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Conclusion on the peer review of metam

CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion regarding the peer review of the pesticide risk assessment of the active substance metam

Issued on 26 November 2008

SUMMARY

Metam is one of the 84 substances of the third stage Part B of the review programme covered by Commission Regulation (EC) No 1490/2002[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise upon request of the EU-Commission a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within six months a conclusion on the risk assessment to the EU-Commission.

Belgium being the designated rapporteur Member State submitted the DAR on metam in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 10 September 2007. The peer review was initiated on 4 October 2007 by dispatching the DAR for consultation of the Member States and the main notifier Taminco. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by the EFSA to identify the remaining issues. The identified issues as well as further information made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in June – July 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in October 2008 leading to the conclusions as laid down in this report.

This conclusion was reached on the basis of the evaluation of the representative uses as a nematicide, fungicide, herbicide and insecticide by soil fumigation prior to the planting of carrot, lamb's lettuce, cucumber, aubergine, pepper, potato, strawberry, tomato and grapes. Full details of the GAP can be found in the attached list of end points.

[1] OJ No L 224, 21.08.2002, p. 25, as amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)

The representative formulated product for the evaluation was "Metam sodium 510 g/L", soluble concentrate (SL), registered under different trade names in Europe.

Adequate methods are available to monitor all compounds given in the respective residue definition. However, it should be noted that the residue definition for plants and ground water are provisional. Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. There is a data gap for the flash point of the TK. Storage stability data where the relevant impurities are analysed for was also identified as a data gap. Spectra are available for the relevant impurity MITC[2] but not for the other relevant impurity DMTU[3] so this has also to be a data gap. As MITC is currently not specified in the technical specification a new specification is needed.

As for mammalian toxicology, metam sodium is harmful by oral ingestion and inhalation (R22 and R20 proposed). In irritation tests, metam sodium was not irritant to eyes but was corrosive to skin, therefore R34 ("Causes burns") was proposed. Metam sodium is a skin sensitiser (R43 "May cause sensitisation by skin contact" proposed). The relevant short term No Observed Adverse Effect Levels (NOAELs) are 0.1, 0.5 and 0.8 mg/kg bw/day in dogs, rats and mice, respectively. In particular, the occurrence of severe hepatotoxicity in dogs was considered to support the proposal of R48/22 ("Danger of serious damage to health by prolonged exposure if swallowed") to the European Chemicals Agency (ECHA). Metam did not show any genotoxic potential, but caused angiosarcomas in mice, therefore R40 ("Limited evidence of a carcinogenic effect") was proposed. The relevant long term NOAEL was 1.5 mg/kg bw/day based reduced bodyweight gain, specific lesion within the nasal passages, and changes in some haematology and spleen (haemosiderin depots) parameters in rats. In multigeneration tests, the relevant parental, reproductive and offspring NOAELs were 4, 12 and 4 mg/kg bw/day, respectively. Tested in developmental toxicity studies, metam sodium caused an increased incidence of variations and retardations at maternally toxic dose in rats and decreased number of live foetuses, increased number of dead implants in rabbits, with relevant maternal and developmental NOAEL in rats of 5 mg/kg bw/day and of 5 and 10 mg/kg bw/day, respectively, in rabbits. The malformations occurred at low incidences (sometimes in singularity), but in a consistent manner, at the top-doses, in the presence of quite severe maternal toxicity. Effects were clearly treatment related and associated with maternal toxicity: the classification as R63 ("Possible risk of harm to the unborn child") was proposed for consideration to the ECHA. The Acceptable Daily Intake (ADI) and Acceptable Operator Exposure Level (AOEL) are 0.001 mg/kg bw/day, based on the 1-year dog study NOAEL with a Safety Factor (SF) 100; the Acute Reference Dose (ARfD) is 0.1

[2] MITC: methyl isothiocyanate
[3] DMTU: N,N'-dimethylthiourea

mg/kg bw based on an overall rat developmental toxicity NOAEL and supported by rabbit developmental study.

MITC is toxic via ingestion (R25 proposed) and via inhalation (R23 proposed). It is harmful in contact with skin (R21 proposed). In skin irritation tests it was corrosive to skin (R34 proposed). It was also irritative to the respiratory system (R37 proposed). It is a skin sensitiser (R43 proposed).

The relevant NOAEL for short term exposure to MITC is 0.04 mg/kg bw/day, based on the thymus involution and liver vacuolation at 0.4 mg/kg bw/day. MITC did not show any genotoxic, carcinogenic, reproductive and developmental toxicity potential. The relevant NOAEL for long term toxicity is 0.44 mg/kg bw/day based on haematological changes in rats; the relevant parental NOAEL is 0.7 mg/kg bw/day, the reproductive and offspring NOAEL is >3.6 mg/kg bw/day. The relevant maternal and developmental toxicity NOAELs in rats are 3 and 10 mg/kg bw/day. The ADI and AOEL are 0.004 mg/kg bw/day based on the 1 year and 90-day studies in dog, respectively; the ARfD is 0.03 mg/kg bw based on NOAEL for rat maternal toxicity with SF 100. The operator exposure in open field is below the AOEL with the use of Respiratory Protective Equipment (RPE); the bystander and worker exposure in the open field is below the AOEL without the use of Personal Protective Equipment (PPE).

The PRAPeR meeting of experts considered the impurity DMTU as relevant, due to the lack of toxicological information.

Metabolism studies were supplied but no metabolites were identified. It was noted that the majority of the metabolism studies were under dosed. The meeting of experts considered the under dosing and lack of identification. It was concluded that as long as fate and behaviour had not identified any significant metabolites in soil then the metabolism data could be accepted. At this time fate and behaviour are unable to conclude on this issue and therefore a data gap has been set to address this. As some of the impurities in the technical material are applied at significant levels the consumer risk for the impurities still has to be addressed. A data gap for new residue trials was identified. Currently the need for processing studies, rotational crops and livestock studies are not triggered. However, this is subject to the data gaps. The risk assessment can not be finalised and MRLs can not be proposed at this time as the residue trials data are identified as a data gap.

Degradation of metam and its known active metabolite MITC in soil was investigated in four soils under dark aerobic conditions at 20 °C. The experts in the meeting were not confident that these experiments provided a realistic representation of the fate and behaviour of metam and MITC in soil mainly due to the mode of application used in the study with respect to the application in field where volatilization is minimized by compacting soil or with plastic films. However, the meeting noted that a number of scientific studies investigating the persistence of metam and MITC are available in the public domain and to regulatory authorities. Consequently, a data gap was identified by the meeting of experts to address the range of half-lives available for metam and MITC and whether they are applicable to metam EU risk assessment. The notifier should address the different variables that might impact on the degradation in soil, such as method of application dose rate and soil adaptation.

Taking into consideration the application rates of metam (306 – 612 kg / ha), during the peer review it was considered that impurities need to be addressed for the potential environmental and ground water contamination. The notifier submitted an overview of the main impurities present in the technical material that was summarized by the RMS in the addendum (June 2008). The meeting of experts in toxicology agreed that the impurity DMTU should be regarded as toxicological relevant and therefore a will need a ground water exposure assessment.

