific Consensus Meeting at Långholmen in Stockholm.

Mølhave, L., Bach, B., and Pedersen, O.F., 1986. Human reactions to low concentrations of volatile organic compounds. *Environment International*, Vol. 12, Nos. 1-4, pp. 167-176.

Letters

Alfred Hodgson Responds to Mølhave's Comments

We invited Alfred Hodgson to offer his views on Mølhave's comments. Al is with the Indoor Environment Program, Lawrence Berkeley National Laboratory, in Berkeley, California.

I am in basic agreement with Dr. Mølhave's comments. It appears that much of the scientific community may be moving in a similar direction with respect to the analysis and interpretation of exposures to volatile organic compounds (VOCs) in indoor environments.

The measurement of total VOCs (TVOC) in indoor air is limited in its usefulness for a variety of reasons. The measurements themselves are highly uncertain (although general consistency can be achieved among several of the predominant methods). Important compounds with respect to health effects may not be measured while the biological potency of individual compounds typically included in the measurements often varies by orders of magnitude. Finally, associations between TVOC concentrations and health effects have not been convincingly demonstrated.

Nevertheless, I agree that TVOC is still useful as a screening tool. In particular, it is useful for general building investigations in which no attempt is being made to diagnose specific complaints, such as odor or sensory irritation. If concentrations of TVOC are found to be elevated with respect to typical TVOC concentrations, then a strong source(s) and/or inadequate ventilation is suggested. This is useful information warranting further investigation. A prudent response might dictate reducing occupant exposures through increased ventilation or another form of source management.

When specific complaints are being investigated which could conceivably be due to exposures to VOCs, it is my experience that it is necessary to identify and quantify individual VOCs. It is not currently possible to combine this speciation data into a useful predictor of health effects, such as sensory irritation. However, the speciation data may show the presence of compounds, which are either know to be strong irritants or which are representative of irritant classes of compounds. The data may also suggest the possible source(s) these compounds which can be confirmed by further investigation. Once identified, the source can be managed to reduce exposures. Obviously, this approach can not guaranty success in solving the complaint problem, but it is reasonable, best practice based on our current state of knowledge.

More useful metrics for assessing the health impacts of exposures to complex mixtures of VOCs in indoor air are clearly needed. Our research program has been working on such an approach that is based on the hypothesis that sensory irritation effects are additive for individual compounds at relatively low concentrations. The available human and animal bioassay data on irritancy are used to calculate the irritancies of the individually quantified compounds relative to a standard compound, such as toluene. The usefulness of this approach is limited by the lack of consistent health effects data for a number of compounds of potential interest. However, principal components analysis using source categories for which we have some indicator compounds may be one way to account for compounds without health effects data or which may not be included in our standard analyses of VOCs. This later approach has shown a relationship between exposures to VOCs and certain health effects for a group workers in 12 California office buildings. The next step is to attempt to confirm the relationship using another appropriate data set.

There is another need, which is to define a standard set of target compounds to be measured in systematic investigations of VOCs in buildings to help us understand the potential relationships between VOC exposures and health effects. This set should include: 1) compounds which are strong irritants or odorants at relatively low concentrations; 2) compounds which are indicative of particular sources which have the potential to cause health effects; and 3) compounds produced by reaction of ozone with indoor surfaces. Many of these compounds will be oxidized species, for which we have very little systematic data. For practical reasons the set should probably contain no more than about 50 compounds. Perhaps the ***BULLETIN*** can serve as a discussion forum for developing such a list.

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Letters

Lance Wallace Responds to Mølhave's Comments

We also invited Lance Wallace of the US EPA to offer his views on Mølhave's comments. Dr. Wallace's comments are made in his capacity as a private citizen and scientist and do not necessarily represent the position of the EPA.

As usual, I find myself in agreement with nearly everything Lars Mølhave has to say. Like Lars, I am shocked by the idea that major decisions would be made on the basis of TVOC alone. (I have no personal knowledge of such actions, however, and I hope and presume that they are few and far between.) Possibly unlike Lars, however, I would view this misuse of the TVOC concept as one of several reasons to avoid using the concept as much as possible.

I have always felt that individual VOCs should be measured and reported, both because dose-response functions are sometimes known, unlike for TVOCs, and also because the individual VOCs carry information about the possible source. For example, a cluster of C10-11 hydrocarbons might implicate a wet-process copying machine, or a very high level of *p*-dichlorobenzene might indicate overuse of toilet deodorizers.

All of the work that the Research Triangle Institute (RTI) carried out for EPA on VOCs, both in residences and buildings, reported individual compounds and made no use of the TVOC concept. It was only as an attempt to add useful measured data to the TVOC discussion that I supported going back to the 2700 samples we had collected over 8 years and calculating the total VOC loadings (Wallace, Pellizzari, and Wendell, Indoor Air 4:465-477, 1971).

