

## Why MCS provocation studies are so unreliable, and how to make them better



**Provocation studies are often considered proof that MCS is a psychosomatic illness, but the reality is that they are very unreliable. Most existing studies are deeply flawed and provide no proof of anything.**

*Keywords: MCS, chemical sensitivity, provocation test, challenge study, inhalant study*

Provocation studies test people by exposing them to a noxious chemical. Most studies also use an inert placebo, with the test persons not knowing when it is the chemical or the placebo they are exposed to.

On the surface it seems very straightforward to do these tests, but in reality there are so many factors to keep under control that such studies become complicated and expensive. Most scientists take too many short-cuts, which make their studies unreliable.

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Another major problem is that humans are simply not reliable testers, whether they have MCS or not. Studies of people who do NOT have MCS show a great many feel sick if they think they are exposed to a toxic chemical. This alone explains why so many MCS provocation studies fail to prove anything, as people with MCS are just as prone to this effect as regular people.

In the 1980s there were several provocation studies exposing asthmatics to cigarette smoke. These studies also provided contradictory results (Stankus 1988).

This document discusses these many difficulties. We hope to make it clear why these studies are so unreliable and contradictory. We also hope it will help future scientists design provocation studies that are better and more fair.

In praxis it may not be realistic to make reliable and fair provocation studies using inhalants.

### **High stakes**

MCS is presently widely believed to be psychosomatic, with some scientists, journalists, and other people pointing to provocation studies as “proof.”

About fifty provocation studies have been done on people with MCS. The scientific community is divided on how to interpret them (Das Munshi 2006; Goudsmit 2008; Viziano 2018).

This results in people feeling justified denying requests from MCS patients to accommodate their basic needs. This is commonly seen with health providers, co-workers, bosses, and family members,

Health providers tend to ignore patients with MCS, and some suggest they go see a psychiatrist (even though there is hardly any science supporting psychiatric treatments, and some that find them harmful).

Those who get so sick with MCS they can no longer work have a hard time getting on disability because of the controversies. Some do not succeed and live in poverty.

Another effect is that scientists and funders of science don't see MCS as a legitimate field to study. Thus there is very little research done that can help the sufferers, and help make MCS legitimate. It is so bad that when Harvard University was bequeathed \$5 million for MCS research, they took the money, and did no real MCS research.

## **The types of provocation studies**

We have found four types in the scientific literature:

- Inhalant
- Oral
- Dermal
- Eye

The inhalant studies are by far the most common, perhaps because people with MCS complain mostly about inhalants. However, inhalant studies may also be the most difficult to do well.

Inhalant studies usually use some sort of exposure chamber where gasses are pumped in or evaporates from a canister.

Oral provocations usually use capsules that are swallowed, though could also use regular meals with/without the test ingredient mixed in to mask any taste, color, and smell.

Derma testing is either on the skin surface or intradermally.

Eye tests are rare. The idea is that fumes can enter the bloodstream through the thin membrane around the eye.

## **Overview of confounding factors**

- Symptoms are poor indicators
- Nocebo effect
- Inert placebo is not inert
- Levels of sensitivity vary
- Individual variability
- Adaptation (“masking”)
- Overconfident test subject
- Below olfactory threshold
- Sensory fatigue
- Sensitization with multiple exposures
- Screening of participants
- Selection bias
- Exposures before arriving

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- Exposures from testing venue and staff
- Delayed reactions
- Researcher bias

### **Symptoms are poor indicators**

Relying on symptoms as indicators of whether a substance is a problem or not is really difficult, especially with people who are chronically ill and typically reactive to a great many things in their environment.

People who are chronically ill have their good days and bad days, without any apparent cause. This is not just the case with MCS patients.

People with MCS are usually also reactive to pollen, mold, foods, food additives, and much else. But the exact list of problem substances varies with the person. Each person is probably not even aware of the full list.

In the hours before the testing, the person may be exposed to all sorts of things in their food and air, both at home and on their way to the laboratory/testing venue. Some of these substances the person may not even be aware of.

When the testers finally sit in the test chamber, how well do they actually feel to start with? Can they really tell reliably whether the symptoms they get there are truly new, and not just coming from whatever else they are dealing with?

### **Nocebo effect**

The nocebo effect is when a person reports symptoms from a harmless (sham) exposure. Since there have been many of those in MCS provocation studies, some researchers have concluded MCS is psychosomatic. It is not that simple.