PEC soil for metam and MITC were calculated for the worst case use in field tomato (612 kg a.s. / ha) assuming 15 cm incorporation. Time dependent PEC soil need to be updated once the data gaps identified for persistence in soil are solved. Initial PECs in soil may be used for the EU risk assessment.

Mobility of metam was investigated by the HPLC method. According this experiment metam may be considered to be very high mobile in soil. A batch adsorption / desorption study is available for MITC in four soils. This compound was very high mobile in these soils (K_{foc} = 27 mL / g). The meeting of experts concluded that adsorption in this study may have been overestimated due to the fact that experimental K_{oc} values are simultaneously affected by degradation and volatilization during the experiment. Therefore, the meeting of experts proposed a data gap for a new soil adsorption desorption study conducted with consideration of the volatility and the low adsorption properties of MITC (e.g. with shorter equilibration times, soil solution ratios of 1:1, high organic carbon soils).

After the meeting of experts, a new data gap has been identified by EFSA to address the mobility of impurity DMTU in soil in order to obtain adequate input parameters for ground water modelling.

Hydrolysis of metam is relatively fast at any pH. Hydrolysis of MITC at 25 °C occurs with half-lives of ≈ 40 d (pH 4), 50 d (pH 7) and 11 d (pH 9). Major hydrolysis products of MITC were DMU, DMTU and MDTA (metam). The fact that one of the major metabolites of MITC is metam indicates that in water metam and MITC are in equilibrium.

Aqueous photolysis of metam under simulated sunlight is very fast (DT_{50} = 12 min; equivalent to 27.8 min at 38 °N). No readily biodegradation study is available and therefore the substance is considered to be non readily biodegradable.

In the aerobic water /sediment experiment (25 °C) metam degrades rapidly in the whole system ($DT_{50\text{whole system}}$ = 0.32 h). The meeting agreed that the information provided by the notifier did not allow any quantitative estimation of the effect of temperature on the volatilization. Consequently, the meeting of experts identified a data gap to address the effect of temperature on the dissipation of MITC from water by volatilization. Depending on the results of the volatilization assessment, a new water sediment study at lower temperature may be necessary. The data from the anaerobic water sediment study were considered not relevant for the representative uses and it was not found scientifically justified to average dissipation rates from aerobic and anaerobic experiments

Due to the data gaps identified on the derivation of various key modelling input parameters and to the fact that FOCUS SW modelling does not consider volatilization-deposition route of entry in surface water, the available PEC_{SW} were not considered appropriate for the EU risk assessment. The meeting of experts identified a data gap for worst case PEC_{SW} estimations of MITC taking into consideration short range transport and deposition to surface water bodies and potential exposure via drainage with adequate input parameters.

The meeting of experts identified the need to recalculate MITC PEC_{GW} values with adequate input parameters (when available) using FOCUS GW or higher tier approach if appropriate.

After the meeting of experts, a new data gap has been identified by EFSA to address the potential ground water contamination of impurity DMTU.

The meeting of experts identified a data gap to address the atmospheric fate and behaviour of MITC including global warming (ozone depletion), long range transport and deposition, and to address the potential contamination of surface water and soil by deposition in the vicinity of the applied areas.

The notifier and the RMS proposed in the DAR that due to the method of application of metam-sodium, the risk to birds and mammals was considered acceptable for the intended field uses. Member States experts suggested that the most probable contaminated food items for birds and mammals would be the soil invertebrates (including earthworms). The experts in the PRAPeR 53 agreed that the notifier should provide an acute risk assessment to assess the effects of metam-sodium and its metabolite MITC to terrestrial vertebrates feeding on soil invertebrates. The acute risk assessment should also be provided for the metabolite MITC using the lowest endpoint available of 100 mg a.s./kg bw, which was agreed during the meeting. Metam-sodium and its relevant metabolite MITC were very toxic to aquatic organisms based on the available data. Due to the rapid degradation of metam-sodium in soil, surface water contamination with the parent molecule could be excluded. Aquatic organisms may be exposed to the metabolite MITC as result of the drainage and run-off. The experts in the Fate and Behaviour meeting agreed that the PECsw for the MITC should be re-estimated by the notifier. As a consequence the aquatic risk assessment should be revisited, once the new PECsw could be available. An extended laboratory study was conducted with *Aloechara bilineata* and this aged residue study demonstrated that *A. bilineata* was able to recolonise the field after 55 days. From an extended laboratory study it was only possible to assess the potential for re-colonisation, but not the actual recovery. Therefore, the experts agreed that further refinement was required to address the recovery potential of the non-target arthropods and soil non-target macro-organisms.

An earthworm field study was conducted with the metam-sodium. The experts agreed that after the application of the 608.4 kg a.s./ha, there was no clear indication of full recovery after one year. A further refinement was required from the notifier to address concerns on recovery/recolonisation of earthworms this should be include considerations on effects on recovery of different ecological groups as well as known data on migration distances.

The risk of metam and its metabolite MITC to other soil macro-organisms should be addressed. The risk of metam and its metabolite MITC to bees, soil micro-organisms, non-target plants and biological method of sewage treatment was assessed as low from out-doors uses.

The risk of metam and its metabolite MITC to terrestrial vertebrates, aquatic organisms, bees and non-target arthropods was assessed to be low in greenhouse uses.

Key words: metam, metam-sodium, metam potassium, peer review, risk assessment, pesticide, nematicide, fungicide, herbicide and insecticide

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BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000 as amended by Commission Regulation (EC) No 1095/2007, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Metam is one of the 84 substances of the third stage, part B, covered by the Regulation (EC) No 1490/2002 designating Belgium as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Belgium submitted the report of its initial evaluation of the dossier on metam, hereafter referred to as the draft assessment report, received by EFSA on 10 Seotember 2007. Following an administrative evaluation, the draft assessment report was distributed for consultation in accordance with Article 11(2) of the Regulation (EC) No 1490/2002 amended by the Regulation (EC) 1095/2007 on 3 December 2007 to the Member States and on 4 October 2007 to the main notifier Taminco as identified by the rapporteur Member State. The present DAR is only based on the Taminco dossier. The European Metam Sodium Task Force that is composed of the companies FMC Foret and Lainco has submitted a dossier that has been considered incomplete.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, EFSA identified and agreed on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, a scientific discussion took place in expert meetings in June – July 2008. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in October 2008 leading to the conclusions as laid down in this report.

In accordance with Article 11c(1) of the amended Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (rev 1-1, 16-04-2008)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation,
- the evaluation table (rev. 2-1. 24-11-2008)

Given the importance of the draft assessment report including its addendum (compiled version of September 2008 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Metam is the ISO common name for N-methyldithiocarbamic acid (IUPAC). Due to the fact that metam sodium is a variant of metam and is used in the formulated product, it should be noted that the evaluated data belong to the variant metam-sodium, unless otherwise specified.

Metam is a MITC[4] generator and this is the moiety that has the biological activity, the compound dazomet is also a MITC generator.

MITC interferes at the level of enzymatic activity. It disturbs the absorption of oxygen during the process of cellular respiration by chelating enzymes having a metal radical. The efficacy on nematodes is probably due to the ability of MITC to deactivate the sulfuric groups of essential enzymes.