This exercise was useful in showing that the 25-32 targeted VOCs in our studies accounted for only 3-20% of the total VOCs collected by the Tenax samplers. It also extended the TVOC concept to personal exposures — 1500 personal samples had a geometric mean of 1.1 mg/m^3, compared to 0.7 mg/m^3 for 198 residential indoor air samples and 0.3 mg/m^3 for 371 outdoor air samples at homes.

However, these numbers may not be directly comparable to other TVOC values determined by methods different from the one we employed — namely, calculation of individual total ion current (TIC) relative response factors (RRF) for 17 chemicals followed by application of the mean RRF to every computerized GC/MS scan between chloroform and dodecane. So once again interpretation of the absolute TVOC numbers is difficult, although the observed personal:indoor:outdoor ratio of approximately 3:2:1 for several hundred residences is probably highly trustworthy.

(This raises an interesting point that I am not sure has been fully discussed. Mølhave's studies of the 22-compound mixture measured indoor concentrations in a small chamber, which would be expected to be equal to the personal exposures of the subjects. However, in a real-world situation, personal exposures to VOCs at the office may be rather different from the concentrations measured by a fixed sampler. People move about and may be close to a major source such as a copier for a period of time, resulting in higher personal exposures than the concentration measured at the fixed sampler. Since the dose-response function was based on personal exposure, then possibly the corresponding guideline for indoor concentrations should be ratcheted downward to take into account the likely increment in personal exposures due to source proximity. A proper test of this possibility would require simultaneous personal and indoor air monitoring in the office environment, a study that I am not aware has ever been carried out.)

Had we measured only TVOC in these studies, the loss of information would have been devastating. We would not have discovered the high levels of chloroform in homes due to use of chlorinated water; the high levels of *p*-dichlorobenzene in some homes due to use of moth cakes and room air fresheners; the infiltration of benzene and other gasoline vapors from attached garages; the extensive personal exposure and elevated indoor concentrations from wearing and storing dry-cleaned clothes, etc.

In our building studies, TVOC measurements alone would certainly have shown the 50-fold difference between new buildings and old, but would not have told us that most of the difference in two buildings was due to xylenes, decane, and undecane, whereas in a third building a chlorinated chemical — 1,1,1-trichloroethane — was a major actor.

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Letters

Michael Hodgson Responds to Mølhave's Comments

We also solicited an opinion from Michael Hodgson. Michael, an MD, is an associate professor at the University of Connecticut School of Medicine, Occupational Medicine Program, in Farmington, Connecticut.

Your newsletter is starting to serve an interesting purpose in providing such a formalized discussion. This is actually fun, stimulating, and probably quite useful. You asked for comments on the viability of TVOC.

Ideas live in a cave, far removed from life as we know it. That cave is also inhabited by other ideas, some conflicting, some contradictory, some consistent but not derivable. Gödel demonstrated the weakness inherent in our attempts to maintain consistency in every aspect of what we do.

The concept of dose-response relationships is fundamental to environmental health, implying that more exposure causes more effect. Nevertheless, such exposure-effects relationships can be defined in more than one way. In fact, in the world of toxicology, we distinguish between theoretical models (quantitative structure activity relationships, such as those developed by Abraham, Alarie, Cain, and Nielsen); isolated, organ-based, cell-based studies (none available for indoor air); animal studies (Alarie, Nielsen); and human studies. The latter include chamber and field studies (epidemiology).

Both exposures and effects must be measured, and both are then no longer pure ideas but defined in our world. Measurement error, problems of definition (construct and face validity, external validity, precision and accuracy), and temporal patterns serve to influence the relationships.

There has long been controversy on how to "add" exposures. The ACGIH and the OSHA Standard provide a simplistic approach on how to sum up the effects on one organ. Bill Cain (1995, Milan) has provided some data that "addition" may be an oversimplification. Few formal data sets have been collected in an attempt to sum up effects. Where they have, interactions were common. One need only remember the combined effects of trauma and radiation exposure or of asbestos and cigarette smoking to recognize how complicated the topic is.

Research is generally performed in one of two settings. In the lab, under controlled conditions, specific, well-defined hypotheses are tested on a well-defined population. Spatially homogenous and species-defined controlled exposures allow testing of well defined problems. These allow documentation of mechanisms and D-R relationships. The results may be extrapolated to a distinct set of conditions similar to those found in the experimental setting. Field studies, with all of their messiness, may identify susceptible populations and provide estimates of the magnitude of effects.

