Re-evaluation of safety of the 'other substance' methylsulfonylmethane (MSM) in food supplements

by

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Table of content

Summary 4

Norsk sammendrag 6

Abbreviations 8

Background 9

New literature searches 9

Description of included publications 9

Studies of MSM alone in adults (≥18 years) 10

Studies of MSM in multicomponent dietary supplements in adults (≥18 years) 12

Studies of MSM alone in children and adolescents 17

Studies of MSM in multicomponent dietary supplements in children and adolescents .. 17

Table 1. Study characteristics of the included human studies of oral MSM exposure. 19

Risk of bias (RoB) evaluations of the included human studies 25

Table 2. Classification of studies into tiers according to overall RoB. 25

Miller et al. (2021) (Tier 3) 25

Muizzuddin and Benjamin (2022) (Tier 3) 26

Toguchi et al. (2023) (Tier 1) 27

Guaitolini et al. (2019) (Tier 1) 29

Liu (2020), Liu et al. (2020; 2021) (Tier 1) 30

McFarlin et al. (2021) (Tier 1) 32

Tanner et al. (2022) (Tier 3) 34

Desideri et al. (2022) (Tier 3) 35

Pogacnik et al. (2023) (Tier 1) 36

Adams et al. (2022) (Tier 3) 37

Table 3. Dose and duration of MSM exposure, and RoB evaluations, for the included studies. 38

Summary of included new human studies 39

Study used as PoD in the VKM report 40

Other relevant information 40

Discussion on the appropriate size of the uncertainty factor (UF) 41

Study quality 41

Exposure length 42

Interindividual human variation 42
NIPH's conclusion on choice of a total UF 43
Conclusions on safety of MSM for adults 43
Conclusions on safety of MSM for children and adolescents 43
Uncertainties and perspectives in this re-evaluation 44
References 45
Appendices 49
Appendix A. Search strategy - Medline 49
Appendix B. Search strategy - EMBASE 51

Summary

The Norwegian Institute of Public Health (NIPH) was asked by the Norwegian Food Safety Authority (NFSA), to reevaluate the safety of methylsulfonylmethane (MSM) in food supplements for both sexes in the Norwegian population, in adults (≥18 years) and in children and adolescents in the age groups - <10 years, 10 - <14 years and 14 - <18 years. The doses of MSM to evaluate for safety were 3 g, 2 g, 1.5 g, 1 g or 0.5 g per day or 302 mg per day, in all age groups.

New literature searches similar to the searches in Medline and EMBASE used by the Norwegian Scientific Committee for Food and Environment (VKM) in their previous risk assessment of MSM in 2021 were performed. Seventeen publications were included in this re-evaluation of MSM from the literature search. Seven of these reported original research on effects of MSM, and so did three publications found outside the search, thus, ten studies described in 12 publications (the same study was described in Liu (2020), Liu et al. (2020) and Liu et al. (2021)) were described and underwent risk of bias (RoB) evaluations.

Of the ten included new human studies considered relevant for an evaluation of adverse effects of MSM, five were scored as Tier 1 and five were scored as Tier 3 in the RoB evaluations. Only one study that scored Tier 1 used exposure in adults to MSM alone, as 2 g/day for 3 months. Two other studies using MSM alone in adults were scored Tier 3, thus having more bias, and used 1 or 3 g/day of MSM for 4 months. Among the studies of MSM in multicomponent dietary supplements in adults, four were considered Tier 1, using MSM in 0.4 to 1.5 g/day for 1-3 months. Two studies scored Tier 3 used 0.2 or ca. 1.0 g/day of MSM for 6 months or 1 month in adults, respectively. Only one of the new human studies included children and adolescents, as well as adults, with autism spectrum disorder. A multicomponent dietary supplement that also contained MSM was given in doses depending on their body weight (and thus, also age), from 500 mg/day (3-14 years of age) to 1000 mg/day (10-18 years of age). The exposure was reported to vary from 3-5 months to more than 4 (or 6) years, with median usage of ca. 12 months. However, this information on duration of exposure was not linked to individual data on age or body weight, and thus, dose of MSM. These studies appeared to be without treatment-related significant adverse effects or the adverse effects/events were not different between the MSM and placebo/control groups.

None of the new studies used a higher dose of MSM than the study used as PoD by VKM in 2021 (Crawford et al., 2019b). One study had a longer exposure period (6 months), however, they used a lower dose of MSM (0.2 g/day). Therefore, the study by Crawford et al. (2019b) was still considered to be the most relevant to use as PoD in a re-evaluation of MSM by NIPH. Parameters of physiology, hematology, liver and kidney functions showed no significant difference between MSM and placebo values in this study. This study was also supported by another publication on humans, given slightly lower total MSM dose, which reported no major adverse events and with side-effects with comparable frequency in the MSM and placebo groups.

MSM is an endogenously formed substance, which is also ingested through food. No interactions of MSM with medications are known and it was shown to have a low potential for cytochrome P450-mediated drug interactions with for instance osteoarthritis medications that are likely to be co-administered.

In this re-evaluation of MSM, the appropriate size of the uncertainty factor (UF) to be used was re-considered. VKM (2021) used an UF of 6 for extrapolation from short-term (4 months) to chronic exposure, an UF of 2 for uncertainty related to data quality and an UF of 2.5 for potential interindividual human variation in susceptibility to MSM, adding up to a total UF of 30. Using a PoD of 6 g/day of MSM led to a conclusion of 0.2 g of MSM per day as the highest safe dose in adults.

However, NIPH proposes an UF of 2 for extrapolation from short-term (4 months) to chronic exposure, no UF for data quality, since the publication used for PoD was scored Tier 1 in the RoB evaluation, and an UF of 2.5 for interindividual human variation in susceptibility in adults, resulting in a total UF of 5.

When using a total UF of 5 on the PoD of 6 g/day, this will result in 1.2 g/day as the highest safe dose. Then the doses of 302 mg/day, 0.5 g/day and 1 g/day of MSM for up to 4 months are considered safe for adults. The safety of the doses 1.5 g/day, 2 g/day and 3 g/day of MSM for up to 4 months for adults is uncertain based on the available data.

Ideally, for 'other substances' used in food supplements, the risk assessments should be based on toxicity data from experimental studies with chronic exposure. NIPH is not aware of the usual or recommended length of exposure to MSM.

No conclusions on safety when using MSM for children and adolescents in the age groups 3 - <10 years, 10 - <14 years and 14 - <18 years can be drawn for any doses in this updated risk assessment, because only one study was found with bias (Tier 3) and information about doses and duration of exposure not linked to age (or body weight).

Norsk sammendrag

Folkehelseinstituttet (FHI) ble bedt av Mattilsynet om å revurdere tryggheten til metylsulfonylmetan (MSM) i kosttilskudd for begge kjønn i den norske befolkningen, hos voksne (≥18 år) og hos barn og ungdom i aldersgruppene <10 år, 10-<14 år og 14-<18 år. Dosene av MSM som ble vurdert med tanke på helsemessig trygghet var 3 g, 2 g, 1,5 g, 1 g eller 0,5 g per dag eller 302 mg per dag.

Nye litteratursøk tilsvarende søkene i Medline og EMBASE som ble brukt av Vitenskapskomiteen for mat og miljø (VKM) i sin tidligere risikovurdering av MSM i 2021 ble utført. Sytten publikasjoner ble inkludert i denne revurderingen av MSM fra litteratursøket. Syv av disse rapporterte original forskning på effekter av MSM, og det samme gjorde tre publikasjoner funnet utenom søket. Dermed ble ti publikasjoner beskrevet og vurdert med tanke på risiko for skjevheter (dvs. systematiske feil) (RoB).

Av de ti inkluderte nye studiene på mennesker som ble ansett som relevante for en evaluering av skadelige effekter av MSM ble fem scoret som nivå 1 og fem ble scoret som nivå 3 i RoB-evalueringene. Bare én studie som ble scoret til nivå 1 eksponerte voksne for MSM alene, som 2 g/dag i 3 måneder. To andre studier som administrerte MSM alene til voksne, ble scoret som nivå 3, og hadde dermed mer skjevhet, og brukte 1 eller 3 g MSM/dag i 4 måneder. Blant studiene av MSM i flerkomponent-kosttilskudd hos voksne (dvs. de som inneholdt andre stoffer i tillegg til MSM), ble fire ansett som nivå 1 og brukte MSM i doser på 0,4 til 1,5 g/dag i 1-3 måneder. To studier som ble scoret nivå 3 brukte 0,2 eller ca. 1,0 g MSM/dag i henholdsvis 6 måneder eller 1 måned hos voksne. Bare én av de nye studiene på mennesker inkluderte barn og ungdom, i tillegg til voksne, med autismespekterforstyrrelser. Et flerkomponent-kosttilskudd som også inneholdt MSM ble i denne studien gitt i doser avhengig av kroppsvekt (og dermed også alder), fra 500 mg/dag (3-14 år) til 1000 mg/dag (10–18 år). Eksponeringen ble rapportert å variere fra 3-5 måneder til mer enn 4 (eller 6) år, med en medianbruk på ca. 12 måneder. Denne informasjonen om eksponeringsvarighet var imidlertid ikke knyttet til individuelle data om alder eller kroppsvekt, og dermed dose av MSM. Disse studiene så ut til å være uten behandlingsrelaterte signifikante skadelige effekter, eller bivirkningene var ikke forskjellige mellom MSM-gruppen og placebo/kontrollgruppen.

Ingen av de nye studiene brukte en høyere dose av MSM enn studien som ble brukt som utgangspunkt (PoD) for risikovurderingen av VKM i 2021 (Crawford et al., 2019b). Én studie hadde en lengre eksponeringsperiode (6 måneder), men de brukte en lavere dose av MSM (0,2 g/dag). Derfor ble studien av Crawford et al. (2019b) fortsatt ansett som den mest relevante å bruke som PoD i en ny risikovurdering av MSM utført av NIPH. Parametere for fysiologi, hematologi, lever- og nyrefunksjoner viste ingen signifikante forskjeller mellom verdier etter MSM- og placebo-eksponering i denne studien. Denne studien ble også støttet av en annen publikasjon på mennesker, gitt en litt lavere total MSM-dose, som ikke rapporterte noen større skadelige effekter og med bivirkninger med sammenlignbar frekvens i MSM- og placebogruppene.

MSM dannes endogent i kroppen og inntas også gjennom mat. Ingen interaksjoner mellom MSM og medisiner er kjent, og MSM ble vist å ha et lavt potensiale for cytokrom P450-enzym-medierte legemiddelinteraksjoner med for eksempel slitasjegiktmedisiner som kan bli administrert samtidig.

I denne revurderingen av MSM ble den passende størrelsen på den totale usikkerhetsfaktoren (UF) diskutert. VKM (2021) brukte en UF på 6 for ekstrapolering fra kortvarig (4 måneder) til kronisk eksponering, en UF på 2 for usikkerhet knyttet til datakvalitet og en UF på 2,5 for potensiell interindividuell menneskelig variasjon i følsomhet for MSM, noe som gir en total UF på 30. Fra en utgangsdose på 6 g/dag førte dette til en konklusjon på 0,2 g MSM per dag som den høyeste trygge dosen for voksne.

NIPH foreslår imidlertid en UF på 2 for ekstrapolering fra kortvarig (4 måneder) til kronisk eksponering, ingen UF for datakvalitet, siden publikasjonen som ble brukt for PoD ble scoret Tier 1 i RoB-evalueringen, og en UF på 2,5 for interindividuell menneskelig variasjon i følsomhet hos voksne. Dette resulterer i en total UF på 5.