The representative formulated product for the evaluation was "Metam sodium 510 g/L" a soluble concentrate (SL), registered under different trade names in Europe.

The evaluated representative uses were as a nematicide, fungicide, herbicide and insecticide by soil fumigation prior to the planting of carrots, lamb's lettuce, cucumber, aubergine, pepper, potato, strawberry, tomatoes and grapes. Full details of the GAP can be found in the attached list of end points.

[4] MITC: methyl isothiocyanate

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The purity range of metam-sodium TK is 400 g/kg-442 g/kg. The calculated minimum purity on a dry weight basis is metam-sodium 983 g/kg. The FAO specification 20.1Na/13/S/15, published in AGP:CP/82 (1979) states the following "The metam-sodium content shall be declared (g/L at 20°C or % w/w). When the combined carbon disulphide is determined and expressed as metam-sodium the content obtained shall not differ from that declared by more than ± 5% of the declared content." The technical materials are in compliance with the FAO specification. The currently agreed specification is in the June 2008 Addendum to Vol. 4. The calculated technical specification on a dry weight basis is in the August 2008 Addendum to Vol 4. However, since the specifications for the Tominco source does not list the relevant impurity MITC it has to be considered provisional. A new specification will be required where MITC is listed with a maximum value.

The technical material contains MITC and DMTU[5] which have to be considered as relevant impurities. The maximum content in the technical material should not be higher than 23 g/kg DMTU on a dry weight basis. A maximum value for MITC can not be given as it is currently not included in the specifications for Taminco.

According to the equivalence assessment of the different technical materials it is concluded that the reference source is the Taminco metam-sodium. The Taminco metam-potassium was considered to be equivalent to the sodium salt on the basis of a Tier II equivalence assessment. During the peer review process it was considered that the sodium and potassium salts were proposed for a full assessment and data gaps were identified for the sodium salt and potassium salt. However, during the writing of the conclusion it was discovered that toxicology and ecotoxicology had only considered it for equivalence. As this is the case, this conclusion is only based on the sodium salt and only the equivalence of the potassium source is considered.

The Lainco source did not have a supported specification and therefore it will not be considered further. The FMC foret source is not equivalent at Tier I but ecotoxicology and mammalian toxicology considered them as equivalent in a Tier II assessment in accordance with Sanco/10597/2003 –rev. 8.1-1. However, the equivalence can only be considered as provisional as a new specification containing MITC is required for the reference source.

The content of metam-sodium in the representative formulation is 510 g/L (pure).

[5] DMTU: N,N'-dimethylthiourea

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of metam-sodium, metam potassium or the respective formulation. However, the following data gaps were identified:

- spectra for the relevant impurity DMTU, spectra are already available for the other relevant impurity MITC.
- Flash point of the metam-sodium TK.
- Storage stability data with analysis of the relevant impurities before and after storage.

The main data regarding the identity of metam-sodium and its physical and chemical properties are given in appendix 1. This appendix also contains some data on MITC that has been used in the risk assessment.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of metam in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.
Adequate methods are available to monitor MITC in plant commodities, soil, water and air. Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues. It should be noted however, that the residue definitions for food of plant origin and ground water are provisional.

Residues of MITC in products of plant origin are analysed by GC-MS with an LOQ of 0.01 mg/kg. Soil, water and air are analysed by GC-NPD. The LOQ's are 0.02 mg/kg soil, 0.1 µg/L water and 0.5 µg/m³ air. For confirmation a column of different polarity is used.

An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed (see 3.2)

As the breakdown product MITC is classified as very toxic methods have been supplied for body fluids and tissues. Blood, plasma and urine are analysed by LC-MS with confirmation by LC-MS/MS with a LOQ of 0.05 mg/L for the analyte (N-acetyl-S-[(methylamino)carbothioyl]cysteine. The method for tissues is GC-NPD and confirmation is by using a column of different polarity. The LOQ was 0.1 mg/kg for the analyte MITC.

2. Mammalian toxicology

Metam was discussed in the PRAPeR meeting of experts 54 (subgroup 1) held in Parma in July 2008.

The meeting discussed the identity of the a.s. under peer review, whether it was metam or variants metam sodium or metam potassium. It was noted that bridging data is available on metam sodium and metam potassium. The phys-chem opinion is that the active substance is metam. The meeting agreed the active moiety is metam; results in the endpoint list and in the conclusion will be expressed as metam sodium as the majority of studies have been performed with this variant. However a conversion factor of 1.2 from metam sodium to metam based on molar conversion was defined.

The toxicological profile of metam was discussed in relation to the toxicological role of MITC, which is a major metabolite of metam. Degradation of MITC into the metabolites carbon disulfide (CS_2) and carbonyl sulphide (COS) in the rat is only a minor metabolic pathway, while most is eliminated following conjugation. MITC has lower toxicological endpoints compared to parent. It was noted that metam is almost instantly hydrolysed to MITC, so it was discussed whether the interest should be focused on MITC instead of metam, although metam is heavily classified. For operators applying metam, the relevant assessment is for MITC. The meeting agreed that the operator, worker and bystander risk assessment should be performed for MITC.

Experts discussed the impurities, which were described in the DAR and were considered of relevance. It was agreed that none of the impurities were of toxicological concern at concentrations below 1 g/kg. Specifically, they agreed on the relevance of the impurity N,N'-dimethylthiourea (DMTU) as no data were available. This impurity was present at 1% in a lot of the tox batches used (the specification is 0.7%) thus not giving rise to any toxicological concerns. MITC was considered as relevant but extensively covered by toxicological studies where specific reference values have been established.

Beside the reference source, two additional sources (FMC and Lainco) were presented. From the comparison with the reference source, the experts did not expect a different toxicological profile. In particular, for FMC the equivalence check was performed based on tier 2, whereas for Lainco that was not possible.

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Oral absorption of metam is rapid and almost complete (85%) based on urinary and expired air excretion (50 and 35%, respectively). Metam is uniformly distributed with slight accumulation in the thyroid. The metabolism is extensive and rapid, suggesting a decomposition of metam into MITC, CO_2, and COS. MITC is further conjugated to glutathione and excreted in urine while CO_2 and COS are excreted via expired air. The other significant pathway for metam is the release of CS_2, which could be related to the acidic conditions existent in the stomach of the rat (pH=3.8-5) following oral ingestion. Excretion is almost complete within 24-48 h after administration, with minor portions excreted up to 168 h after dosing.

2.2. ACUTE TOXICITY

Metam

Metam sodium is harmful by oral ingestion and inhalation (R22 and R20 proposed).

In irritation tests, metam sodium was not irritant to eyes but was corrosive to skin, therefore R34 ("Causes burns") was proposed. Metam sodium is a skin sensitiser (R43 proposed).

MITC

MITC is toxic via ingestion (R25 proposed) and via inhalation (R23 proposed). It is harmful in contact with skin (R21 proposed). In skin irritation tests it was corrosive to skin (R34 proposed). It was also irritative to the respiratory system (R37 proposed). It is a skin sensitiser (R43 proposed).

2.3. SHORT TERM TOXICITY

Metam sodium

Rats and mice received metam sodium in drinking water for a 90-day period. Due to the instability of metam sodium in water, the doses of metam sodium actually received were recalculated assuming maximum degradation.