Work using the "Mølhave mixture" has suggested dose-response relationships for symptoms (eye, nose) and perfomance (cognitive impairment). As only one (or including the EPA, with a minor modification two) specific mixture(s) have been used, the data have limited extrapolatability in a strict scientific sense. In field studies (Franck and Skov, Kjaergard) these relationships have been difficult to replicate suggesting larger inter-subject variability. On the other hand, there is evidence on other levels of the importance of VOCs, in general (Menzies and Nunes in humans; Alarie, Nielsen and Wolkoff in animals).

I've been trying to do field work with screening techniques, recognizing the cost of triple sorbent tubes for each individual would break my unfunded budget. We have found weak though somewhat consistent relationships in two separate field studies of non-problem buildings. In the first (1991), VOCs measured with a photoionization detector (that responds more strongly to "reactive" than to "non-reactive" compounds) suggested a direct relationship. This pushed me away from my interest in particles and bioaerosols, at least in "non-problem" buildings. In a follow-up study, using a very poor instrument (Bruel and Kjaer PAD), we found relationships only after controlling for work stress, lighting and noise. So I'm meanwhile convinced that it is now appropriate to study VOCs more formally in the field with personal sampling, with triple-sorbent tubes, given the problems of exposure heterogeneity. The correct sampling interval remains to be determined.

I agree with Lars that an argument like TVOC is dead misses the point. The Olf may be dead too, but Ole Fanger's important documentation, that HVAC systems may be primary sources of contaminants, is meanwhile pretty much unchallenged. Science, and its revolutions, go on without philosophizing — although I really like to do so too.

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Air Change Effectiveness

In Vol. 3, No. 7 of the ***BULLETIN*** *we featured comments by several international IAQ experts on their perceptions of important findings at Indoor Air '96. David Wyon's comments included one we omitted that suggested his colleague at JCI, Cliff Federspiel, had an important paper. Wyon's omitted comment follows:*

> "...I would recommend to your attention the two papers by my JCI colleague Cliff Federspiel. His "reverse engineered" method of rapidly and effectively detecting step-changes in occupancy from a knowledge of system parameters and the initial rate of change of CO^2 in exhaust air (3:395) involves some heavy mathematics: the (1994) conference paper in which it was presented was judged the most significant paper of the session by the control engineers who understand it. The rest of us can appreciate that the practical applications in building management are not limited to demand-controlled ventilation, but may extend to lighting control (detecting occupants), security (detecting intruders) and fire prevention (detecting smouldering concealed fires), once CO^2 detectors become cheap enough to be located in every zone, or even in every room, and connected to a central building management computer. His demonstration that recirculation is an almost universal source of large and systematic error in calculating air change effectiveness from age-of-air measurements (3:971) may seem esoteric but addresses a source of major and previously unsuspected error in published IAQ research and HVAC practice."

Our omission led to this letter from Cliff Federspiel followed by a comment by Bill Fisk.

Engineers measure air-change effectiveness (also called ventilation effectiveness, ventilation efficiency, and air diffusion efficiency) to determine one of the following: (1) the "flow pattern" in the space (*e.g.*, the amount of "short-circuiting" or "displacement" flow), (2) how much higher or lower the ventilation rate (*e.g.*, in air changes per hour) in the occupied zone would be if the space were perfectly mixed. The most popular measurement methods involve the use of tracer gases and the calculation of age of air. Information about air-change effectiveness and age of air can be found in [1,2,3]. Here are two facts regarding the measurement methods:

1) In general, measurement methods designed to determine (2) cannot be used to quantitatively determine (1) because the determination of (1) requires that the age of the supply air be measured, while the determination of (2) does not [4,5]. The exception is when the age of the supply air is zero.

2) If a method designed to evaluate (2) is used to evaluate (1), the relative error may be as large as 100%. "Errors of this magnitude have been identified and are described in [4,5]."

References

[1] Sandberg, M., (1992), "Ventilation Effectiveness and Purging Flow Rate - A Review," *Proceedings of the 1992 International Symposium on Room Air Convection and Ventilation Effectiveness*, Eds. S. Murakami, M Kaizuka, H. Yoshino, and S. Kato, pp. 17-28.

[2] Persily, A. K., (1992), "Ventilation Effectiveness and Purging Flow Rate - A Review," *Proceedings of the 1992 International Symposium on Room Air Convection and Ventilation Effectiveness*, Eds. S. Murakami, M Kaizuka, H. Yoshino, and S. Kato, pp. 201-212.

[3] Fisk, W. J. and D. Faulkner, (1992), "Ventilation Effectiveness and Purging Flow Rate - A Review," *Proceedings of the 1992 International Symposium on Room Air Convection and Ventilation Effectiveness*, Eds. S. Murakami, M Kaizuka, H. Yoshino, and S. Kato, pp. 213-223.

[4] Federspiel, C. C., (1996), "The Effect of Recirculation on Air-Change Effectiveness Calculations," *Proceedings of Indoor Air '96*, Vol. 3, pp. 971-976.