Når man bruker en total UF på 5 på en PoD-verdi på 6 g/dag, vil dette resultere i 1,2 g/dag som den høyeste trygge dosen. Da vil dosene på 302 mg/dag, 0,5 g/dag og 1 g/dag med MSM i opptil 4 måneder ansees som trygge for voksne. Om dosene 1,5 g/dag, 2 g/dag og 3 g/dag er trygge for bruk i opptil 4 måneder for voksne er usikkert, basert på de tilgjengelige dataene.

Ideelt, for 'andre stoffer' brukt i kosttilskudd bør risikovurderinger baseres på toksisitetsdata fra eksperimentelle studier med kronisk eksponering. FHI kjenner ikke til den vanlige eller anbefalte lengden på bruken av MSM.

Ingen konklusjoner om trygg dose ved bruk av MSM for barn og ungdom i aldersgruppene 3 - <10 år, 10 - <14 år og 14 - <18 år kan trekkes i denne oppdaterte risikovurderingen for noen av dosene, fordi det bare ble funnet én studie med skjevhet (nivå 3) hvor informasjon om doser og eksponeringsvarighet ikke var knyttet til alder (eller kroppsvekt).

Abbreviations

ADME	-	absorption, distribution, metabolism and excretion
AE	-	adverse effects/events
ASD	-	autism spectrum disorder
FHI	-	Folkehelseinstituttet
HOA	-	hand osteoarthritis
MCN	-	multicomponent nutraceutical
MSM	-	methylsulfonylmethane
NFSA	-	Norwegian Food Safety Authority
NIPH	-	Norwegian Institute of Public Health
PoD	-	point of departure
RCT	-	randomised controlled trial
RoB	-	risk of bias
UF	-	uncertainty factor
US-FDA	-	United States Food and Drug Administration
VAS	-	visual analogue scale
VKM	-	Norwegian Scientific Committee for Food and Environment

Background

The Norwegian Institute of Public Health (NIPH) was asked by the Norwegian Food Safety Authority (NFSA), to reevaluate the safety of methylsulfonylmethane (MSM) for both sexes in the Norwegian population, in adults (≥18 years) and in children and adolescents, in the age groups 3 - <10 years, 10 - <14 years and 14 - <18 years. The dose of MSM to evaluate for safety, from applications on sale of MSM in Norway that NFSA had received, was first 3 g per day, and if that dose was found not to be safe, to evaluate which lower doses could be considered safe (e.g. 2 g, 1.5 g, 1 g or 0.5 g per day or 302 mg per day). No information was given on the expected duration of exposure, however, chronic exposure was considered by NIPH as more relevant compared to acute exposure to this food supplement.

In the request from NFSA, NIPH was asked to evaluate whether any new literature similar to the publications from Medline and EMBASE used by the Norwegian Scientific Committee for Food and Environment (VKM) in their previous risk assessment of MSM (VKM, 2021) would change VKM's conclusions on adults. Further, NIPH was asked whether there now were sufficient data to conclude on safety of MSM also for children and adolescents.

New literature searches

The new searches were performed on 09.06.25, from 01.01.2019 in order not to miss any publications, thus, with some overlap with VKM's search, in Ovid Medline and EMBASE, using the same search strategy as used 18.12.2000 in VKM (2021). Three separate searches were performed; on adverse effects, genotoxicity, and absorption, distribution, metabolism and excretion (ADME). However, some more synonyms were included in this updated search and the searches were restricted to the English language. In the three categories, 23, 2 and 10 publications were obtained in Medline, and 112, 6 and 45 publications were obtained in EMBASE, in total 135, 8 and 55 publications, respectively (in total 198 publications). After removal of duplicates, 115 publications were read as title and abstract. From these, 42 publications were further scrutinized in full-text and 17 publications were found relevant for this risk assessment.

Description of included publications

No new publications on genotoxicity of MSM or new animal studies on MSM were found in the literature searches. One new study on ADME (metabolism) by Kim et al. (2023) was found (see Other relevant information). However, there were some new relevant publications on human studies of beneficial effects of MSM as the primary objective, which also did (or could have) mentioned adverse effects. Publications on MSM on adults, adolescents or children not being included in VKM (2021) were evaluated, including studies of multicomponent products containing MSM. This last group of studies were considered informative, when they reported no adverse effects of the treatments. In total, 17 publications were included in this re-evaluation of MSM. Seven of these publications reported original research on effects of MSM on humans, which were described in the following and which underwent risk of bias (RoB) evaluations (OHAT, 2015; 2019). Three additional studies relevant for evaluation of adverse effects of MSM (Desideri et al., 2022 (protocol described in VKM's report without published results); Muizzuddin and Benjamin, 2022; Pogacnik et al., 2023) found by snowballing or free text search on internet were treated similarly.

The main study used by VKM as point of departure (PoD) in their risk assessment of MSM (Crawford et al., 2019b) was also described in this re-valuation for information. Some other references and databases from VKM (2021) were also included in this evaluation as additional relevant information, i.a. about MSM in the body and in foods (AECOSAN, 2014; Hansen et al., 2006; PubChem, 2004), as well as methodological references (EFSA, 2012; OHAT, 2015; 2019). This work was performed by one experienced risk assessor and discussed with two others.

The included 10 new human studies relevant for evaluation of adverse effects of MSM were summarised in the following text and in Table 1.

Studies of MSM alone in adults (≥18 years)

The purpose of the investigation by Miller et al. (2021) was to determine whether MSM supplementation improved cardiometabolic health, markers of inflammation and oxidative status. A randomised, double-blind, placebo-controlled design was utilised with a total of 22 overweight or obese adults completing the study (MSM, n = 13, placebo, n = 9). The participants of both sexes, mean age ca. 41-44 years) received either capsules with a placebo (white rice flour) or **3 g MSM (OptiMSM®, Bergstrom Nutrition, Vancouver, WA, USA)** daily for **16 weeks**. Measurements occurred at baseline and after 4, 8 and 16 weeks. Outcome measures included fasting glucose, insulin, blood lipids, blood pressure, body composition, metabolic rate, and markers of inflammation and oxidative status. Serum MSM concentrations were significantly elevated after 4 weeks of supplementation in the MSM group. High-density lipoprotein cholesterol was elevated at 8 and 16 weeks of daily MSM consumption compared to baseline (P = 0.008, P = 0.013), although there were no significant differences between the groups. C-reactive protein (CRP) was significantly lower compared to placebo at week 16 (P = 0.04). The other measured parameters showed no significant differences between the MSM and placebo groups. The participants were asked to report any side-effects experienced and whether they believed they were consuming MSM or placebo at each follow-up visit. However, there were no results describing how the side-effects were recorded or reported, and none were mentioned in the publication.

The study was funded in part by Bergstrom Nutrition, manufacturer and provider of OptiMSM®. According to the authors, the funders took no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript or in the decision to publish the results.

Comment:
There was a lack of a cross-over study design and there was homogeneity among the participant population (i.e. normal vs. high fasting blood glucose levels) and a relatively small sample size.

The study by Muizzuddin and Benjamin (2022) was conducted in two steps; in Part I (pilot study) a panel of 20 participants ingested either **3 g per day of MSM (OptiMSM®)** (n = 11) or placebo (rice flour) (n = 9) in capsules for **16 weeks**. Visual and subject self-assessments of wrinkles and skin texture as the predominant sign of ageing were observed. In Part II (dose-response study), 63 participants ingested either **1 g or 3 g per day of MSM (OptiMSM®) for 16 weeks**, n = 31-32 per group. All participants were healthy females between the age of 35 and

59 years. Expert clinical grading, instrumental measurements and consumer perception were used to evaluate skin conditions, such as lines and wrinkles. Additionally, instrumentational analysis was conducted using corneometer and cutometer for investigation of skin hydration, firmness and elasticity. Part I of the study clearly indicated that oral ingestion of MSM (3 g/day) reduced signs of ageing like facial wrinkles ($P < 0.05$) and skin roughness ($P < 0.05$) as compared to placebo. Detailed analysis in Part II instrumentation assessments showed a significant ($P < 0.05$) improvement from baseline in the severity of facial wrinkles, as well as improved skin firmness, elasticity and hydration with MSM. Some of these parameters exhibited a good dose-response, indicating that the higher dose (3 g/day) of the supplement was more effective than the lower dose of 1 g/day, but generally the lower dose of 1 g/day appeared to be sufficiently effective in reducing the facial signs of ageing. This study indicated that MSM was effective in reducing visual signs of skin ageing even at a low dose of 1 g/day. There is no mention of recording or reporting of adverse effects in this study, therefore, the potential adversity at these exposures to MSM cannot be evaluated.

Both authors received personal fees from the producer of OptiMSM®, Bergstrom Nutrition.

Comment:
There was no placebo control included in Part II of this study.

Toguchi et al. (2023) conducted a randomised, double-blind, placebo-controlled trial of oral consumption of MSM on mild pain of the knee joint in healthy adult Japanese participants of both sexes. A total of 88 adult participants were enrolled in the safety analysis in this study and randomly assigned to MSM (OptiMSM®, Bergstrom Nutrition, Vancouver, WA, USA) consumption (n = 44) and placebo control (n = 44) groups. Both groups of participants took 10 tablets, each containing **200 mg MSM (i.e. a dose of 2 g)** or lactose, **per day for 12 weeks**. The total score of the Japanese Knee Osteoarthritis Measure (JKOM) at 12 weeks after test sample consumption in the MSM group was significantly lower than in the placebo group. The health conditions of the JKOM of the MSM group at 12 weeks were also significantly lower than those of the placebo group. Decreases in the JKOM total scores and the health condition scores indicated improvement of the knee and systemic health conditions of the participants by MSM consumption. The MSM group showed significant improvements compared to placebo at 12 weeks, in terms of morning pain, pain while standing and health condition in the JKOM questionnaires. The safety evaluation was performed through physical examination, urine analysis, peripheral blood test and medical interview, and the results revealed no health problems during the study period and no adverse events were reported (see detailed results in link: https://www.mdpi.com/article/10.3390/nu15132995/s1, Supplementary Table S3: Urine analysis of safety evaluation; Supplementary Table S4: Blood analysis of safety evaluation (1); Supplementary Table S5: Blood analysis of safety evaluation (2)).

The test tablets were provided by CIC Fronter (Tokyo, Japan), who supported this work.

According to the company Balchem (2025), OptiMSM® is the first MSM recognized as a food with functional claims (FFC) in Japan, based on the publication by Toguchi et al. (2023).

Crawford et al. (2019a) evaluated current research on 19 dietary ingredients, including MSM, for chronic musculoskeletal pain for Special Operations Forces (SOF) personnel to inform decisions for practice and self-care. A steering committee developed research questions and factors required for decision-making. Key databases were searched through August 2016. Eligible systematic reviews and randomised controlled trials were assessed for methodological quality. Meta-analysis was applied where feasible. GRADE was used to determine confidence in the effect estimates. The committee made evidence-informed judgments and recommendations for practice and selfcare use. Evidence-based recommendations were based on current conditions and factors considered specific to SOF populations. The committee, known as the Holistic Evidence Review Board (HERB), included a diverse group of stakeholders and subject matter experts, both within and outside the military, from research, clinical (patient and practitioner perspective) and policy realms. Committee members were well-rounded with expertise in human performance, dietary supplements and nutrition, as well as pain and pain management. The HERB only recommended ingredients that showed a benefit and did not negatively impact other areas (e.g. alleviating bodily pain but increasing financial stress due to the cost of an ingredient). The HERB grouped recommendations for practice into three tiers based on their collective judgment. Recommendations were made against the current use of MSM based on five studies.

According to Yang and Lin (2019), MSM is a nutritional supplement that is commonly found in detox products (e.g. cortex and basic detox nutrients). There is a report of acute angle-closure glaucoma (AACG) associated with MSM use as a detox supplement. MSM has a sulfonyl moiety that is similar to that found on other sulfa-based drugs (e.g. topiramate and hydrochlorothiazide). Like topiramate-induced AACG, MSM-induced AACG is due to uveal effusion and anterior rotation of the lens-iris diaphragm. Treatment with peripheral iridotomy and miotic agents is likely to be ineffective and can worsen the situation.