In rats, the olfactory epithelium in the posterior nasal passage was affected and Bowman's glands were prominent and/or vacuolated and disorganized. The NOAEL was set at 0.5 mg/kg bw/day.

In mice, mucosal hyperplasia and epithelial eosinophilia were apparent in the urinary bladder. Nasal cavity was not affected. An NOAEL at 0.8 mg/kg bw/day was proposed.

In a 90-day inhalation study in rats (5 days of exposure per week), the NOAEL was set at 6.5 mg/m³ (corresponding to 1.75 mg/kg bw/day) based on a mild degree of mucigenic epithelial hyperplasia as well as lymphocitic rhinitis in nasal passages, as well as pulmonary histiocytosis and gastric erosions of the stomach.

In dogs, metam sodium was given in capsules for 90 days and caused treatment-related hepatitis at 5 mg/kg bw/day onwards. During the meeting it was discussed whether the increase of Alanine Transaminase ALT (starting around 13th week) in one female in the 1 mg/kg bw/day dose group should be regarded as an outlier or as the LOAEL. The finding appeared to be dose related (effect also seen in the one year study). It was difficult to determine its significance, as in the 90-day study no changes on liver weights or histopathology data on the liver at 1 mg/kg bw/day were observed. Although only one dog was affected at 1 mg/kg bw/day, the number of animals treated was small. The majority of experts agreed it was a NOAEL. After 1-year, hepatotoxicity was more evident in female dogs as suggested by increased ALT and some liver histopathological findings. The relevant NOAEL was agreed at 0.1 mg/kg bw/day based on histopathological liver findings.

During the meeting, the RMS proposal of R48/22 ("Danger of serious damage to health by prolonged exposure if swallowed") for the occurrence of severe hepatotoxicity in dogs at 10 mg/kg bw/day in the 90 day study was discussed. It was noted that at the top-dose of 10 mg/kg bw/day, 2/8 animals were terminated because of severe hepatic dysfunction (liver enzymes, hepatitis). Hepatitis with histopathological sings was observed in 5/8 and 8/8 animals at 5 and 10 mg/kg bw/day respectively. Although the classification assessment criteria do not mention other species (e.g. dogs) but rats, it was considered that findings in other species may be taken into account if appropriate. Overall, agreement that R48/22, as proposed by the RMS, should be left in place.

Rabbits did not show systemic toxicity after dermal exposure for 21 days to metam sodium. The NOAEL for local effects was 31.25 mg/kg bw/day based on local skin reactions such as erythema, oedema and rhagades at higher doses.

MITC

A 4-week inhalation rat study was performed with MITC. At doses of 100 mg/m^3, lung weight was increased, and was associated with bronchopneumonia and epithelial proliferation in bronchi and bronchioles. At this dose level, proliferation in tracheal epithelial cells, inflammatory changes in the nasal cavity and atrophy of the olfactory epithelium, as well as focal metaplasia of squamous epithelial cells in the area of respiratory epithelium were reported. A NOAEL for systemic effects is proposed at 5 mg/m^3 (1.35 mg/kg bw/day) and agreed in the meeting. A local NOAEL was established at <1.35 mg/kg bw/day.

In a 90-day dog study by gavage with MITC, at dose levels of 0.4 mg/kg bw/day onwards, thymus involution and liver toxicity was suggested by periportal hepatocyte vacuolation and lipid deposition.

During the meeting the relevance of thymus involution and liver vacuolation at 0.4 mg/kg bw/day was discussed. Some experts considered effects at mid-dose level (0.4 mg/kg bw/day) were not marked, but could not be compared with findings from a one year dog study. The study showed inconsistency in findings. However the majority of effects were indicating treatment related effects, consistent at the highest dose tested. Therefore it was agreed the NOAEL is 0.4 mg/kg bw/day.

2.4. GENOTOXICITY

Metam

Metam-sodium was evaluated in a battery of *in vivo* and *in vitro* tests.

Metam-sodium revealed a slight clastogenic activity in the presence and absence of metabolic activation in a first chromosome aberration test, and only in the presence of metabolic activation system in a second test, both performed in human lymphocytes. Increases in structural chromosomal aberrations were observed at cytotoxic concentrations, impairing chromosomal morphology, and thus preventing metaphases from accurate analysis for structural chromosomal aberrations.

In the *in vitro* UDS assay metam-sodium did not induce unscheduled DNA synthesis even at concentration being cytotoxic. Metam-sodium did not induce micronuclei in bone marrow polychromatic erythrocytes in CD-1 mice. In the *in vivo* chromosome aberration test performed in Chinese hamsters, Metam-sodium was not clastogenic.
The genotoxicity testing and potential of metam was discussed at the meeting. Equivocal effects were recorded in the HPRT test, but dose-response was not clear. In two chromosomal aberration tests rather weak findings were observed. Two *in vivo* studies showed negative results. However, in hamster bone marrow cells, there was a slightly increased incidence of polyploid cells, but likely due to cytoxicity/systemic toxicity. RMS overall considered that the compound was devoid of genotoxic potential. The meeting agreed with this conclusion.

MITC
MITC was not mutagenic in *Salmonella thyphimurium* strains TA98, TA100, TA1535, and TA1537 in the presence and absence of metabolic activation. MITC has no chromosomal damaging effects in an *in vitro* test using human lymphocytes. MITC was further negative in recombination assays in *Bacillus subtilis* strains H17 and M45 with and without metabolic activation.
In the *in vivo* mouse micronucleus test, MITC did not increase the number of micronucleated polychromatic erythrocytes. The conclusion that MITC was not genotoxic, was supported by studies from open literature.

2.5. LONG TERM TOXICITY

Metam
Metam sodium was administered to rats in drinking water for 2 years. Rats showed reduced bodyweight gain, specific lesion within the nasal passages, and changes in some haematology parameters and spleen (haemosiderin depots) and a slight increase in the severity but not of incidence of degenerative myopathy of the voluntary muscle. The incidence of haemangiosarcoma in males in the mesenteric lymph nodes was slightly higher than the control at the intermediate dose of 0.056 mg/ml but this effect was not observed at top dose. In view of the overall results obtained in this carcinogenicity study, it was concluded that metam sodium is not carcinogenic in rats. An NOAEL was established at 1.5 mg/kg bw/day.