[5] Federspiel, C. C., (1996), "The Effect of Recirculation on Air-Change Effectiveness," *Proceedings of the 17th AIVC Conference*, Gothenburg, Sweden, Vol. 1, pp. 15-23.

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Fisk on Federspiel's Letter

I believe that most of the major researchers of ventilation efficiency (*e.g.*, of air change effectiveness, etc.) have recognized for a very long time that both the indoor air flow pattern (inside the room) and mechanical recirculation are important and that both phenomena influence measurement results. In the case of pollutant removal efficiencies, we also recognize that the nature of the pollutant source, such as location, velocity, is important. The research community (at least the majority) has not had major flaws in their thinking about this subject. For example, my work, both field and laboratory studies, has often included measurements with 100% outside air and measurements with mechanical recirculation. We have, in many cases, been guilty of sloppy language, often stating without qualification that the ACE is a indicator of the indoor air flow pattern. The concepts are complex and difficult to describe concisely in writing. For example, one can think of the indoor air flow pattern as just the pattern of flow in the occupied space or as the pattern of flow in the building with an HVAC system, which includes mechanical recirculation. Also, one can think about the short circuiting flow patterns of air within a room or one can think about the effective short circuiting,

just of outside air, between the outside air intake and the building exhaust. None of these conceptual models meets all of our needs. The application of age of air theory to this field has brought substantial mathematical rigor, but we still try to use simple conceptual models (*e.g.*, amount of short circuiting) to explain what is happening. Different people use different internal conceptual models, which makes communication difficult.

I believe that Clifford has developed a model (mathematical, not conceptual) that relates ACE with recirculation to that without recirculation. This model is an important addition to the research literature and may be shown in the future to have considerable practical value, but it does not invalidate prior research.

[This] discussion should help us to clarify our language in future papers.

William J. Fisk, Ph.D., Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, 94720.

SBS

Discovery of Causes Trails Discovery of Preventive Measures

The history of medicine is full of cases where preventive measures for important diseases were found long before causative mechanisms or therapeutic activities were understood. The same principle applies for SBS.

E. L. Wynder discussed some of the classic examples of the long lag time between the discovery of preventive measures and the discovery of the "true causative or preventive agent" in the *American Journal of Epidemiology.* Wynder clearly shows some representative examples from the history of medicine in Table 5. It shows the gap between when preventive measures based on clinical or epidemiological observations were known and the time causative or curative agent became known. In the case of scurvy, the gap was 175 years. For pellagra, scrotal cancer, and smallpox, the gap was more than 150 years.

For diseases, as important as mechanistic studies are to understanding disease pathogenesis, the preventive measures can reduce disease incidence decades or even centuries before our understanding of the intricate pathogenesis is complete.

Wynder says that if Americans didn't smoke, "...lung cancer would be about as uncommon as it was in 1912 when I. Adler apologized for writing a monograph on a disease as rare as lung cancer." According to Wynder, the "...major causes of death, notably cardiovascular diseases, cancers, and acquired immunodeficiency syndrome, are related to lifestyle and environmental variables. Much of this disease burden could be significantly reduced on the basis of existing evidence without much more knowledge than we have now about the specific mechanisms by which these factors induce disease."

The same can be said for SBS and building-related illness. We know how dramatically to reduce the incidence of these and other building problems. These also involve simple "lifestyle" changes.

Reference

E. L. Wynder, 1994. "Invited Commentary - Studies in Mechanism and Prevention: Striking a Proper Balance." *American Journal of Epidemiology*, Vol. 139 (6): 547-549.

Table 5 - Comparison of the date of discovery of a measure to prevent a disease with the date of identification of its true causative or preventive agent. * References in the table are available in Wynder, 1994 or upon request from the ***BULLETIN.***

Disease	*Discoverer of preventive measure **	*Discovery of preventive measure*	*Discovery of agent*	*Causative or preventive agent*	*Discoverer of agent **
Scurvy	J. Lind	1753	1928	(Ascorbic acid)	A. Szent-Gyorgi
Pellagra	G. Casal	1755	1924	(Niacin)	J. Goldberger *et al.*
Scrotal cancer	P. Pott	1775	1933	Benzo[a]pyrene	J. W. Cook *et al.*
Smallpox	E. Jenner	1798	1958	Orthopoxvirus	F. Fenner
Puerperal fever	I. Semmelweiss	1847	1879	Streptococcus	L. Pasteur
Cholera	J. Snow	1849	1893	Vibrio cholerae	R. Koch
Bladder cancer	L. Rehn	1895	1938	2-Napththylamine	W.C. Hueper *et al.*
Yellow fever	W. Reed *et al.*	1901	1928	Flavivirus	A. Stokes *et al.*
Oral Cancer	R. Abbe	1915	1974	N-nitrosonormicotine	D. Hoffmann *et al.*