In the Osteoarthritis 2019 guideline updates and best practices (Mospan, 2021), it is stated that MSM is “commonly found in combination with glucosamine- and chondroitin-containing products, (and) has been proposed to have anti-inflammatory and analgesic properties. Although MSM has been well tolerated in clinical trials and causes no more side-effects than placebo, trials have had a maximum duration of 12 weeks. Based on insufficient evidence, MSM is not recommended. It has been shown to modestly reduce pain and swelling but has no impact on joint stiffness.”

Studies of MSM in multicomponent dietary supplements in adults (≥18 years)

The clinical/instrumental randomised controlled trial (RCT) by Guaitolini et al. (2019) evaluated the safety and efficacy of a multicomponent nutraceutical (MCN) for targeting most of the skin aging processes. A randomised, placebo-controlled, single-blind trial was conducted involving two groups of female subjects affected by facial skin photoaging. For **two months (60 days)**, volunteers (aged 40-65 years) took a daily dose of the MCN Hyaluseon, Proeon SURL, San Benedetto del Tronto, Italy, as tablets (oral exposure) containing 200 mg/day of hyaluronic acid (molecular weight: 1200–1500kDa) of vegetable origin, 500 mg of L-carnosine and **400 mg of MSM**, or placebo tablets. The MCN and placebo groups each included 25 volunteers (mean

ages: 49.3 and 47.8 years, respectively). In Group A, 25 subjects took two tablets of MCN per day for two months, whereas 25 subjects in Group B took two tablets of the placebo daily for two months. Both groups of subjects were unaware of the nature of their tablets.

The patients were invited to report any side-effects throughout the study period and were educated regarding the necessity of maintaining a stable nutrition regimen and lifestyle, without intake of any other medications or supplements or use of topical substances (e.g. creams, oils) with known activity on the investigated parameters. One case of epigastralgia (pain or discomfort in the epigastric region, which is the upper central area of the abdomen, just below the breastbone) and one case of atypical vaginal itching (the latter was not believed to be linked to intake of the active substances) were recorded in two subjects taking MCN, without any other side-effects reported by patients in either group. This results confirmed the absence of any significant adverse effects in the investigated cohort of subjects. The two cases of transient and possibly MCN-related side-effects (one of them of probable casual concomitant onset) were not severe enough to cause the volunteers to discontinue use of the nutraceutical.

Proeon SURL provided the placebo and MCN tablets but had no involvement in the collection or analysis of the data, nor in the preparation of the paper.

The RADIANT study is an internet-based, parallel, double-blind, placebo-controlled, randomised, two-arm clinical trial on efficacy and safety of a supplement combination for hand osteoarthritis pain, for which the **protocol** was described in one abstract (Liu, 2020) and one publication (Liu et al., 2020). According to the protocol, the active treatment group will receive a supplement combination composed of: (1) combined supplement containing *Boswellia serrata* extract (BSE) (Boswellin Super) 250 mg/day, pine bark extract (PBE) (Fenoprolic 70 Organic) 100 mg/day and MSM 1500 mg/day, as three capsules daily or (2) curcumin (Flexofytol) 168 mg/day, as four capsules daily, for 12 weeks. The placebo groups will receive: (1) placebo-combined supplement and (2) placebo-curcumin. Adverse events will be monitored weekly throughout the study.

The **results** of this study were reported in the publication by Liu et al. (2021). One hundred and six participants over 40 years with painful hand osteoarthritis (HOA) and structural change on X-ray (Kellgren and Lawrence grade (KLG) ≥2) were included, with mean age 65.6 years and 81% were women. Forty-five % of the participants were graded as KLG 4, 40% as KLG 3, 15% as KLG2 and 39 (37%) had erosive osteoarthritis. There was no significant difference in hand pain reduction assessed using a visual analogue scale (VAS) between groups. The adjusted between group difference in means (95% CI) was 5.34 (-2.39 to 13.07). The authors concluded that there were no significant differences in symptomatic relief between the two groups over 12 weeks. These findings did not support the use of the supplement combination for treating hand pain in people with HOA.

The participants were asked to report any adverse events in a weekly survey with detailed information about starting/resolving dates, medical attention and use of medication. Thirty-six of 51 participants (71%) in the supplement combination group and 38 of the 54 participants (70%) in the placebo group reported a total of 141 adverse events (AE) (see Supplementary

Table 2 in the publication). One participant in the placebo group developed a serious adverse event, which was a renal abscess, and was hospitalised. Regarding severe AE, one participant in the supplement combination group had starvation ketoacidosis, and two in the placebo group had gallbladder infection and sciatic pain with surgery needed for their condition. **Both the serious and severe adverse events were deemed unrelated to the study treatments.** Five participants (10%) in the supplement combination group discontinued study treatment due to adverse events vs. four participants (7%) in the placebo group. Most of the adverse events were mild to moderate. Gastrointestinal symptoms were the most reported adverse events by both groups, particularly diarrhoea and nausea.

The **protocol** of a similar study was described in an abstract by Liu et al. (2024) and a publication by Shahid et al. (2024) on participants with knee osteoarthritis (KOA) pain, who will be given almost the same combination treatment as for HOA in the study above, i.e. a combined supplement containing *Boswellia serrata* extract (BSE) (Boswellin Super) 250 mg/day, pine bark extract (PBE) (Fenoprolic 70 Organic) 100 mg/day, curcumin 500 mg/day, piperine 5 mg/day and **MSM 1500 mg/day**, or placebo, as four capsules daily, for **12 weeks**. Self-reported adverse events data will be collected weekly throughout trial treatment. Reported adverse events will be assessed by the trial doctor and adverse events related (possibly, probably, definitely) to the trial intervention will be followed until resolution. Knee OA flare-ups will not be considered reportable adverse events. Expected adverse reactions to the trial intervention may include diarrhea, bloating, abdominal pain, nausea, gastro-esophageal reflux, dizziness, hypotension, headache, fatigue, insomnia, increased risk of bleeding and bruising, itching or worsening of allergy symptoms, and possible decrease in blood sugar level. A summary of adverse events will be reported to the Data Safety and Monitoring Board every six months. However, no results from this trial are yet published (per 23.09.2025).

The purpose of the study by McFarlin et al. (2021) was to determine the effect of dietary supplementation with optimized curcumin, pomegranate ellagitannins (R) and MSM (R + MSM) on immune-associated mRNA during early recovery (i.e. up to 8 h post-exercise) following all-out running efforts (5-km, 10-km and 21.1-km). Adult subjects (n = 14) were randomised to either a supplement (R + MSM, n = 6, age 39 ± 6 years) or a control group who did not consume a supplement (n = 8, age 40 ± 7 years), using an open label design. The study was completed over a 31-day period prior to a scheduled half-marathon race.

During days 0-27, the daily dose of the experimental supplement was 1000 mg of a proprietary synergistic polyphenol blend (optimized curcumin and pomegranate ellagitannins; Restoridyn®, Verdure Sciences Corp, Indianapolis, IN, USA) and **500 mg of MSM (OptiMSM®, Bergstrom Nutrition, Vancouver, WA, USA**). During days 0-27, participants also consumed an additional daily dose (booster dose) within 1 h of completing a run of 9.6 km or longer (5.3 ± 3.3 total booster doses consumed per subject). The 5-km and 10-km laboratory time trials were completed at 3 and 2 weeks, respectively, prior to the 21.1-km road race. During days 28, 29 and 30, the dose was doubled (Restoridyn® 2000 mg/day; **OptiMSM® 1000 mg/day**), and the participants were instructed to taper their running distance and to discontinue use of

booster doses. The 21.1-km road race was completed on day 31. The intake of MSM was **in total up to ca. 21.3 g OptiMSM® during 31 days (ca. 0.7 g/day**).

Venous blood samples were collected at baseline, and at 2, 4 and 8 h after each running effort. A 574-plex mRNA Immunology Array (NanoString) was measured for each sample and ROSALIND® Advanced Analysis Software was used to examine changes in 31 annotated immune response pathways and specific mRNA changes. The greatest change in immune pathways occurred at 2 h (GSS > 3) followed by 4 h (GSS 2–3) and 8 h (GSS 1– 2). R + MSM was associated with an increase in innate immunity (CAMP, LTF, TIRAP, CR1, IL1R1, CXCR1, PDCDILG2 and GNLY) and a blunted/smaller increase in damage-associated molecular pattern (DAMP) signaling/inflammation (TLR4, TLR5, S100A8, S100A9 and IFP35). They also found changes in immune-associated mRNA that have not been previously linked to exercise recovery (SOCS1, SOCS2, MME, CECAM6, MX1, IL-1R2, KLRD1, KLRK1 and LAMP3). Collectively, according to the authors, these results demonstrated that supplementation with a combination of optimized curcumin, pomegranate ellagitannins and MSM resulted in changes that may improve biological recovery from all-out running efforts.

The authors reported that no negative effects were observed associated with supplementation, but a capability to improve the innate immune response and reduce inflammation early in the exercise recovery process (2-8 h post exercise).

This study was funded by grants and in-kind support (i.e. provided in a form other than money) to the University of North Texas from Verdure Sciences Corp. and Bergstrom Nutrition.

Comments:
There were few subjects (only n = 6 were given the treatment with MSM) and short duration of exposure (31 days). There was no description of how adverse effects should be recorded and reported.

In a similar open-label pilot study with 15 young healthy exercise-trained men and women by Tanner et al. (2022), 5 participants (aged 40 ± 3 years) were given the intervention of 1000 mg/day of a mix of 50:50 optimized curcumin (Longvida®) and pomegranate extract with high amounts of ellagitannins and primarily punicalagins (Pomella®) (Restoridyn®, Verdure Sciences Corp, Indianapolis, IN, USA) and **500 mg/day of MSM (OptiMSM®, Bergstrom Nutrition, Vancouver, WA, USA)** for 26 days. The control group received no supplements (n = 10, aged 39 ± 6 years). During the 26-day period, participants were instructed to consume a booster dose, an additional 1500 mg, in addition to the daily dose, when their training sessions were greater than six miles. On average, participants took two booster doses per week during the initial 26 days of supplementation. Three days prior to and one day after a half-marathon race, the intervention group also doubled their daily dosages of each supplement. The intake of MSM was **in total up to ca. 26.0 g OptiMSM® during 27 days** (**ca. 1 g/day)**.

The supplements' safety was assessed by measuring serum alkaline phosphatase, a liver-function biomarker. The participants reported no adverse side-effects with the supplementation regime. No differences existed between the groups in conditions and values,

which were within the normal range of 20-140 IU/L, with the control group at 33.1 ± 11.9 and the intervention group at 51.2 ± 21.1.

In-kind support was provided to the University of North Texas by Verdure Sciences (Restoridyn®) and Bergstrom Nutrition (OptiMSM®). The authors of this work were not directly compensated for the completion of this work.

Comment:
There were few subjects (only n = 5 given the treatment with MSM) and a short duration of exposure (27 days). Adverse effects were evaluated by analysis of one liver enzyme, and thus, this evaluation was very limited. There was no description of how adverse effects should be recorded and reported by the participants.