Mice received metam sodium in their drinking water for 24 months. The relevant NOAEL of the 2 year drinking study in mice was discussed in the meeting. There was a treatment-related increased incidence of angiosarcomas, in the spleen in the males and the females at the mid- and the top-dose (combined incidence 5/3/11/19). However, it was noted there was no clear dose-dependency in other organs such as the liver (0/6/3/7 on a total of 55 male animals). Overall, tumour incidence was increased only at the highest tested dose. However, as the overall incidence was 7/12/12/27 in the males (4/2/6/10 in the females), the carcinogenicity NOAEL at the *lowest* dose was questioned. The control group incidence was well within the range of historical control data (5-18%), while the incidence in the treated groups (22-51%) exceeded this range. RMS considered that the incidence was not exceeded in the spleen at the lowest dose, but the picture is confused by a inconsistently increased tumour incidence seen in other organs, including the liver, at the lowest dose tested, however with a lack of dose-responsiveness. Whereas it was agreed that the tumours are treatment-related, it was thought initially that a NOAEL could not be set, although the dose response was not clear. The mechanism of action for the angiosarcoma tumours remained unexplained. No information was available on the historical background range of incidences in particular organs (only the total incidence at any site available). It was reported that the US Environmental Protection Agency (US EPA) agreed on a NOAEL =0.019 mg/kg bw/day, based on systemic effects (bodyweight changes). However, the EPA report further highlighted that a statistical increase was observed in the males at the two top-doses in the decedents (12/14/*32/***49%), and at the top-dose in the terminally sacrificed animals (14/35/11/*50%), further indicating the lack of meaningful effects at the lowest dose. Later in the meeting, the RMS asked to reopen the discussion regarding the angiosarcoma incidence (liver and global), and the experts agreed that the lowest dose used was a NOAEL rather than a LOAEL, taking account that the findings in the liver showed no dose response. The experts agreed that a classification as Carc. Cat 3 (R40, "Limited evidence of carcinogenic effect") was justified, based on the effects seen in the spleen only.

MITC

Rats received MITC via drinking water at 2, 10 or 50 ppm over 104 weeks. White blood cell parameters, histopathological findings such as bone marrow hyperplasia, increased kidney microcalculi, liver effects, and spleen hyperplasia/increased haematopoiesis were reported at the highest dose (1.6 mg/kg bw/day) and could be related to MITC exposure.

MITC was not carcinogenic under these experimental conditions. A NOAEL=10 ppm (0.44 mg/kg bw/day) was proposed. MSs discussed the use of proposed MITC intake in the 2 year rat study with MITC. The derivation of doses tested was discussed due to the fact that MITC is not stable in aqueous solution, with different degradation rates at different doses tested. It was noted this is a problem for all studies as MITC is a volatile compound, not just for the 2 year rat study. The RMS calculated the ingested doses using a correction factor of 87.7%, obtained using the analytical measurements of the 10 ppm dose group, in the drinking water bottles used during the greatest part of the study. The correction factor for this was considered acceptable.

An NOAEL was set at 20 ppm (3.3 mg/kg bw/day) taking into account the different slight effects seen at 80 ppm (12 mg/kg bw/day), such as the increased incidence of clinical signs, slight decreased body weight and body weight gain, slight effects in blood and altered organ weights. MITC is not carcinogenic in mice.

2.6. REPRODUCTIVE TOXICITY

Metam

In rats, metam sodium was tested in a multigenerational drinking water study. At the top dose, body weight and food consumption were reduced. In females, minimal to marked Bowman's gland duct hypertrophy with loss of alveolar cells was detected in the olfactory mucosa lining the nasal septum and turbinate bones at all levels of the nasal cavity, together with degeneration/ disorganization/atrophy of the olfactory epithelium. The percentage of pups live born was in excess of 94% for each group in both generations. There were no litter losses. There was a reduction in individual pup weight and in total litter weight and a reduction of pup weight gain at top dose in both generations. One female pup of top dose had no ocular tissues. Bilateral anophthalmia occurred spontaneously in the strain used and considered to be of no toxicological significance.

Developmental studies were performed in rats by gavage at doses ranging from 5 to 120 mg/kg bw/day. Maternal toxicity started at 10 mg/kg bw/day (reduced body weight gain). Reproduction parameters were not affected. At 40 mg/kg, bw/day there was also some evidence for foetotoxicity. Foetotoxicity was evident at 80 mg/kg bw/day with a reduced mean foetal weight. A significantly increased post-implantation loss was reported at 120 mg/kg bw/day. At 120 mg/kg bw/day, the number of live foetuses was reduced and means foetal weight was significantly lower. Major defects were reported at 120 mg/kg bw/day, two fetuses/1 litter exhibited a meningocele (neural tube closure defect) and another foetus had bilateral microphthalmia. At 80 mg/kg bw/day, one foetus had a meningocele. At 60 mg/kg bw/day 5 fetuses/5 litters were affected: defects of eyes (3 foetuses with other head defects); 1 fetus had a shortened jaw and cleft lip, 1 had meningocele, 1 foetus had unossified 2nd, 3rd and 4th arches of the cervical vertebrae, and one foetus displayed an abnormal zygomatic arch. None of which has been seen historically in controls in the laboratory. At 20 mg/kg, one foetus had four major defects, including a shortened lower jaw, which has not been seen in historical data. At 5 mg/kg bw/day, two fetuses in the 5 mg/kg group had abnormal zygomatic arch. Whilst this defect was not seen at 20 mg/kg, a single incidence was seen at 60 mg/kg.

During the meeting the relevant NOAEL of the developmental toxicity study in rat with metam (Tinston 1993) was discussed. RMS considered that some effects were dose dependent. 5 mg/kg bw/day was proposed as NOAEL for maternal findings. For foetal findings, there were clear treatment related effects for major malformations. The proposal from the RMS of 5 mg/kg bw/day for the developmental NOAEL was agreed, for both maternal and developmental toxicity.

In rabbits, body weight gain of dams at 100 mg/kg bw/day was decreased on most days of treatment. At 60 mg/kg bw/day, dams lost considerable weight after starting of dosing and food consumption was reduced. Similar but less marked changes were seen in the 20 mg/kg bw/day group.

At 100 mg/kg bw/day, the number of dead implants was increased, especially due to the high number of early resorptions. Increased post implantation loss was seen at 100 and 60 mg/kg bw/day, and reduced number of live foetuses/pregnant female was seen at 30, 60 and 100 mg/kg bw/day. At 60 mg/kg bw/day, foetal weight was decreased. Percentage of male foetuses was reduced and litters containing five or less foetuses did not included males. Two fetuses in two litters of 100 mg/kg bw/day showed a meningocele or spina bifida. These are rare anomalies in the strain of rabbits used in this study. There was a slight dose-related increase in sternebra asymmetry. Foetuses showed retarded ossification in head but also in limbs, thoracic vertebrae, sternum, and these effects were seen at doses with maternal toxicity.

The proposed classification as Repr. Cat.3 (R63 "Possible risk of harm to the unborn child") was discussed.

The malformations occurred at low incidences (sometimes in singularity), but in a consistent manner, at the top-doses, in the presence of quite severe maternal toxicity. In certain studies, single rare malformations were also present at lower doses, however in these cases, no dose-dependency was demonstrated. Concerns were expressed during the meeting whether Cat. 2 (R61?) may be justified as effects were clearly treatment related. However, they were associated with maternal toxicity, which would lead to Cat. 3 classification. Overall, it was agreed the European Chemical Agency would reflect further on this.

MITC

In a 2 generation rat drinking water study, variations in weight gain were observed in both sexes at top dose which occasionally attained statistical significance. Gestation and lactation weight were not altered. Mating performance and fertility were not adversely affected. The number of pups born/female was marginally decreased at 10 and 50 ppm without reaching statistical significance. Physical and functional development of pups was comparable amongst all groups. Slight delays in the onset of eye opening and pinna unfolding were observed at top dose but were considered incidental to treatment, as there were no delays in the completion of each parameter. Functional development of top dose pups was comparable to controls on days 1, 17 and 21.