First of all, there are several ways a test person can get symptoms that *appear* to be caused by the placebo, but is actually caused by something else that is not realized. This includes a placebo that is not truly inert, a poorly controlled test, and much else. These factors are discussed later on.

There are of course also real nocebo effects to truly harmless sham exposures. But that also happens to people who do not have MCS, and there is no evidence that people with MCS are more prone to nocebo reactions than other people. Studies show that 30 to 50 percent of regular healthy people can have nocebo reactions.

This problem alone can explain why the provocation studies fail to prove MCS. The studies and reviews assume that any nocebo effect means that the person with MCS is psychosomatic, thus they demand that MCS test subjects are “superior beings” compared to regular people. That is an impossible demand.

The subject of nocebo effects in people with MCS and in regular people is discussed in detail (with references) at [www.eiwellspring.org/edu/Nocebo.html](http://www.eiwellspring.org/edu/Nocebo.html).

### **“Inert” is not inert**

People with MCS can be sickened by a great many things that are considered inert by many scientists. That can include preservatives, any sort of scent (including essential oils), the excipients used to manufacture pills, and many more. If a person is reacting to a supposedly inert placebo, it may not be the nocebo effect.

### **Levels of severity**

MCS can vary from mild to very severe. The severe cases comprise about 4 percent of the total MCS population (Kreutzer 1999; Berg 2008).

People with severe MCS are more likely to react to the venue and other factors. Those with mild MCS may not even react to the challenges.

Dividing the test subjects into groups according to how severe their MCS is can make the data more clear (Berg 2011).

### **Individual variability**

A major difficulty in the studies is that no two people with MCS react exactly the same way.

They do not all react to the same chemicals, at least not in the low concentrations of interest. Fragrances are the most common complaint, but 14% report they are fine with fragrances (Steinemann 2018). Some even use fragrances themselves.

They do not all have the same symptoms. Brain fog is a common and distinct symptom, but it is not universal. A wide variety of systems can be affected, though the most common is neurological (Lacour 2005).

The severity can vary dramatically, though those with the most severe effects are unlikely to volunteer for a provocation test. Even if they do participate, they may have to withdraw (Rea 1989).

The time from the start of the challenge and until symptoms manifest is also highly variable. For inhalants it can vary from a minute to hours, at the same level of concentration.

The time to recover from an exposure also varies. For a mild and short exposure it could vary from five minutes to several hours, sometimes, days.

### **Adaptation**

Some people are so adapted to certain kinds of incitants that they cannot detect them (called “masking” in MCS parlance). But they can still have chronic symptoms from them and not be aware of the cause.

This is very common among people who have only had MCS for a few years, especially if they do not socialize in person with other people who have the disease (who may more easily point out a problem).

Provocation with an adapted-to substance will give very unreliable results.

### **Overconfident test subjects**

Be aware that test subjects can be overconfident in their ability to discern things, and on how non-toxic their own clothes are (as they are masked/adapted to them).

Anyone who has spent weeks at a large MCS clinic should have seen some of the many surprises that commonly show up.

### **Below olfactory threshold**

It is a common myth that people with MCS are reactive to smells only. Some are so sensitized they can be sickened by fumes so faint they are not able to smell them (Rea 1989).

It appears to take longer to elicit a reaction at such low levels, and it is not everybody who are that sensitive (Rea 1989).

We know one person who has no sense of smell at all. She has been that way since a small child. She still reacts to “smells,” and without her nose to warn her she has to be extra careful and regularly gets sickened when out in public.

### **Sensory fatigue**

Each test person should not be challenged more than once a day, or at least with several hours of recovery time between each challenge.

Symptoms do not just disappear once the challenge is removed. There may also be a build-up or an adaptation effect, by which subsequent exposures either have stronger or weaker effects.

Any exposures prior to the test, whether in the subjects home, en route, entering the lab building, or sitting in a waiting room, can skew the results because of sensory fatigue (or adaptation).

### **Sensitization upon long or multiple exposures**

Some people with MCS quickly sensitize to something they are exposed to. This is especially the case for inhalants.

If a person inhales the same substance four days in a row, there may be no reaction on the first day, while there may be a reaction on the fourth day. (Timing is very individual).

Then if there is no exposure for some time (weeks/months/years) then there may again be no reaction when inhaling it.

This is similar to people who are fine the first days of pollen season, and increasingly miserable the rest of the season. Then again losing most of their sensitivity during the following winter.