Aromatase inhibitors (AI) are recommended for the adjuvant treatment of hormone receptor positive breast cancer in both high-risk pre-menopausal and post-menopausal populations. Arthralgia is the main cause of discontinuation of therapy and affects up to 25% of population on AI treatment. The objective of the prospective phase II, monocentre, self-controlled clinical trial by Desideri et al. (2022) was to evaluate **OPERA® (GAMFARMA srl, Milan, Italy)**, a dietary supplement where α-lipoic acid (240 mg), *Boswellia serrata* (40 mg), **MSM (200 mg)** and bromelain (20 mg) were combined in a single hard-gelatin capsule to be taken once a day. Forty-six adult patients (mean or median? age 59 years, range 43-82) with arthralgia (pain in a joint) (National Cancer Institute - Common Toxicity Criteria for Adverse Event (NCI-CTCAE) v4.0 grade ≥1) occurring during AI therapy were enrolled. All patients received OPERA® from enrolment (T0) up to **sixth months** (T3). Patients' AI-related arthralgia was evaluated every two months with Visual Analog pain Scale (VAS) Scale, Patient-Reported Arthralgia Inventory (PRAI) questionnaire and CTCAE scale. The primary endpoint was the number of patients with symptom resolution (G0) at T3 if compared to T0, according to CTCAE and VAS scales. The secondary endpoints were decrease in arthralgia intensity measured with PRAI score at T3 compared to baseline, safety of OPERA® evaluated with NCI-CTCAEv4.0 and rate of AI interruption. Treatment with OPERA® supplement was overall well tolerated; no relevant toxicities related to OPERA® intake were reported using . No significant acute toxicity related to the intake of OPERA® was reported during the study period; only two patients (4.35%) reported a G1 gastralgia, with no discontinuation of tablets. Seven subjects (13.2%) were not included in the final analysis because of consent withdrawal. Forty-six participants were eligible for final analysis. According to CTCAE scale, 10 out of 46 patients reported symptoms resolution at 6-month follow-up from the time of enrolment T0 (P = 0.0009). According to VAS score, 5 patients reported complete resolution of symptoms at T3 if compared to baseline T0 (P = 0.0222). Analysis of PRAI score showed a significant reduction in arthralgia-related pain perceived (P = 0.0001). According to the authors, OPERA® was able to reduce the intensity of arthralgia related to AI therapy.

This study was included in VKM's report as a notification of the clinical trial without any results. It was not found in the current literature search, but by internet searching.

The aim of the single-centre, randomised, double-blind, placebo-controlled four-way study by Pogacnik et al. (2023) was to investigate and compare the effects of **12-week** daily dietary supplementation of a syrup with products containing 10 g hydrolysed fish collagen (HC) or a combination of 5 g or 10 g HC with 1.5 g MSM on facial dermis density in healthy human subjects (n = 107, females, mean age 52.2 ± 6.7 years). The ColMSM-LD group received hydrolysed fish collagen (5 g), **MSM (1.5 g)** from **Tosla d.o.o., Ajdovscina, Slovenia**, and vitamin C (80 mg), the ColMSM-HD group received hydrolysed fish collagen (10 g), **MSM (1.5 g)** and vitamin C (80 mg). The placebo group received no active ingredients (not even vitamin C) and the Col-HD group received hydrolysed fish collagen (10 g) and vitamin C (80 mg). The secondary objectives were to investigate the effects on a variety of other skin parameters. The study results showed improved dermis density, skin texture and reduced wrinkles for all the active products. However, products containing MSM were superior in the improvement of skin thickness and roughness, and a higher dose of HC combined with MSM was crucial for improvement in hydration. On the other hand, no significant effects of the supplementation on viscoelasticity and transepidermal water loss were determined with any of the products. No side-effects or adverse events of any kind were reported.

The authors acknowledged support from Tosla d.o.o., Ajdovscina, Slovenia, which produced and supplied the tested products.

Comment:
There was no information about how side-effects or adverse events should be recorded or reported by the participants.

Studies of MSM alone in children and adolescents

No studies were found with only MSM studied in children or adolescents.

Studies of MSM in multicomponent dietary supplements in children and adolescents

The retrospective research survey by Adams et al. (2022) collected evaluations from 161 persons of both sexes (86% males, 14% females) about the effectiveness of ANRC-Essentials Plus (ANRC-EP), a vitamin/mineral/micronutrient supplement designed for children and adults with autism spectrum disorder (ASD). The supplement contained **500 mg MSM in 6 capsules**, which is the daily dose for a 60 pound child (60 x 0.453592 = 27.2 kg, corresponding to 3-14 year-olds); dosages were adjusted by body weight (1 capsule per 10 pounds (~4.5 kg, corresponding to 0.3 month-olds), to a maximum of 12 capsules for 120 pound (120 x 0.453592 = 54.4, corresponding to 10-18 year-olds) or higher. Lower, gradually-increasing doses were recommended for the first month. The body weight in kg and the corresponding approximate age was reported by NIPH (EFSA, 2012). The children included were from one year and up to adulthood. The mean age was 12.7 ± 9.1 years (range 1-74). The age distribution of the participants was 1-5 years (n = 27, 17%), 5-10 years (n = 53, 33%), 11-15 years (n = 32, 20%), 16-20 years (n = 31, 19%) and 21-74 years (n = 17, 10%). The duration of usage of ANRC-EP varied from 3-5 months to >4 years (or even 6 years), based on varying information in the publication, with median usage of ca. 12 months. Daily use was reported for 151 (94%) of the participants and 10 participants (6%) reported less than daily use (average 3.4 days/week). The full dose was taken by 103 participants (64%), whereas 58 (36%) took less than full dose. The

reasons given for taking a lower dose were hyperactivity (n = 11, 7%), anxiety/aggression/irritability (n = 5, 3%), reflux (n = 2, 1%) and other adverse effects (n = 6, 4%) at higher doses.

One hundred and twenty-seven participants (79%) reported no adverse effects, 27 (17%) reported mild, 5 (3%) reported moderate and 1 (0.6%) reported severe adverse effects. In 78% of the cases, the adverse effects could be reduced by reducing the dose. The Overall Adverse Effect score was low (0.25/3.0), similar or slightly higher than other nutraceuticals, and much lower than the average of 28 psychiatric and seizure medications (0.9/3.0). The authors concluded that ANRC-EP had low adverse effects. However, they considered that there may be some underreporting of AE, since persons who stopped using the supplement before 3 months were not included.

Comment:
The study did not specify adverse effects related to the various age groups (or body weight). However, this publication was included as the only study found on children and adolescents.

The included new studies are summarized in Table 1. All these studies appeared to be without treatment-related significant adverse effects or the adverse effects/events were not different between the MSM and placebo/control groups, although such results were not reported in detail for some of the studies and were not mentioned at all in one study (Muizzuddin and Benjamin, 2022).

Table 1. Study characteristics of the included human studies of oral MSM exposure.

Authors (publication year). Funding, support or employment from producer (Yes/No)	**Type of study**	**Dose and duration of exposure to MSM, and product name**	**Participants (age, sex, number)**	**Outcome relevant for adverse events/effects**
Studies of MSM alone in adults (≥18 years)				
Miller et al. (2021) Yes	Randomised, double-blind, placebo-controlled trial	**3 g/day**, 16 weeks of OptiMSM®	Overweight/obese adults studied for cardiometabolic health, markers of inflammation and oxidative status (both sexes, mean age ca. 41-44 years). OptiMSM® (n = 13), placebo (n = 9)	The participants were asked to report any side-effects experienced. However, there were no results describing how the side-effects were recorded or reported, and none were mentioned in the publication
Muizzuddin and Benjamin (2022) Yes	1) Pilot clinical placebo-controlled study 2) Clinical dose-response study	1) **3 g/day**, 16 weeks of OptiMSM® 2) **1 g or 3 g/day**, 16 weeks of OptiMSM®	Adult women with facial skin wrinkles and lines (age 35-49 years) 1) MSM (n = 11), placebo (n = 9) 2) n = 31-32 per dose group, no placebo group	There is no mention of recording of adverse effects, therefore, the potential adversity at these exposures to OptiMSM® cannot be evaluated
Toguchi et al. (2023) Yes	Randomised, double-blind, placebo-controlled trial	**2 g/day**, 12 weeks of OptiMSM® or placebo	Healthy adults with mild pain of the knee joint, both sexes MSM (n = 44), placebo (n = 44)	The safety evaluation was performed through physical examination, urine analysis, peripheral blood test and medical interview, and the results revealed no health problems during the study period and no adverse events were reported (see their

				Supplementary Tables S3, S4, S5)
Studies of MSM in multicomponent dietary supplements in adults (≥18 years)				
Guaitolini et al. (2019) Yes	Clinical/instrumental randomised, placebo-controlled, single-blind trial	Multicomponent nutraceutical (daily dose of 400 mg Hyaluseon, consisting of 200 mg hyaluronic acid, 500 mg L-carnosine and 8**00 mg MSM**, or placebo, for 60 days (n = 25 per group)	Adult females with facial skin photoaging (age 40-65 years) (n = 25 per group)	The patients were invited to report any side-effects throughout the study period. One case of epigastralgia (pain or discomfort in the epigastric region) and one case of atypical vaginal itching (not believed to be linked to intake of the active substances) were recorded in two subjects taking MCN, without any other side-effects reported by patients in either group.
Liu (2020), Liu et al. (2020; 2021) No	Internet-based, parallel, double-blind, placebo-controlled, randomised, two-arm clinical trial	A supplement combination composed of: (1) combined supplement containing *Boswellia serrata* extract (BSE) (Boswellin Super) 250 mg/day, pine bark extract (PBE) (Fenoprolic 70 Organic) 100 mg/day and **MSM 1500 mg/day**, as three capsules daily or (2) curcumin (Flexofytol)	Adults with varying grades of hand osteoarthritis (>40 years, 81% women). Supplement combination group (n = 52), placebo group (n = 54)	Adverse events (AE) were monitored weekly. Seventy-one % in the supplement combination group and 70% in the placebo group reported a total of 141 adverse events (see their Supplementary Table 2). One participant in the placebo group developed a serious AE (a renal abscess) and was hospitalised. Regarding severe AE, one

		168 mg/day, as four capsules daily, for 12 weeks. Placebo +/- curcumin		participant in the supplement combination group had starvation ketoacidosis, and two in the placebo group had gallbladder infection and sciatic pain with surgery needed for their condition. Both the serious and severe AE were deemed unrelated to the study treatments. Five participants (10%) in the supplement combination group discontinued study treatment due to AE vs. four participants (7%) in the placebo group. Most of the AE were mild to moderate. Gastro-intestinal symptoms were the most reported AE by both groups, particularly diarrhoea and nausea
McFarlin et al. (2021) Yes	Open label study	Restoridyn® (optimized curcumin and pomegranate ellagitannins), 1000 mg/day, and OptiMSM® (days 0-27: 500 mg/day OptiMSM® + one booster dose of 500 mg OptiMSM® on some of	Exercise-trained adults (both sexes), supplement group (n = 6, age 39 ± 6)), control (n = 8, age 40 ± 7). Studied effects on immune-associated mRNA during early recovery (i.e. up to 8 h post-exercise) following	They reported that no negative effects were observed associated with supplementation. However, there was no description of how adverse effects were recorded and reported by the participants

		these days (5.3 ± 3.3 total booster doses consumed per subject), days 28-30: Restoridyn®, 2000 mg/day, and OptiMSM® 1000 mg/day, without booster doses (**in total up to ca. 21.3 g OptiMSM® during 31 days; ca. 0.7 g/day**)	all-out running efforts (5-km, 10-km and 21.1-km). The study was completed over a period of 31-day prior to a scheduled half-marathon race	
Tanner et al. (2022) Yes	Open label pilot study	Restoridyn® (50:50 optimized curcumin and pomegranate ellagitannins), 1000 mg/day, and OptiMSM®, 500 mg/day, in 26 days. OptiMSM® doses (days 1-26: 500 mg/day OptiMSM® + one booster dose of 1500 mg OptiMSM® on some of these days (on average 2 booster doses per week)), days 23, 24, 25 and 27: 1000 mg/day OptiMSM®) (**in total up to ca. 26.0 g OptiMSM® during 27 days; ca. 1 g/day)**. The control group received no supplements	Exercise-trained adults of both sexes), supplement group (n = 5, aged 40 ± 3 years), control group (n = 10, aged 39 ± 6 years)	The supplements' safety was assessed by measuring serum alkaline phosphatase, a liver-function biomarker. The participants reported no adverse side-effects with the supplementation. No differences existed between the groups in conditions and values, which were within the normal range of 20-140 IU/L, with the control group at 33.1 ± 11.9 and the intervention group at 51.2 ± 21.1