In a developmental rat study, MITC was given by gavage at 0, 3, 10 or 30 mg/kg bw/day. At the end of the treatment, several dams at top dose had sticky and/or moist fur in the area of the snout before, and at the same location reddish but mainly dry fur. Body weight and body weight gain were significantly reduced at top dose and marginally at intermediate dose. Water consumption was increased in individual dams at 10 and 30 mg/kg bw/day. Reproduction data were no significantly affected in the groups. The number of foetuses weighing <75% of the mean foetal weight/litter was increased, and placenta weight was significantly lowered at top dose. Sex distribution was comparable in the different test groups. One anomaly (anophthalmia) was detected in one foetus/one litter at 10 mg/kg bw/day. No retardations were seen in any group. There were no statistically significant differences between the treated groups and the controls with regard to anomalies, variations and /or retardations.

In rabbits, MITC was given by gavage at 1, 3 or 10 mg/kg bw/day. No test article related signs or symptoms were observed in any female of the different groups. At top dose, a slightly higher reduction of mean body weight was considered to be compound-related. Food consumption was reduced at top dose from day 6-11. No effects were seen on the mean number of implantations, pups or embryonic deaths. Body weights of foetuses were not affected. Sex ratio was similar in all groups. Investigations of the crania and body cavity and skeletal of the foetuses did not show compound-related effects.

2.7. NEUROTOXICITY

An acute neurotoxicity study was performed with metam sodium administered to rats. The NOAEL for systemic toxicity was <50 mg/kg bw/day and no neurotoxicity was seen in this study (NOAEL acute neurotoxicity >1500 mg/kg bw/day). In a repeat dose study, where metam sodium was administered in drinking water at doses up to 15-18 mg/kg bw/day, there were no signs of neurotoxicity.

2.8. FURTHER STUDIES

The toxicity of MITC was investigated by the company and a full dossier is included and reported in parallel to metam sodium.

During the meeting it was noted that according to guidance on relevance of metabolites in groundwater, if the parent was classified as Cat. 3, the metabolites should be considered relevant. DMTU may occur in groundwater above 0.1 µg/L; however DMTU is an impurity, not a rat metabolite and no further studies are available. Its toxicity was considered equivalent to the toxicity of the parent compound based on chemical structure, based on the lack of data on DMTU and considering the toxicological properties of the parent compound. Since metam sodium was tested with batches containing 1% of DMTU, it was considered that all toxicity endpoints and related classifications sufficiently covered the toxicity of this impurity. It was noted that, as metam is applied at a rate of 612 kg/ha, this would result in approximately 4 kg/ha of DMTU.

2.9. MEDICAL DATA

No medical surveillance data for manufacturing plant personnel was found for metam sodium.

After an accidental spillage in California in 1991, over 700 persons in the area sought medical attention for symptoms ranging from nausea and dizziness to irritation of the eyes and upper respiratory tract. A number of persons reported exacerbation or induction of asthma following exposure. The follow up of the involved people during the first month post-spill included headache (64%), nausea (46%), eye irritation/blurring (40%), dizziness (30%), shortness of breath (27%) and diarrhoea (25%). Complaints of depression, disorientation, drowsiness, dry mouth, earache, fatigue, fever, hot flashes, irritability, memory reduction, nosebleed, numbness, pain in the arms or legs, tinnitus (ringing in the ear) and sweating were also reported at medical centers. Sixty-one percent of the spill residents showed clinical abnormalities. Significantly higher blood pressure and less fluctuation of salivary cortisol levels were found. More neurological, memory and concentration, anxiety, depression, sleep disorders, headaches, visual, olfactory, dermatological, gastro-intestinal and cardiac symptoms were reported than the controls.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

Reference values of metam sodium and MITC were agreed on in the meeting.

<u>ADI</u>

Metam

The ADI proposed by the RMS in the DAR was 0.001, based on 1 year dog study with SF 100. It was considered that the Margin of Safety (MOS) of 7200× to the long-term mouse study LOAEL (tumourigenic effects at 7.2 mg/kg bw/d and above) was sufficiently high. The meeting therefore agreed that the ADI was acceptable.

MITC

ADI proposed by the RMS was 0.0004 mg/kg bw/day based on 90 day dog study, with SF 100. The NOAEL agreed for 90 day dog study in the expert meeting is now 0.4 mg/kg bw/day, it was agreed to establish the ADI at 0.004 mg/kg bw/day applying a SF of 100.

<u>AOEL</u>

Metam

The AOEL originally proposed was 0.005 mg/kg bw/day, based on the 90-day rat drinking water study, with an SF of 100. It was agreed that the AOEL should be based on the one-year dog capsule feeding study at the same value as the ADI (0.001 mg/kg bw/day).

MITC

The RMS proposed an AOEL of 0.0135 mg/kg bw for MITC, based on a rat 4 wk inhalation study. It was noted that the overall database for MITC was on oral studies, but inhalation was the critical route of exposure. However, as the inhalation study was somewhat limited in duration (only 4 wk study), it was therefore considered whether to use a NOAEL from the 90 day oral dog study, as this was a more adequate duration for operator exposure assessment. Also, the AOEL is normally based on oral exposure studies, and. the dog was also a more sensitive species. However, the RMS stressed that the 4 wk study on MITC was also supported by the 90 day inhalation study using metam (where the NOAEL of metam, applying a molar conversion factor, would indicate a NOAEL for MITC of about 1 mg/kg bw/day, in line with the NOAEL in the 4 wk MITC study).

On balance the experts agreed the 90 day dog study on MITC should be used to set the AOEL, as it was considered that a 4-week would not be sufficient to cover the application window (especially if the a.s. was applied by contractors). This study was also used for the ADI. The AOEL agreed was 0.004 mg/kg bw/day for MITC.

ARfD

Metam

ARfD proposed was based on developmental study in rat with SF 100: 0.05 mg/kg bw/day. The meeting considered whether a SF of 100 was sufficiently high. The meeting agreed the ARfD is 0.1 mg/kg bw/day based on overall rat developmental study and supported by rabbit developmental study.

MITC

The meeting agreed an ARfD of 0.03 mg/kg bw/day based on NOAEL for rat maternal toxicity with SF 100.

2.11. Dermal absorption

The new data provided by the RMS were discussed during the meeting. About 1% dermal absorption for the concentrate was shown. There was discussion whether a value should be used for dilution (12% is available for this). Overall the experts agreed 1% for the concentrate, and 12% for the dilution. The studies were performed with the representative formulation METAM 510 g/L SL.

2.12. Exposure to operators, workers and bystanders

METAM 510 g/L SL is an aqueous solution containing about 510 g/L a.s. and is equivalent to the technical active substance as manufactured. Metam-sodium is a soil fumigant used to prepare soils for planting as well as drip irrigation in greenhouses.

Application of Metam-sodium is carried out by a soil-injection technique using tractor-mounted equipment as well as by drip irrigation in greenhouses. For the application by soil injection automated direct transfer systems is used for the mixing/loading procedure. When metam sodium comes into contact with soil, it decomposes into gaseous MITC within a few hours, which is in fact the active ingredient

Operator exposure

Metam

Only the UK POEM and the German model are available for the estimation of operator exposure towards metam sodium during the preparation of equipment (mixing/loading) for drip irrigation and for soil injection application. However, the models are not suitable as Metam is used as it is, and is not subject to M/L steps. Further the technical a.s. is not sprayed but the liquid applied by mechanised soil incorporation or drip irrigation.