A similar effect has been observed in healthy women (Dalton 2002).

### **Screening of participants**

Screening is important to exclude people who do not actually have MCS (but think they do) and people who have other problems that can interfere.

Lacour et al. (2005) lists several diseases than may mimic MCS, such as anemia, diabetes, kidney disease, schizophrenia, and many others.

Many older MCS studies used as their sole criteria for inclusion that subjects believed they had MCS, or they considered themselves “unusually sensitive” to fragrances or other chemicals. Newer studies tend to use the QEESI questionnaire.

Some ask if they have been diagnosed with MCS by a physician, besides the more generalized 1999 Consensus Criteria, or the stricter Lacour criteria (Lacour 2005).

Very few provocation studies use exclusion criteria to remove subjects who have problems that would make them unreliable testers, such as those with major mental illnesses. We are only aware of a few (Fiedler 2000; Hillert 2013; Viziano 2016).

People with severe MCS often have chronic or near-chronic symptoms. And they may have conditions that produce similar symptoms, such as Chronic Fatigue Syndrome (CFS/ME). They often don't really know where one condition ends and the other starts. Such people are best screened out.

Some studies use people who are in the process of applying for disability or other compensation. That is a high-stress situation, since failure can result in permanent poverty and even homelessness in a way few non-patients can appreciate. People in that situation may not be suitable testers.

### **Two-stage studies**

A significant number of people do not make “good testers” due to nocebo effects or other issues. Consider screening them out in a first stage.

Such an initial screening stage could test if they have symptoms from the test venue and staff, or they produce false reactions from placebos.

Unfortunately, such screening is almost never done, which may be another major factor in the failure of these provocation studies.

### **Selection bias**

How are the participants recruited? Most studies were done at psychiatric clinics; could that skew the clientele? This writer would be very reluctant to participate in a study at such a place, since bias and poor accommodation can be expected. If the people conducting the study believe MCS is all mental, they are much less likely to provide a non-toxic venue.

We have also seen studies where participants were recruited through a psychiatric clinic, meaning the participants may not be representative of the MCS community.

### **Beware of the paragon bias**



People from all backgrounds get MCS. A study may include some poorly educated people whose opinions can be a culture shock to a highly educated scientist who otherwise never associate with that strata of American society.

Then add that most people with MCS have lost faith in mainstream physicians because of how they were ignored, mistreated, accused of malingering, and much else. People with MCS are not paragons, they do not all understand science, physics, and biology.

We've seen one psychiatrist who in his study of 18 people with MCS made much of one person's beliefs in pendulums and other dubious ideas (no mention of the other 17 people's ideas). If you take a true cross-section of Americans, you will find some with such ideas whether they have MCS or not.

### **Recovery time**

The test participants need ample recovery time. If they are still affected by a provocation, then they cannot participate in a new provocation. Sometimes the participants are not fully aware that they are still affected, especially those who have more or less chronic symptoms.

Some symptoms may show an hour after the provocation exposure ends. They may even manifest the following day.

There should never be more than one provocation challenge in one day, and much preferable some days in between.

In clinical studies of people with asthma and allergies, they recommend 2 to 3 weeks between each challenge (Gauvreau 2022).

### **Comparison studies**

If doing a provocation study that compares an MCS group to another group, make it fair! The comparison group should also be chronically ill, as chronic illness in itself can affect people's responses and mental state. This issue should be pointed out in the report.

### **Focus on objective measurements**

Objectively measured parameters are of course superior to subjective symptoms. But which ones? A few provocation studies have found objective signs, which

should be retested (Elberling 2007; Belpomme 2015; Dantoft 2015; Wardly 2018; Rea 1978).

Asthma is very common among people with MCS (Steinemann 2018a, 2018b). Since asthma can be objectively verified in provocation tests (Gauvreau 2022), it makes sense to do some studies exclusively with subjects who have both MCS and chemically-induced asthma.

## **Inhalant studies**

Inhalant studies are particularly difficult. How to provide a truly inert placebo, and at the same time make sure the test subjects do not use any odor cue to identify the active challenge?

Several studies added some sort of masking agent to both the fresh air placebo and the active challenge, so they smelled the same. But no masking agent is inert, so the fresh air is no longer fresh!

Any kind of VOC/SVOC, whether natural or artificial, is problematic. This includes all essential oils. The only inert inhalant placebo is fresh air, relatively free of mold, pollen, and dust.