Desideri et al. (2022) No	Prospective phase II, monocentre, self-controlled clinical trial	OPERA®, a dietary supplement where α-lipoic acid (240 mg), *Boswellia serrata* (40 mg), **MSM (200 mg)** and bromelain (20 mg) were combined, given once daily up to 6 months	Adult female patients with hormone receptor positive breast cancer on adjuvant therapy with aromatase inhibitors causing them arthralgia (pain in a joint), n = 53, median age 59 years, range 43-82	Treatment with supplement was overall well tolerated; no relevant toxicities related to supplement intake were reported. No significant acute toxicity related to the intake was reported during the study period; only two patients (4.35%) reported a G1 gastralgia, with no discontinuation of tablets
Pogacnik et al. (2023) Yes	Randomised, double-blind placebo-controlled four-way study	The ColMSM-LD group received hydrolysed fish collagen (5 g), **MSM (1.5 g)** and vitamin C (80 mg), the ColMSM-HD group received hydrolysed fish collagen (10 g), **MSM (1.5 g)** and vitamin C (80 mg). The placebo group received no active ingredients (not even vitamin C) and the Col-HD group received hydrolysed fish collagen (10 g) and vitamin C (80 mg), daily for 12 weeks	Healthy females (n = 107, mean age 52.2 ± 6.7 years), were studied for effects on facial dermis density, skin texture and wrinkles	It was stated that no side-effects or adverse events of any kind were reported. However, there was no information about how side-effects or adverse events were to be recorded or reported by the participants
Studies of MSM alone in children and adolescents				
No studies found				

Studies of MSM in multicomponent dietary supplements in children and adolescents				
Adams et al. (2022)	Retrospective research study	ANRC-Essentials Plus (ANRC-EP), a vitamin/ mineral/micronutrient supplement containing **500 mg MSM** in 6 capsules, which is the daily dose for a 60 pound child (60 x 0.453592 = 27.2 kg, corresponding to 3-14 year-olds); dosages were adjusted by body weight (1 capsule per 10 pounds (~4.5 kg, corresponding to 0.3 month-olds), to a maximum of 12 capsules for 120 pound (120 x 0.453592 = 54.4 kg, corresponding to 10-18 year-olds) or higher	Children and adults with autism (n = 161), aged from 1 year to adulthood. The duration of usage of ANRC-EP varied from 3-5 months to >4 years. Daily use was reported for 151 (94%) of the participants and 10 participants (6%) reported less than daily use (average 3.4 days/week). The full dose was taken by 103 participants (64%), whereas 58 (36%) took less than full dose	The reasons given for taking a lower dose were hyperactivity (n = 11, 7%), anxiety/aggression/irritability (n = 5, 3%), reflux (n = 2, 1%) and other adverse effects (n = 6, 4%) at higher doses. In this study, the Overall Adverse Effect score was low (0.25/3.0), similar or slightly higher than other nutraceuticals, and much lower than the average of 28 psychiatric and seizure medications (0.9/3.0). One hundred and twenty-seven participants (79%) reported no adverse effects, 27 (17%) reported mild, 5 (3%) reported moderate and 1 (0.6%) reported severe adverse effects. The authors concluded that ANRC-EP had low adverse effects

Risk of bias (RoB) evaluations of the included human studies

Risk of bias (RoB) was evaluated using the OHAT (Office of Health Assessment and Translation) tool (OHAT, 2015; OHAT, 2019) for the included human studies, in a similar way as done in VKM (2021) for the human intervention studies.

The response options and symbols used for rating of RoB:

- Definitely low risk of bias ++
- Probably low risk of bias +
- Probably high risk of bias/not reported –
- Definitely high risk of bias – –

The questions 1, 2, 3, 5 and 6 were defined as key questions (in bold in the tables below for the included publications), whereas questions 4, 7 and 8 were defined as non-key questions, as in VKM (2021).

Based on the overall RoB evaluation, the publications are classified in three tiers (Table 2).

Table 2. Classification of studies into tiers according to overall RoB.

Tier	1	2	3
Criteria for classification	All key questions are scored +/++ AND No more than one non-key question is scored – AND No non-key question is scored – –	All combinations not falling under Tier 1 or 3	Any key or non-key question is scored – – OR More than one key question is scored –

Miller et al. (2021) (Tier 3)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	There is direct evidence that subjects were randomised to MSM or placebo groups.	+
	2	Was allocation to study groups adequately concealed?	There is indirect evidence that at the time of recruitment the research personnel and participants did not know what study group participants were allocated to.	+

Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	There is direct evidence that during the study the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and final.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	It is deemed that the proportion lost to follow-up would not appreciably bias results (although exceeding 20% in each group, but the reasons were described (i.a. covid precautions) and were similar in treatment and placebo groups).	+
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is direct evidence that the exposure was sufficiently characterised (including compliance with the treatment, which was assessed by verbal questionnaires at each visit and increased serum concentrations of MSM), and indirect evidence that the participants had been followed for the same length of time in both study groups, although purity and stability of the test substance were not mentioned.	+
	6	Can we be confident in the outcome assessment?	The participants were asked to report any adverse effects experienced.	++
Selective reporting bias	7	Were all measured outcomes reported?	There were no results describing how the adverse effects were recorded or reported, and none were mentioned in the publication.	– –
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods were appropriate (but not used on adverse effects). The study protocol was registered and approved. The study was funded, in part, by Bergstrom Nutrition, manufacturer and provider of OptiMSM®.	–
Tier				**3**

Muizzuddin and Benjamin (2022) (Tier 3)

Type of bias	No.	Question	RoB evaluation	RoB rating

Selection bias	**1**	Was administered dose or exposure level adequately randomised?	There is no mention of randomisation to treatment or placebo groups in Part I, or to the different dose groups in part II of this study.	– –
	2	Was allocation to study groups adequately concealed?	There is no mention in Part I of the study that allocation was concealed for both participants and evaluators, and it was not concealed in Part II for the participants, taking either 1 or 3 capsules of MSM daily.	–
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	Part I of the study was double-blinded, but Part II was not blinded for the participants, taking either 1 or 3 capsules of MSM daily.	–
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	There is no information of whether anybody was lost to follow-up.	– –
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is no mention about compliance with the treatment, and the purity and stability of the test substance were not stated.	– –
	6	Can we be confident in the outcome assessment?	There is no mention of recording or reporting of adverse effects, therefore, the potential adversity at these exposures to OptiMSM® cannot be evaluated.	– –
Selective reporting bias	7	Were all measured outcomes reported?	There is no mention of recording or reporting of adverse effects.	– –
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods were appropriate (but not used on adverse effects). Study protocol was not mentioned, but the study was overseen by an institutional review board. Both authors received personal fees from the producer of OptiMSM®, Bergstrom Nutrition.	–
Tier				**3**

Toguchi et al. (2023) (Tier 1)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	There is direct evidence that subjects were randomised to MSM or placebo groups.	++

	2	Was allocation to study groups adequately concealed?	There is direct evidence that at the time of recruitment the physicians, investigators, analysts and participants did not know what study group the participants were allocated to, using computer-generated random numbers.	++
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	There is direct evidence that during the study the research personnel and subjects were blinded, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and final. The MSM and placebo tablets were identical in appearance and indistinguishable by smell.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	In the safety analysis population, none were lost to follow-up and the numbers were similar in both treatment and placebo groups.	++
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised (including compliance with the treatment), although purity and stability of the test substance were not mentioned.	+
	6	Can we be confident in the outcome assessment?	The safety evaluation was performed through physical examination, urine analysis, peripheral blood test and medical interview, and the results revealed no health problems during the study period and no adverse events were reported.	++
Selective reporting bias	7	Were all measured outcomes reported?	There is likely that all measured outcomes in the safety evaluation were reported, since there are three large tables of supplementary data on urine and blood analyses.	++
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods were appropriate. The study protocol was approved. The test tablets were provided by CIC Fronter (Tokyo, Japan), who supported this work.	–
Tier				**1**

Guaitolini et al. (2019) (Tier 1)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	There is direct evidence that subjects were randomised to MCN or placebo groups using an online randomiser.	++
	2	Was allocation to study groups adequately concealed?	There is indirect evidence for allocation to study groups concealed for the participants, but not for the evaluators.	+
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	There is direct evidence for allocation to study groups concealed for the participants, but not for the evaluators.	+
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	It seems likely, since it was reported that one case of epigastralgia and one case of atypical vaginal itching (the latter was not believed to be linked to intake of the active substances) were recorded in two subjects taking MCN, without any other adverse effects reported by patients in either group.	+
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised. At the final investigation, one patient in the MCN group was lost to follow-up due to inability to adhere to follow-up timing. The final statistical analysis included 24 subjects in the MCN group and 25 subjects in the placebo group. Purity and stability of the test substance were not stated.	+
	6	Can we be confident in the outcome assessment?	The patients were invited to report any adverse effects throughout the study period. All data were collected and stored for statistical analysis.	++
Selective reporting bias	7	Were all measured outcomes reported?	It is likely that all adverse effects were reported, i.e. that one case of epigastralgia and one case of atypical vaginal itching (the latter was not believed to be linked to intake of the active substances) were recorded in two subjects	+

			taking MCN, without any other adverse effects reported by patients in either group. The two cases of transient and possibly MCN-related side-effects (one of them probable casual concomitant onset) were not severe enough to cause the volunteers to discontinue use of the MCN.	
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods were appropriate. The study was performed adhering to ethics protocol as per Helsinki Declaration. Proeon SURL provided the placebo and MCN tablets.	–
Tier				**1**

Liu (2020), Liu et al. (2020; 2021) (Tier 1)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	An independent statistician prepared a computer-generated randomisation schedule using random permuted block sizes with a 1:1 allocation rate and stratified by erosive hand osteoarthritis (HOA) and non-erosive HOA. They were randomised (1:1) to receive either the MCN or the placebo.	++
	2	Was allocation to study groups adequately concealed?	There is direct evidence that the treatment allocation was concealed in sequentially numbered opaque, sealed and stapled envelopes, which were prepared by an independent researcher.	++
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	There is direct evidence that treatment assignment was masked from study physician, study coordinator, staff responsible for dispensing, statistician and the investigator performing the analysis, and maintained until all data were collected, confirmed for accuracy, cleaned and statistical analyses were performed. Participants were also masked until the completion of the end of the study. Both MCN and placebo were	++

			in identical capsules with the same size and appearance.	
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	It seems likely, since adverse events were reported in a table as supplementary data.	+
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised, including compliance. Adherence with the study treatment was established by participant-reported missed doses (weekly) and participant-reported capsule counting for leftover products at the end of the trial. Nine participants discontinued treatment during the study (5 in supplement group and four in placebo group) and 91 participants (86%) completed the study treatment according to the protocol (i.e. treatment adherence ≥80%). All participants completed the main assessment surveys at weeks 6 and 12, and only two participants in the placebo group failed to report their week 2 assessments. Purity and stability of the test substance were not stated.	+
	6	Can we be confident in the outcome assessment?	The participants were asked to report any adverse events in a weekly survey with detailed information about starting/resolving dates, medical attention and use of medication.	++
Selective reporting bias	7	Were all measured outcomes reported?	It is likely that all adverse events (AE) were reported. Thirty-six of 51 participants (71%) in the supplement combination group and 38 of 54 participants (70%) in the placebo group reported a total of 141 adverse events. One participant in the placebo group developed a serious adverse event, which was a renal abscess, and was hospitalised. Regarding severe AE, one participant in the supplement combination group had starvation ketoacidosis and two in the placebo group had gallbladder infection and sciatic pain with	++

			surgery needed for their condition. Both the serious and severe AE were deemed unrelated to the study treatments. Five participants (10%) in the supplement combination group discontinued study treatment due to AE vs. four participants (7%) in the placebo group. Most of the AE were mild to moderate. Gastrointestinal symptoms were the most reported adverse events by both groups, particularly diarrhoea and nausea.	
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods were appropriate. The study protocol was published. The material used was sourced from Bod Australia who was contracted to provide reliable supplements and responsible for the quality of the ingredients, but had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.	+
Tier				**1**