MITC – greenhouse
In greenhouse, MITC air concentration just after application of metam sodium reaches 65 mg/m^3 making operator exposure above the AOEL. In these conditions, wearing of a mask reduces exposure but not sufficiently to reduce exposure below the AOEL.
The field study using soil incorporation was discussed during the meeting. It was noted that the study was only on a small scale, and commercially a greater area would be treated. Also the working rate was only 2 hrs. The RMS reported that due to the technique used in the study, exposure was above the original AOEL. There was agreement not to use this study due to these limitations. No safe use for glasshouse application was demonstrated (there is no information on drip irrigation available), therefore a data gap was identified.

MITC – soil injection
During the PRAPeR meeting the field studies summarized in the DAR were discussed. Some of them showed some outliers with regard to the AOEL, but the RMS assessed the risk considering the average exposure values (which indicated exposure below the original AOEL). It was agreed that the outliers in the studies (i.e. measurements exceeding the AOEL) should be considered as they reflect actual conditions of use. It was also agreed that the RMS should re-calculate the exposure estimates based on the field studies worst case values (and not the average), using the revised AOEL.
The exposure to MITC was shown to be above the AOEL for the operator, in the absence of RPE. In the presence of RPE, the measured exposure was about 9% of the AOEL.

<u>Worker exposure:</u>

MITC – soil injection
Under field conditions, for a 7 hour working day, worker re-entry exposure calculations based on measurements of MITC concentrations in air are below the AOEL proposed by the RMS. Concentrations of MITC outside the greenhouse reached sometimes 168% of the AOEL 1 day after application.
The exposure of the worker to MITC, on d14 following application of Metam did not give rise to concern in open field. According to revised input parameters exposure to MITC is demonstrated at around 30% (using the new AOEL, 7 hrs exposure and 70 kg bw). It was agreed that a safe worker exposure was demonstrated for field application.

MITC – greenhouse
It was agreed not to discuss glasshouse application, as no safe use has been demonstrated.

<u>Bystander exposure:</u>

MITC – soil injection

Inhalation exposure of bystanders might occur for MITC, the volatile degradation product of Metam-sodium. The company provided studies where MITC concentrations in air were measured directly during and after application of Metam-sodium. Based on these studies, it can be estimated that bystander exposure for 1 hour to MITC during or after application of metam sodium is below the AOEL proposed by the RMS.
Taking into the rapid degradation of Metam-sodium, and the particular way of application in the soil (soil injection or drip irrigation), the issue of bystander exposure to Metam itself was considered irrelevant.
As for MITC, the exposure of a bystander, staying 1h in the neighbourhood of a freshly fumigated field was estimated to be below the AOEL, amounting to 19% of the AOEL in the worst case.

MITC – greenhouse
It was agreed not to discuss glasshouse application, as no safe use has been demonstrated.

3. Residues

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

Metabolism studies were conducted using N-methyl-^{14}C-(Thiocarbonyl)-Metam. The metabolism of Metam has been investigated in various crops (radishes, Chinese cabbage, tomatoes and turnips).
These studies were representative of the following categories of crops: root and tuber vegetables, leafy and fruiting vegetables and therefore can be considered to cover the supported uses on carrots, corn salad, cucumber, eggplant, pepper, potato, strawberry, tomato and grapes by soil injection or drip-irrigation of Metam on the planting row.

In radish roots and leaves, neither the parent compound nor its soil metabolite MITC (which is the biologically active compound) and the methylthiourea/ureas derivates were detected in the different extracts. The TLC analysis of the organic extracts revealed broad zones of radioactivity spreading over the plates.
All the characterized compounds had a rather high polarity as concluded from their extractability into the aqueous soluble partitioned fractions and considering their chromatographic behaviour.

In Chinese cabbage leaves, partitioning of the extracted fractions revealed that the radioactivity was recovered mainly in the aqueous soluble phase.
The radioactive residues in Chinese cabbage leaves were found to have a highly polar character based on the extractability design and its behaviour on the TLC plates.
Neither the parent compound nor its metabolites MITC or the methylureas/methylthioureas could be identified in the different extracts.

Ultrafiltration performed on the aqueous soluble fraction demonstrated that this fraction was related to very small molecules.

In tomatoes, the highly polar character of the radioactive residues in the extracted fractions was confirmed by their chromatographic behaviour.
Neither parent compound nor its metabolite MITC was present in detectable amounts.
No other metabolite could be detected since TLC analysis of the extracts demonstrated that sufficient isolation of the different fractions was impossible. In most cases, the radioactivity was spread widely over the plates.
As shown by ultrafiltration, a non negligible amount of radioactivity exhibited a molecular weight less than 500 but further characterization was not possible as these polar radioactive residues could not be cleaved by enzymatic incubation (proteinase, β -glucosidase).

In turnip roots, TLC analysis of the hydrolysates extracts indicated a significant digestion of polar oligomers (radioactivity retained at the origin) and an increase in sugar and carbohydrate residues in the aqueous soluble fractions.
No Metam or its primary metabolite, MITC was found in either turnip root or top matrices.
No degradation of the parent compound into its substituted thioureas or methylated –ureas was observed.
The sequential hydrolysis of the post extraction solids with enzymes selective for cellulose, starch, protein and pectin and finally lignin extraction showed the distribution of the radioactivity over a variety of natural products such as cellulose, hemicellulose, starch, proteins, pectin and lignin.
The radioactive residues of Metam were mainly characterized as natural products and the identification of glucose in the extractable residues suggested a complete incorporation of this compound into the carbon pool of the turnip crop.

The meeting of experts discussed the fact that all the studies except turnip were underdosed. And it was considered that if they had been dosed at the correct level maybe some metabolites could have been identified.

The meeting concluded that as long as environmental fate and behaviour confirm that there are no other significant metabolites in soil then the plant metabolism studies could be accepted. After the meeting this issue was raised with an EFSA environmental fate and behaviour expert but it was not possible to conclude on this as there are data gaps in the environmental section. Therefore a data gap for further metabolism data must be set. A provisional residue definition of MITC for risk assessment and monitoring was set because of its high toxicity.

Usually the impurities in the technical material are not of a concern for residues. However, as the application rate is so high they will be applied in kg/ha rates and could therefore be present in crops at harvest. The meeting of experts considered a case from the notifier and concluded that for one of the impurities this was not an issue. For the two organic impurities the meeting of experts rejected the case and therefore the notifier has to explain further why these compounds are not relevant for consumer risk.

For the field trials the method of analysis was not validated, the reported LOQ was too high and they were all conducted in the USA so a data gap was identified. Given that MITC is volatile the residue trials should not be stored but should be analysed immediately. No processing data were available and because of the lack of residues data this may need further consideration

3.1.2. Succeeding and rotational crops

The need for rotational crops was not triggered as the DT90 in soil was less than 100 days. In the meeting of experts this was discussed further and it was considered that given the use pattern as a soil sterilent before the crop is planted that the primary plant metabolism would cover rotational crops. This may need to be reconsidered when the data gap for the primary crops are addressed.