It is no wonder such inhalant studies fail to show MCS patients can reliably distinguish between “inert” placebos and active challenges (Staudenmayer 1993). The MCS-skeptics do not see it that way, but says the MCS sufferers simply react to placebos (Das Munshi 2006).

Some studies have used odor-free irritants, such as capsaicin (Ternesten-Hasseus 2013). Though critics dismiss them as irrelevant, since capsaicin is not seen as a “classic” MCS problem (Das Munshi 2006).

Other studies have used nose clips to block the olfactory sense, but that also omits what may be an important part of the mechanism of MCS (Millqvist 1999).

In 1989, fifty MCS patients were housed in a controlled environment so they were fully de-adapted (unmasked). They were exposed to chemicals such as formaldehyde and chlorine at levels below the olfactory threshold in a double-blind manner. That was too low a concentration; half of the test subjects didn't react to any challenge and nobody reacted to all types (Rea 1989).

If the stimulation of the olfactory system is an important part of MCS, then it may be impossible to find a suitable placebo.

## **Oral provocation studies**

Any oral placebo must be tested by EVERY test subjects to see if it is truly inert. If using a capsule, it by itself can cause symptoms. So can any kind of filler, dye, binder, or flavoring.

Regular tap water is not benign to many people with severe MCS, depending on its source, chlorination, and other treatments. Bottled water from a spring is essential.

Serving a dish with and without the active challenge mixed in is another possibility. But then the active challenge may be too diluted. Also be aware that people with MCS seem to be better able to tolerate challenges during or shortly after a meal.

What appears to be the first published provocation study was done in 1963, where three people with MCS were exposed to food and water which had been either stored in glass or plastic containers (Kailin 1963). It is possible that the plastic containers imparted a slight taste or smell to the food and water, which gave the testers a cue.

Another possibility is keeping the test in the mouth. This has not been done in clinical studies, but dentists use this method to determine which composite material (dental plastic filling) is most tolerable. Though what to use as the sham is a challenge.

## **Dermatological provocation studies**

Skin testing can be done with patches or intradermally (Berg 2011; Elberling 2004).

Be aware that patch adhesives, and injected preservatives, can produce symptoms on their own. Also check any antiseptic used, which must be fragrance free and as benign as possible (such as benzalkonium chloride, alcohol, or hydrogen peroxide).

## **Provocation through the eye region**

We have found one study where the eyes were exposed to perfume fumes (Millqvist 1999).

They used a special mask that directed fresh air to the mouth and nose. It is essential that both mask and tubing are inert (offgassed) and not causing symptoms. Participants who react to the mask should be screened out before the test.

Since there is no olfactory cue, there is no need for a masking agent, which is a likely confounder. The Millqvist study produced clear distinction between active and sham exposure, and should be replicated with a larger study.

### **The testing venue**

It is important that the venue itself does not cause symptoms to confuse the test. This includes the path of travel into the clinic, the clinic waiting room, bathroom, and testing area (Osterberg 2003).

Air purifiers designed for people with MCS (such as Aireox and Austin Healthmate) can be helpful, but they are not magic. They can only help, not make a terrible place benign. A few people with MCS do not tolerate the filter materials in all types of air purifiers.

Some of the more severe cases of MCS also react to fluorescent lights, televisions, and computers. They may also react to noise, music, whirring fans, and TV sounds. Problems with mold are also very common. Some also have problems with wireless devices and electrical motors (including air purifiers).

Using the clinic of a physician who regularly treats people with MCS may be necessary.

### **Staff and other people**

Any person encountered can provoke a reaction. This can be the receptionist, laboratory staff, people in the waiting room, even other people with MCS who do not share their particular sensitivities and are not sufficiently inert.

Common problems:

- Personal care products
- Laundry chemicals
- Smoking
- Indirect exposures

It is not possible to become non-toxic overnight. It takes weeks or months. This is hard to grasp for people who live the “normal” chemical lifestyle, as they are accustomed to breathing in chemical fumes 24/7 which they barely even notice (adaptation).

It is not just a matter of washing the clothes in baking soda and taking a shower.

Laundry chemicals are embedded in the fibers and are difficult (or impossible) to wash out again. This is especially the case with fabric softeners. It is probably easier to buy new clothes and wash them ten times in baking soda.

If the clothes are washed in a washer or dryer used by others, chemicals from their laundry products will be transferred to the staff member’s “safe clothes.” This is both a problem at home and at a laundromat. And the extent of how many, and which, chemicals are transferred is determined by the recent users of the machines, so it can vary dramatically.