McFarlin et al. (2021) (Tier 1)

Type of bias	**No.**	**Question**	**RoB evaluation**	**RoB rating**
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	There is direct evidence that the subjects were randomised to a supplement group or a control group (no supplement, no placebo).	++
	2	Was allocation to study groups adequately concealed?	There is indirect evidence that the project team was blinded to supplementation assignment throughout the study, including during all running trials, sample analysis and statistical analyses, but it was not concealed for the participants.	+
Performance bias	**3**	Were the research personnel and human subjects blinded to the	There is direct evidence that the project team was blinded to supplementation assignment throughout the study, including	+

		study group during the study?	during all running trials, sample analysis and statistical analyses, but the treatment was not blinded for the participants.	
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	They observed no negative effects associated with supplementation. No further details were given about recording and reporting of adverse events/effects.	+
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised, including compliance. When the participant returned to the laboratory, they were asked to return their previous blister pack to track supplement compliance. Participants were asked to notify a member of the study staff about any missed doses. The subject compliance for the planned doses was >95%. It was reported that two additional participants dropped out of the study due to a scheduling conflict. Purity and stability of the test substance were not stated.	+
	6	Can we be confident in the outcome assessment?	They observed no negative effects associated with supplementation. No further details were given about recording and reporting of adverse events/effects.	+
Selective reporting bias	7	Were all measured outcomes reported?	They observed no negative effects associated with supplementation. No further details were given about recording and reporting of adverse events/effects.	+
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods were appropriate, but not described in detail. The study protocol was approved by an institutional review board. This study was funded by grants and in-kind support (provided in a form other than money) to the University of North Texas from Verdure Sciences Corp. and Bergstrom Nutrition.	–
Tier				**1**

Tanner et al. (2022) (Tier 3)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	The participants were assigned in an alternating manner to either a control (no placebo) or intervention group using an open label design. The participants were recruited in 2 cohorts.	–
	2	Was allocation to study groups adequately concealed?	There is no information about concealment of allocation to treatment for the investigators, but it was not concealed for the participants.	– –
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	There is no information about blinding of the treatment for the investigators, but the treatment was not blinded for the participants.	– –
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	The supplements' safety was assessed only by measuring serum alkaline phosphatase, a liver-function biomarker, and these data do not show number of persons, thus, attrition cannot be evaluated.	–
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised. However, compliance, and purity and stability of the test substance, were not mentioned.	+
	6	Can we be confident in the outcome assessment?	The supplements' safety was assessed by measuring serum alkaline phosphatase, a liver-function biomarker, using an enzymatic assay. Thus, the safety evaluation was very limited. Participants reported no adverse side-effects with the supplementation regime. No differences existed between the groups in conditions and values, which were within the normal range of 20-140 IU/L, with the control group at 33.1 ± 11.9 and the intervention group at 51.2 ± 21.1.	+
Selective reporting bias	7	Were all measured outcomes reported?	The safety evaluation was very limited, since only serum alkaline phosphatase was evaluated.	+

Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods used were not described for the safety analysis. The study was approved by an institutional review board. In-kind support was provided to the University of North Texas by Verdure Sciences (Restoridyn®) and Bergstrom Nutrition (OptiMSM®).	–
Tier				**3**

Desideri et al. (2022) (Tier 3)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	The participants were enrolled and treated with MSM. There was no control or placebo group, i.e. the study was self-controlled. Randomisation was not done in this study.	–
	2	Was allocation to study groups adequately concealed?	There is no information about concealment of allocation to treatment for the investigators, but it was not concealed for the participants.	– –
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	There is no information about blinding of the treatment for the investigators, but the treatment was not blinded for the participants.	– –
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	Apparently, since they reported any disturbance that could be treatment-related and defined them according to NCI-CTCAE (National Cancer Institute - Common Terminology Criteria for Adverse Events) v4.0.	+
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised. Drop-outs were explained (personal reasons). Purity and stability of the test substance were not stated.	+
	6	Can we be confident in the outcome assessment?	Likely, since they reported any disturbance that could be treatment-related and defined them according to NCI-CTCAE v4.0.	+
Selective reporting bias	7	Were all measured outcomes reported?	Apparently, since they reported that treatment with OPERA® supplement was overall well tolerated by patients. No	+

			significant acute toxicity related to the intake of OPERA® was reported during the study period; only two patients (4.35%) reported a G1 gastralgia, with no discontinuation of tablets.	
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods used were appropriate, but not used for the safety analysis. Study design procedures were reviewed and approved by the local institutional ethics committee. No funding was reported.	+
Tier				**3**

Pogacnik et al. (2023) (Tier 1)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	The subjects were allocated randomly to one of four study groups, with 26–27 subjects in each group. Randomisation was achieved using a simple randomisation procedure (computerised random numbers).	++
	2	Was allocation to study groups adequately concealed?	There is indirect evidence that the treatment allocation was concealed since the products were packaged in such a way that neither the study subjects nor the investigators knew which product was being used by each individual subject.	+
Performance bias	**3**	Were the research personnel and human subjects blinded to the study group during the study?	The products were packaged in 500 mL white plastic bottles in such a way that neither the study subjects nor the investigators knew which product was being used by each individual subject.	++
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	It was stated that no side-effects or adverse events of any kind were reported. No further details on recording or reporting of adverse events/effects were given.	+
Detection bias	**5**	Can we be confident in the exposure characterisation?	There is indirect evidence that the exposure was sufficiently characterised. To follow their compliance with the protocol, the subjects kept a diary of test product intake for the whole 12-	+

			week intervention period, which was checked after 6 and 12 weeks of intervention in a concomitant interview with the subjects. Subjects were also asked to record any failure to follow the instructions. At the end of the study, they were required to return any leftover test products. There were 2 dropouts, one in the ColMSMHD group and one in the Col-HD group, both for personal reasons. Purity and stability of the test substance were not stated.	
	6	Can we be confident in the outcome assessment?	It was stated that no side-effects or adverse events of any kind were reported. No further details on recording or reporting of adverse events/effects were given.	+
Selective reporting bias	7	Were all measured outcomes reported?	Apparently, since no side-effects or adverse events of any kind were reported.	+
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods used were appropriate, but not used for the safety analysis. The study protocol was approved by an ethics committee and registered. The authors were supported by Tosla d.o.o., that also produced and supplied the tested products.	–
Tier				**1**

Adams et al. (2022) (Tier 3)

Type of bias	No.	Question	RoB evaluation	RoB rating
Selection bias	**1**	Was administered dose or exposure level adequately randomised?	The subjects were not randomised in this retrospective survey.	– –
	2	Was allocation to study groups adequately concealed?	There were no control or placebo groups included and the study was a retrospective survey, mostly relying on parental reports. Thus, there was no concealment of allocation of treatment for researchers or participants.	– –
Performance bias	**3**	Were the research personnel and human subjects blinded to the	There were no control or placebo groups included and the study was a retrospective survey, mostly relying on parental reports. Thus,	– –

		study group during the study?	there was no blinding of treatment for researchers or participants.	
Attrition/exclusion bias	4	Were outcome data complete without attrition or exclusion from analysis?	There is no information to evaluate attrition or exclusion from analysis.	– –
Detection bias	**5**	Can we be confident in the exposure characterisation?	This was a retrospective survey of consumers who purchased ANRC-EP for a child or adult with ASD. Purity and stability of the test substance were not stated.	+
	6	Can we be confident in the outcome assessment?	Adverse effects were reported as an Overall Adverse Effect score, on a scale of 0-3, using the same scale as in the National Survey on Treatment Effectiveness for Autism (NSTEA). If adverse effects occurred, participants were asked to indicate which ones based on a list from the NSTEA.	+
Selective reporting bias	7	Were all measured outcomes reported?	Apparently, but it cannot be checked since it was self-reported or reported by parents of a child.	+
Other sources of bias	8	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate and researchers adhered to the study protocol)?	The statistical methods used were appropriate, however, no control for multiple analyses was conducted, because the different evaluations were considered to be largely independent of one-another. The study was approved by an institutional review board.	+
Tier				**3**

A shorter table showing the included human studies with only the dose and duration of MSM exposure, as well as the RoB score, is included for easier comparison (Table 3).

Table 3. Dose and duration of MSM exposure, and RoB evaluations, for the included studies.

Authors (publication year)	MSM dose (grams)/day	Ca. duration of MSM exposure (months)	RoB Tier
Studies of MSM alone in adults (≥18 years)			
Miller et al. (2021)	3	4	3
Muizzuddin and Benjamin (2022)	3 1	4 4	3
Toguchi et al. (2023)	2	3	**1**
Studies of MSM in multicomponent dietary supplements in adults (≥18 years)			
Liu (2020), Liu et al. (2020; 2021)	1.5	3	**1**

Pogacnik et al. (2023)	1.5	3	**1**
McFarlin et al. (2021)	up to ca. 0.7	1	**1**
Tanner et al. (2022)	up to ca. 1.0	1	3
Guaitolini et al. (2019)	0.4	2	**1**
Desideri et al. (2022)	0.2	6	3
Studies of MSM alone in children and adolescents			
No studies found			
Studies of MSM in multicomponent dietary supplements in children and adolescents			
Adams et al. (2022)	500 mg/day (3-14 years of age) 1000 mg/day (10-18 years of age)	From 3-5 months to >4 years (or even 6 years) (individual data not specified)	3

Summary of included new human studies

Of the ten included new human studies that were considered relevant for an evaluation of adverse effects of MSM, five were scored as Tier 1 and five were scored as Tier 3 in the RoB evaluations (Table 3). Only one study that scored Tier 1 used exposure in adults to MSM alone, as 2 g/day for 3 months (Toguchi et al., 2023). The safety evaluation in this study was performed through physical examination, urine analysis, peripheral blood test and medical interview, and the results revealed no health problems during the study period and no adverse events were reported. The other two studies using MSM alone in adults were scored Tier 3, thus having more bias, and used 1 or 3 g/day of MSM for 4 months (Miller et al., 2021; Muizzuddin and Benjamin, 2022).

Among the studies of MSM in multicomponent dietary supplements in adults, four were considered Tier 1, using MSM in 0.4 to 1.5 g/day for 1-3 months (Guaitolini et al., 2019; Liu et al., 2021; McFarlin et al., 2021; Pogacnik et al., 2023). Two studies scored Tier 3 used 0.2 or ca. 1.0 g/day of MSM for 6 months or 1 month in adults (Desideri et al., 2022; Tanner et al., 2022), respectively. These studies are less optimal than studies of MSM alone, however, since no adverse effects or events of importance were reported, they can be considered evidence for lack of significant adverse effects/events also of MSM.

Only one of the new human studies included children and adolescents, as well as adults, with ASD (Adams et al., 2022). A multicomponent dietary supplement that also contained MSM was given in doses depending on their body weight (and thus, also age), from 500 mg/day (3-14 years of age) to 1000 mg/day (10-18 years of age). The exposure was reported to vary from 3-5 months to more than 4 years (or even 6 years; varying information in the publication), with median usage of ca. 12 months. However, this information on duration of exposure was not linked to individual data on age or body weight, and thus, dose of MSM.

None of the new studies used a higher dose of MSM than the study used as PoD by VKM (Crawford et al., 2019b). One study (Desideri et al., 2022) had a longer exposure period (6 months), however, they used a lower dose of MSM (0.2 g/day). Therefore, the study by Crawford et al. (2019b) is still the most relevant to use as PoD in a new risk assessment of MSM.

Study used as PoD in the VKM report

The study by Crawford et al. (2019b) is included in this updated risk assessment since it was the main study used by VKM, who concluded that for adults (≥18 years), a point of departure (PoD) of **6 g/day of MSM** could be identified with an exposure length of **16 weeks** based on this RCT (total dose 672 g MSM). The purpose of the safety study by Crawford et al. (2019b) was to ensure that 16 weeks of MSM did not cause adverse effects in relatively healthy patients with musculoskeletal disorders of osteoarthritis and back pain. They carried out a subgroup analysis on data from a randomised, double-blind, placebo-controlled trial, "The use of Methylsulfonylmethane (MSM) in the treatment of low back pain," to determine the safety of taking **6 g daily of MSM (OptiMSM®, Bergstrom Nutrition**). The participants were adults of both sexes, approximately 35% women and 65% men in the MSM group, and 28% women and 73% men in the placebo group). The number of participants given MSM and placebo was 46 (mean age 35 years) and 40 (mean age 36 years), respectively. Both groups were also given Naproxen. Metabolic parameters were monitored to determine whether MSM altered hematologic, liver or kidney function, and physiologic parameters of blood pressure and weight were monitored.

The main outcome measured were metabolic parameters measured by hematologic function (white blood cells (WBC), platelets, hemoglobin (Hb), glucose), liver function as measured by total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Physiologic parameters were measured by weight, diastolic (DBP) and systolic (SBP) blood pressure, and kidney function was measured by creatinine. The analysis of outcome measures showed no significant difference between MSM and placebo values ($P < 0.05$). The authors concluded that MSM had no effects on WBC, platelets, Hb, total bilirubin, AST, ALT, creatinine, weight, DBP or SBP in this study.

Other relevant information

MSM has CAS no. 67-71-0 (PubChem, 2004). MSM is an endogenous oxidative metabolite, found in i.a. blood and breast milk. It is a metabolic product of endogenous methanethiol metabolism and intestinal bacterial metabolism. The natural level of MSM in the circulatory system of an adult man is about 0.2 mg/kg bw (i.e. 14 mg for a person weighing 70 kg) (Hansen et al., 2006). MSM levels have been detected in the range of 0-25 µmol/l in the plasma and cerebrospinal fluid from healthy individuals (AECOSAN, 2014). It is also shown in newer metabolomics studies that endogenous MSM can be affected by type of diet (Trimigno et al., 2020) or by negative health conditions such as cardiac dysfunction (Culler et al., 2024).

MSM is a natural sulphur-containing constituent of the typical diet (i.e. vegetables, grain and meat), resulting in a mean MSM consumption at approximately 2.8 mg/day (0.04 mg/kg bw

per day for a 70 kg human) (US-FDA, 2007). Foods containing MSM include e.g. cow's milk (6-8 µg/g), coffee (1.6 µg/g), tomato (0.86 µg/g), tea (0.3 µg/g), maize (0.11 µg/g) and alfalfa (0.07 µg/g) (AECOSAN, 2014).

The GRAS dossier for OptiMSM® indicated that consumption of OptiMSM® at 3840 mg/day (at the 90th percentile) is generally recognized as safe (GRAS), under the proposed conditions of use. The estimated aggregate consumption of MSM, through natural sources, dietary supplement intake and as OptiMSM® added to food at the 90th percentile, is 4845.6 mg/day (69.2 mg/kg bw for a 70 kg human) (US-FDA, 2007). However, GRAS notifications alone are rarely considered sufficient to establish safety in risk assessments in the EU.

No interactions of MSM with medications are known (RELIS, 2017). A more recent scoping review (Burton and McCormack, 2023) stated that the potential interactions of nutritional supplements with other compounds, medication, dietary factors and chronic diseases are largely undetermined. In a recent study by Kim et al. (2023), dietary supplements, including MSM, were incubated with cytochrome P450 isozyme-specific substrates in human liver microsomes and the formation of marker metabolites was measured to investigate their inhibitory potential on cytochrome P450 (CYP) enzyme activities. The results revealed no significant inhibitory effects on seven CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4(M)-1-OH-midazolam/CYP3A4(T)-6-β-OH-testosterone) by MSM. Therefore, MSM was anticipated to have a low potential for cytochrome P450-mediated drug interactions with osteoarthritis medications that are likely to be co-administered.

Although not relevant for an evaluation of safety, it is of interest that the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) concluded that a cause and effect relationship has not been established between the consumption of MSM, either alone or in combination with glucosamine hydrochloride, and the maintenance of normal joints (EFSA, 2009).

Discussion on the appropriate size of the uncertainty factor (UF)

VKM used a PoD of 6 g/day from Crawford et al. (2019b) as a starting point for their assessment. This PoD of 6 g/day is also supported by another publication on humans (Kim et al., 2006), scored Tier 1, with 21 adults given MSM and 19 adults given placebo for 12 weeks, administrated graded doses of MSM the first week (2 g/day divided in two doses for 3 days and 4 g/day divided in two doses for 4 days) and 6 g/day divided in two doses for 11 weeks, in total 484 g MSM, reported no major adverse events, and reported side-effects with comparable frequency in the MSM and placebo groups. In addition, also scored Tier 1, a cohort study by Satia et al. (2009), reported no increase in hazard ratios in adult lung and colorectal cancer patients who used MSM in unknown doses in the previous 10 years.

Study quality

VKM used Crawford et al. (2019b) as a PoD, and after scoring RoB it was considered a Tier 1 study, i.e. with low risk of bias. This is a safety study with the main aim to look for adverse effects of MSM. The authors have studied various endpoints within hematology, and liver and kidney function, and found no difference between MSM and placebo. There were 40 people who received MSM and 46 who received placebo, respectively, thus, not very low numbers. There were approximately twice as many men as women in both groups in this study. Apart

from one of the ADME studies in VKM's report (Bloomer et al., 2019), which found somewhat higher total plasma concentrations in women (1082 ± 1006 µM) compared to men (845 ± 805 µM), there are no available data suggesting gender differences in susceptibility to adverse effects of MSM. Since both groups received Naproxen, this is of little significance. VKM concluded 'No' ('significant effects reported') on the human studies for all endpoints (Table 4.5-2, page 59). VKM used an additional uncertainty factor of 2 for data quality. Since the study by Crawford et al. (2019b) is considered to have little bias (Tier 1), an UF for data quality of this study is not considered necessary by NIPH.

Exposure length

VKM has further used an UF of 6 on the grounds that 16 weeks (4 months) of exposure is to be considered a sub-acute exposure for humans. According to ECHA (2012), in Table R.8-5 and Table R.8.6, an UF of 6 is recommended for extrapolation from sub-acute to chronic exposure. However, sub-acute refers to a 28-day study - in rodents. A 90-day study is considered sub-chronic, and for the extrapolation from sub-chronic to chronic, a UF of 2 can be used (ECHA, 2012; EFSA 2012). Ideally, one should do a risk assessment of dietary supplements based on chronic exposure. NIPH is not aware of any information on how long exposure time is needed to be considered chronic or sub-chronic in humans. NFSA did not provide any information on how long people take these preparations with MSM, or whether there is a recommendation on the products about maximum duration of intake. In Crawford et al. (2019b), the participants were exposed for 4 months. MSM is not genotoxic. It may be argued that any non-genotoxic adverse effects would probably have appeared after daily use of 6 g/day of MSM for 4 months, if it actually caused adverse effects. Thus, this UF of 6 may be considered unnecessarily high in this case, and an UF = 2 is proposed for less than chronic exposure by NIPH.

Interindividual human variation

Usually, the default UF = 10 is used for interindividual variation in humans. This can be divided in two parts; 3.16 for differences in toxicokinetics and 3.16 for differences in toxicodynamics (3.16 x 3.16 = ~10). VKM used an UF based on both default subfactors divided by 2 (3.16/2 = 1.58, 1.58 x 1.58 = ~2.5) to cover potential differences in toxicokinetics and toxicodynamics in the **adult** population.

There are available data on ADME from both studies on animals (5 publications) and humans (6 publications on adults and one study on a child) in the VKM report. These data show that MSM is rapidly absorbed and distributed in the body. Most of MSM is excreted unchanged, mainly in urine, some in feces, within few hours. Bioaccumulation is minimal. MSM crosses the blood-brain barrier, but is apparently excreted again without effects on metabolites in the brain being observed. There are little data on metabolism in general, but some of the ingested dose may be metabolized to unknown metabolites, probably entering the endogenous sulphur metabolism. The ADME studies used relatively high doses, some for a long time (weeks, months, years), and reported no adverse effects, although this was not the purpose of their investigations and may therefore not have been investigated.

Not all toxicity endpoints are included in the studies in the available literature on MSM, thus, being an argument for caution.

No group in the adult population appears to have been identified as especially susceptible to MSM, e.g. because of polymorphisms in relevant genes. The available studies are mostly on reasonably healthy adults, including persons with overweight/obesity, osteoarthritis or ASD, thus, not representing the full adult population. There were some data on cancer patients. However, persons suffering from any illness or chronic health condition should contact their physician before taking any food supplements.

Additionally, MSM is an endogenously formed substance, which is also ingested through food.

Based on these considerations, using an uncertainty factor for interindividual differences in humans lower than the default value of 10, i.e. 2.5 as used by VKM, is supported by NIPH.

NIPH's conclusion on choice of a total UF

Using an UF of 2 for non-chronic exposure and an UF of 2.5 for potential human interindividual variations in susceptibility, gives a total UF of 5. Dividing 6 g/day by 5, the highest presumed safe dose will be 1.2 g/day.

Conclusions on safety of MSM for adults

The dose of MSM to evaluate for safety in adults was first 3 g per day, and if that dose was found not to be safe, to evaluate which lower doses could be considered safe (e.g. 2 g, 1.5 g, 1 g, 0.5 g per day or 302 mg per day).

If using a total UF of 5 on the PoD of 6 g/day, this will result in 1.2 g/day as the highest safe dose. Then the doses of 302 mg/day, 0.5 g/day and 1 g/day of MSM for up to 4 months are considered safe for adults. The safety of the doses 1.5 g/day, 2 g/day and 3 g/day of MSM for up to 4 months for adults is uncertain based on the available data.

The choice of an uncertainty factor in risk assessments is based on expert judgement. Various experts or risk assessment groups will often put different weight and importance on the many different conditions used and weaknesses observed in a study, which causes a different choice of a total UF, especially in situations when there are not sufficient relevant good quality data available. This is often the situation and it is not always one definitely correct answer on which UF to use in a risk assessment.

Ideally, for 'other substances' used in food supplements, the risk assessments should be based on toxicity data from experimental studies with chronic exposure. NIPH is not aware of the usual or recommended length of exposure to MSM.

Conclusions on safety of MSM for children and adolescents

Only one study with bias (Tier 3), and information about doses and duration of exposure not linked to age (or body weight) was found. Therefore, no conclusions on safety for the age groups 3 - <10 years, 10 - <14 years and 14 - <18 years, as asked by NSFA, can be drawn for any doses in this updated risk assessment.

Uncertainties and perspectives in this re-evaluation

Few persons have been involved in this re-evaluation, and therefore, other persons or groups of persons may have different views on some points, which are evaluated by expert judgement.

Usually, publications scored Tier 3 for RoB are excluded from the evaluation. However, they have been presented here, in order for NSFA to have all the relevant new literature available.

Often for 'other substances' there is very little relevant information on adverse effects available, since most such publications aim to study beneficial effects. For MSM, however, there are more data available than for many other 'other substances' previously evaluated by VKM.