Dry-cleaned clothes must be aired out for several days.

A person who uses fragrances does not become fragrance free by just taking a shower. The fragrance chemicals are stored in the fatty tissues from where they are slowly released into the blood stream for weeks. From there they are carried into the air through the lungs and evaporated by perspiration. A person with severe MCS can smell and react to this for weeks. (There are breath analyzers that can objectively verify this).

Benign personal care products are available, but may not even be stocked at the local health food store. Products containing any amount of essential oils are not acceptable. Products labeled “unscented” may still contain “masking fragrances.”

A smoker breathes out gases and smoke particles for hours after the last cigarette. Particles also hang in the person’s clothes and hair. A non-smoker who visits a smoky room will even breathe out smoke and gases for hours after leaving the room.

Indirect exposures happen when a person’s hair and clothes pick up fumes and particles elsewhere and then slowly release them later on. Sharing a car, subway train, or elevator with fragranced people or smokers will do this. Visiting a fragranced restroom will do it. Even going into most stores will do it.

In principle it is simple enough to go through the clean-up process, but compliance can be difficult to obtain. Little “short-cuts” are tempting and it is easy to re-

contaminate clothes etc, and then blame the problems on the people with MCS as being overly fussy.

You will need the assistance of someone with severe MCS to evaluate whether staff and venue is sufficiently non-toxic. Regular people simply cannot, unless they've lived the non-toxic lifestyle for many months (family members who have to live non-toxic all the time eventually notice chemical smells they did not before, though the fumes don't make them sick).

### **Environmental Control Unit**

Several physicians operated Environmental Control Units in the 1980s. They are in-patient facilities where the environment is rigidly controlled so the MCS patients can better experiment with what may make them sick, including foods and inhalants.

Such a facility can dramatically eliminate many possible confounders in provocation studies, but a research-ECU was never built.

A few provocation studies were done in ECUs, but these ECUs were owned by individual physicians and focused on treating MCS patients on a commercial basis. Operating an ECU is expensive. They became uneconomical and the last was closed in the late 1990s.

### **Researcher bias**

If the researcher starts out with the assumption that MCS is a psychomatic problem, there may be a greater tendency to design the study to arrive at that result. With that stance, the issues described in this document will likely seem overly fussy and unnecessary. Thus the study becomes a self-fulfilling prophecy.

Then, when the results support the theory that MCS is psychosomatic, there may be a tendency to accept that too fast (confirmation bias).

Most of the existing studies were done by psychologists/psychiatrists. Some have expressed rather strong opinions towards dismissing MCS as legitimate. It would be preferable for a study to be done by scientists who do not have a set agenda.

### **Disregard the first challenge session**

It takes some amount of bravery to volunteer to get hurt. There will be a lot of apprehension, especially at the first challenge. Test subjects may be more relaxed

at the following challenges, and thus less prone to false nocebo responses. It may be prudent to disregard the result of the first challenge.

### **Report drop-outs**

The report should state how many people refused to participate or later dropped out (and what their reasons were).

If people drop out because the venue is deemed unsafe, that is an important metric.

### **Learn from studies on healthy people**

Studies on healthy people show that indoor air quality well within accepted standards still affects people's cognitive abilities.

In a simple study, office workers were given either new or offgassed computers (with CRT screens), and their performance measured (Bako-Biro 2004).

Another study exposed professional-class people over six days to varying levels of fresh air in a custom-built office environment, while they did their normal work (Allen 2015).

In both studies the test subjects were blinded to the exposure levels. Both studies clearly showed the difference better air quality makes for healthy people. Then why is it so hard to accept that there is a much larger effect on people on the extreme end of the bell-curve of chemical tolerance?

It is also noteworthy that the Allen study was much better funded and more sophisticated than any MCS provocation studies ever done.

### **Should provocation studies be abandoned?**

Given the difficulty and unreliability of these studies, and that their failures are used to unfairly label a group of patients as psychomatic, some scientists have called for a halt until better protocols can be developed (Brussels Declaration 2015).

An editorial in the prestigious journal *BMJ*, is philosophically opposed to challenge studies of all kinds (Spiegel 2004).

It may simply be impossible or impractical to do a provocation study that is fair to the MCS community.

## More information

General medical information about MCS is available on [www.eiwellspring.org/health.html](http://www.eiwellspring.org/health.html).

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