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Appendices

Appendix A. Search strategy - Medline

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 09, 2025>

1 (("Dimethyl sulfone" or "Methyl sulfone" or "Methylsulfonylmethane" or "DIMETHYLSULFONE" or "Dimethyl sulphone" or "Methane, sulfonylbis-" or "sulfonyldimethane" or "(methylsulfonyl)methane" or "Methylsulfonyl methane" or "METHANESULFONYLMETHANE" or "67-71-0" or "EINECS 200-665-9").mp. and (risk/ or risk assessment/ or risk factors/ or "Chemical and Drug Induced Liver Injury"/ or Immunosuppression/ or Endocrine Disruptors/ or Hypersensitivity/ or Food Hypersensitivity/ or Food Intolerance/ or Anaphylaxis/ or Inflammation/ or Poisoning/ or (adverse effects or toxicity or poisoning).fs. or (risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or hepatotox* or "liver tox*" or nephrotox* or "nephro tox*" or "kidney tox*" or "renal tox*" or immunotox* or "immune system tox*" or "immune tox*" or "immuno tox*" or "immunosystem tox*" or "reproductive tox*" or "developmental tox*" or embryotox* or "embryo tox*" or "lung tox*" or pulmotox* or "pulmonary tox*" or "respiratory tox*" or respirotox* or neurotox* or "skin tox*" or "dermal tox*" or dermatox* or teratogenicity or teratogeneity or "endocrine tox*" or "immune effect" or "immune respons*" or "immuno respons*" or immunorespons* or immunogenesis or "immunologic respons*" or immunosuppress* or "immuno suppress*" or "immune suppress*" or "endocrine disrupt" or anaphylax* or anaphylactic or anaphylactoid or anaphylatoxin or "immune fever" or "food intoleranc*" or "Food Sensitivit*" or "nutritional intolerance*" or "nutrient intolerance*" or hypersensitiv* or hypersensitization or hypersensitisation or hyperergic or hyperergy or erethism or Allergy or Allergies or Allergic or allergen? or allergenic or sensitization or inflammation* or inflammatory or serositis or poisoning?).tw,kf.)) not (comment or editorial or letter).pt. 234

2 (human or child*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 7000203

3 1 and 2 57

4 limit 3 to (english language and yr="2019 -Current") 23

5 (("Dimethyl sulfone" or "Methyl sulfone" or "Methylsulfonylmethane" or "DIMETHYLSULFONE" or "Dimethyl sulphone" or "Methane, sulfonylbis-" or "sulfonyldimethane" or "(methylsulfonyl)methane" or "Methylsulfonyl methane" or "METHANESULFONYLMETHANE" or "67-71-0" or "EINECS 200-665-9").mp. and (Mutation/ or Mutagens/ or Mutagenesis/ or Mutagenicity Tests/ or DNA damage/ or dna breaks/ or dna breaks, doublestranded/ or dna breaks, single-stranded/ or Comet Assay/ or Chromosome Aberrations/ or Cytogenetics/ or Aneugens/ or Micronucleus Tests/ or Sister Chromatid Exchange/ or DNA Adducts/ or Frameshift Mutation/ or Point Mutation/ or Chromosome Duplication/ or Gene Duplication/ or Chromosome Breakage/ or Aneuploidy/ or Noxae/ or (Mutation? or mutagen* or (gene? adj2 alteration?) or mutator? or Genotoxi* or "Genetic Toxicity Test?" or "Ames test*" or "ames salmonella assay?" or "mouse lymphoma tk assay?" or "mouse lymphoma assay?" or "mouse spot test" or mutamouse or (Muta adj2 Mouse) or

"Big Blue" or "LacZ mouse" or "LacI mouse" or "cII gene" or "gpt delta" or (("deoxyribonucleic acid" or DNA) adj (damage* or injur* or lesion? or break* or adduct? or reactivity)) or "strand break*" or "doublestrand break*" or "singlestrand break*" or "comet assay*" or "single cell gel electrophoresis" or "singlecell gel electrophoresis" or SCGE or "alkaline elution" or "unscheduled DNA synthesis" or "unscheduled deoxyribonucleic acid synthesis" or "Rec assay? with Bacillus subtilis" or "SOS test with Escherichia coli" or ((chromosom* or autosom*) adj (aberration? or abnormalit* or anomal* or defect? or error? or duplication? or break* or endoreduplication?)) or cytogen* or clastogen* or aneugen* or "Aneuploidyinducing Agent?" or "Polyploidy Inducing Agent?" or "Polyploidyinducing Agent?" or "micronucleus assay?" or "micronucleus test*" or "MN assay?" or "SOS chromotest*" or "sister chromatid exchange*" or ((Frameshift or "Frame Shift" or "reading frame" or point) adj Mutation?) or "reading frame shift" or ((OutofFrame or "Out of Frame") adj (Mutation? or Insertion? or Deletion?)) or gentox* or "gene duplication?" or "gene doubling?" or Aneuploidy or aneuploid* or (toxic adj (substance? or agent? or chemical? or compound?)) or noxae).tw,kf.)) not (comment or editorial or letter).pt. 27

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8 (("Dimethyl sulfone" or "Methyl sulfone" or "Methylsulfonylmethane" or "DIMETHYLSULFONE" or "Dimethyl sulphone" or "Methane, sulfonylbis-" or "sulfonyldimethane" or "(methylsulfonyl)methane" or "Methylsulfonyl methane" or "METHANESULFONYLMETHANE" or "67-71-0" or "EINECS 200-665-9").mp. and (absorption/ or absorption, physicochemical/ or Metabolism/ or Biotransformation/ or (Absorption or distribution or metabol* or elimination or excretion or degradation or biotransformation? or bioconversion? or "biological transformation?" or toxicokinetic? or clearance or detoxification or detoxication or adme).tw,kf.)) not (comment or editorial or letter).pt. 235

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11 1 and 4 23

12 4 and 5 2

13 4 and 8 10

Appendix B. Search strategy - EMBASE

EMBASE 1974 to 2025 June 09

1 (("Dimethyl sulfone" or "Methyl sulfone" or "Methylsulfonylmethane" or "DIMETHYLSULFONE" or "Dimethyl sulphone" or "Methane, sulfonylbis-" or "sulfonyldimethane" or "(methylsulfonyl)methane" or "Methylsulfonyl methane" or "METHANESULFONYLMETHANE" or "67-71-0" or "EINECS 200-665-9").mp. and (risk/ or risk assessment/ or risk factors/ or "Chemical and Drug Induced Liver Injury"/ or Immunosuppression/ or Endocrine Disruptors/ or Hypersensitivity/ or Food Hypersensitivity/ or Food Intolerance/ or Anaphylaxis/ or Inflammation/ or Poisoning/ or (adverse effects or toxicity or poisoning).fs. or (risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or hepatotox* or "liver tox*" or nephrotox* or "nephro tox*" or "kidney tox*" or "renal tox*" or immunotox* or "immune system tox*" or "immune tox*" or "immuno tox*" or "immunosystem tox*" or "reproductive tox*" or "developmental tox*" or embryotox* or "embryo tox*" or "lung tox*" or pulmotox* or "pulmonary tox*" or "respiratory tox*" or respirotox* or neurotox* or "skin tox*" or "dermal tox*" or dermatox* or teratogenicity or teratogeneity or "endocrine tox*" or "immune effect" or "immune respons*" or "immuno respons*" or immunorespons* or immunogenesis or "immunologic respons*" or immunosuppress* or "immuno suppress*" or "immune suppress*" or "endocrine disrupt" or anaphylax* or anaphylactic or anaphylactoid or anaphylatoxin or "immune fever" or "food intoleranc*" or "Food Sensitivit*" or "nutritional intolerance*" or "nutrient intolerance*" or hypersensitiv* or hypersensitization or hypersensitisation or hyperergic or hyperergy or erethism or Allergy or Allergies or Allergic or allergen? or allergenic or sensitization or inflammation* or inflammatory or serositis or poisoning?).tw,kf.)) not (comment or editorial or letter).pt. 447

2 (human or child*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 29710858

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4 limit 3 to (english language and yr="2019 -Current") 112

5 (("Dimethyl sulfone" or "Methyl sulfone" or "Methylsulfonylmethane" or "DIMETHYLSULFONE" or "Dimethyl sulphone" or "Methane, sulfonylbis-" or "sulfonyldimethane" or "(methylsulfonyl)methane" or "Methylsulfonyl methane" or "METHANESULFONYLMETHANE" or "67-71-0" or "EINECS 200-665-9").mp. and (Mutation/ or Mutagens/ or Mutagenesis/ or Mutagenicity Tests/ or DNA damage/ or dna breaks/ or dna breaks, doublestranded/ or dna breaks, single-stranded/ or Comet Assay/ or Chromosome Aberrations/ or Cytogenetics/ or Aneugens/ or Micronucleus Tests/ or Sister Chromatid Exchange/ or DNA Adducts/ or Frameshift Mutation/ or Point Mutation/ or Chromosome Duplication/ or Gene Duplication/ or Chromosome Breakage/ or Aneuploidy/ or Noxae/ or (Mutation? or mutagen* or (gene? adj2 alteration?) or mutator? or Genotoxi* or "Genetic Toxicity Test?" or "Ames test*" or "ames salmonella assay?" or "mouse lymphoma tk assay?" or "mouse lymphoma assay?" or "mouse spot test" or mutamouse or (Muta adj2 Mouse) or "Big Blue" or "LacZ mouse" or "LacI mouse" or "cII gene" or "gpt delta" or (("deoxyribonucleic acid" or DNA) adj (damage* or injur* or lesion? or break* or adduct? or reactivity)) or "strand break*" or "doublestrand break*" or "singlestrand break*" or "comet assay*" or "single cell

gel electrophoresis" or "singlecell gel electrophoresis" or SCGE or "alkaline elution" or "unscheduled DNA synthesis" or "unscheduled deoxyribonucleic acid synthesis" or "Rec assay? with Bacillus subtilis" or "SOS test with Escherichia coli" or ((chromosom* or autosom*) adj (aberration? or abnormalit* or anomal* or defect? or error? or duplication? or break* or endoreduplication?)) or cytogen* or clastogen* or aneugen* or "Aneuploidyinducing Agent?" or "Polyploidy Inducing Agent?" or "Polyploidyinducing Agent?" or "micronucleus assay?" or "micronucleus test*" or "MN assay?" or "SOS chromotest*" or "sister chromatid exchange*" or ((Frameshift or "Frame Shift" or "reading frame" or point) adj Mutation?) or "reading frame shift" or ((OutofFrame or "Out of Frame") adj (Mutation? or Insertion? or Deletion?)) or gentox* or "gene duplication?" or "gene doubling?" or Aneuploidy or aneuploid* or (toxic adj (substance? or agent? or chemical? or compound?)) or noxae).tw,kf.)) not (comment or editorial or letter).pt. 36

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8 (("Dimethyl sulfone" or "Methyl sulfone" or "Methylsulfonylmethane" or "DIMETHYLSULFONE" or "Dimethyl sulphone" or "Methane, sulfonylbis-" or "sulfonyldimethane" or "(methylsulfonyl)methane" or "Methylsulfonyl methane" or "METHANESULFONYLMETHANE" or "67-71-0" or "EINECS 200-665-9").mp. and (absorption/ or absorption, physicochemical/ or Metabolism/ or Biotransformation/ or (Absorption or distribution or metabol* or elimination or excretion or degradation or biotransformation? or bioconversion? or "biological transformation?" or toxicokinetic? or clearance or detoxification or detoxication or adme).tw,kf.)) not (comment or editorial or letter).pt. 440

9 2 and 8 210

10 4 and 9 45

11 1 and 4 112

12 4 and 5 6

13 4 and 8 45