3.2. Nature and magnitude of residues in livestock

The need for livestock metabolism studies and feeding studies was not triggered. However, this may need to be reconsidered when the data gaps in the primary crop area are addressed.

3.3. Consumer risk assessment

The consumer risk assessment can not be finalised as the residue trials were rejected and a data gap was identified. There is also the issue of the impurities which are applied at kg levels because of the high rate of application of metam.

3.4. Proposed MRLs

No MRLs can be proposed at this time as there is a data gap for residue trials.

4. Environmental fate and behaviour

Fate and behaviour of metam into the environment was discussed in the meeting of experts PRAPeR 52 (July 2008) on basis of the DAR (August 2007) and the addendum to B8 (June 2008).

4.1. Fate and behaviour in soil

4.1.1. Route of degradation in soil

The metabolism of metam in soil was investigated in a study that was found not acceptable by the RMS due to the lack of transparency of the study report with respect to the analytical procedures and the identification of metabolites.

Degradation of metam and its known active metabolite MITC in soil under dark aerobic conditions at 20 °C was investigated in a study with four soils (metam: pH 5.4 – 7.7; OM 1.87 – 6.97 %; clay 11.89 -33.68 %; MITC: pH 4.5 – 7.6; OM 1.53 – 12.41 %; clay 9.58 – 35.45 %) with the compounds ^{14}C labelled at the thiocarbonyl. No other metabolites were identified in these experiments. Radioactivity in the NaOH trap was assumed to be CO_2 and reached levels of 46 – 86 % AR after 21 d. Unextracted radioactivity in soil amounted up to 9.9-38.4 % AR after 21 d. Further details on methodological aspects of this study were provided by the RMS in the addendum (June 2008). The meeting of experts discussed this additional information related to the mode of application of the substances in the studies, the sampling and identification of volatiles, the analytical methods, the nature of the degradation and the kinetic analysis. Experts agreed that the analytical methods, the sampling scheme and the identification of volatiles in the study were appropriate or acceptable. It was also agreed that the degradation observed was probably of microbial origin, since no pH dependence was apparent. However, the experts in the meeting were not confident that these experiments provided a realistic representation of the fate and behaviour of metam and MITC in soil mainly due to the mode of application used in the study with respect to the application in field were volatilization is minimized by compacting soil or with plastic films.

A degradation study of metam in soil under dark anaerobic conditions is available in the dossier. RMS considered that the study was not acceptable. No further study has been required since anaerobic conditions are considered not relevant for the representative use proposed.

A photolysis study in soil was available in the dossier. The study was considered not acceptable by the RMS. No further study has been required to investigate photolysis in soil since for the representative use incorporation would prevent direct exposition of metam to light once applied.

Some studies that investigate the dissipation of metam under field conditions are available in the dossier. 1,3 dimethyl urea was found as a soil metabolite in these studies. However, the RMS did not consider the field studies relevant for the EU risk assessment since the application technique did not reflect the supported uses in EU. Furthermore, field studies were not triggered based on the laboratory data available in the dossier.

Taking into consideration the application rates of metam (306 – 612 kg/ha), during the peer review it was considered that impurities present in the technical material need to be addressed for the potential environmental and ground water contamination. For example, an impurity present at 1 % (w/w) in the technical material is applied to the field at levels of up to 6 Kg/ha. This rate of application is substantially higher than the rate at which most common pesticides are applied. Since the properties of the impurities may diverge considerably from those of the pure active substance, potential effect of impurities into the environment and contamination of ground water may not be precluded based solely on the assessment of the active ingredient. The notifier submitted an overview of the main impurities present in the technical material that was summarized by the RMS in the addendum (June 2008). Many of the impurities are also environmental transformation products of the parent and have been addressed as such. However, the impurity DMTU was considered to be a possible impurity of concern. The notifier claimed that the substance employed in ecotoxicological studies already contained this impurity. With respect to the potential ground water contamination the meeting decided to address a question to the toxicology experts meeting on the toxicological relevance of this impurity. The meeting agreed that in case the impurity was considered toxicological relevant, ground water assessment would be necessary. The meeting of experts in toxicology agreed that the impurity DMTU should be regarded as toxicological relevant and therefore a ground water exposure assessment is needed. Therefore, a data gap has been identified after the meeting of experts by EFSA to address the fate of DMTU in soil in order to obtain adequate input parameters for ground water modelling.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Rate of degradation of metam and its active metabolite in soil was investigated in the same study commented in the route section. In this study metam and MITC were very low and low persitent in soil respectively (metam DT_{50} = 9 – 17 min; MITC DT_{50} = 1.0 – 2.9 d). With respect the kinetic analysis the experts meeting agreed with the RMS that the use of linear regression of data (instead of non-linear) would not have a significant impact in the half lives calculated in this case. Even some deficiences were identified in some of the experiments, the derivation of kinetic parameters was considered acceptable. However, the meeting noted that a number of scientific studies investigating the persistence of metam and MITC are available in the public domain and to regulatory authorities (eg. dazomet DAR,[6] California evaluation on MITC[7] and the references there in). Some of this information has already been considered by regulatory authorities in EU Member States. The information available in the dazomet DAR was briefly discussed by the meeting of experts. In this dossier, a study is available were half life of MITC was between 5 to 13.6 d. Metam notifier claimed

[6] DAZOMET, Draft assessment report prepared by Belgium (April 2007)
[7] Evaluation of Methyl Isothiocyanate as a toxic air contaminant. California Department of Pesticide Regulation, California Environmental Protection Agency, August 2002.

that the difference on the half lives may be due to a slower formation of MITC from dazomet; however, the RMS confirmed after the meeting of experts that in the dazomet study the half life was derived by kinetic analysis and represents true degradation, not dependant on the rate of formation from the parent. Consequently, a data gap was identified by the meeting of experts to address the range of half lives available for metam and MITC and whether they are applicable to metam EU risk assessment. The notifier should address the different variables that might impact on the degradation in soil, such as method of application, dose rate and soil adaptation.

PEC soil for metam and MITC were calculated for the worst case use in field tomato (612 kg a.s. / ha) assuming 15 cm incorporation. Time dependent PEC soil need to be updated once the data gaps identified for persistence in soil are solved. Initial PECs in soil may be used for the EU risk assessment.

4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction products

Mobility of metam was investigated by the HPLC method. Metam sodium was eluted from the column more quickly than acetaniline (reference standard for the lowest literature value of K_{oc}). Therefore, metam may be considered to be very high mobile in soil (K_{oc} < 17.8 mL/g). Whereas the HPLC method is generally not considered to provide reliable values for the adsorption in soil, no further data has been required since the worst case is covered by the result obtained. Additionally, if the low half life in soil is confirmed, the relevance of metam mobility is low with respect to its metabolite MITC.

A batch adsorption / desorption study is available for MITC in four soils (pH 6.2 – 7.6; OC 0.69 – 2.56 %; clay 7.2 – 23.8 %). This compound exhibits very high mobility in these soils. Of the four experiments, three were considered not appropriate by the meeting of experts (only 3 – 4 % MITC found back on the soil) (K_{Foc} = 27 mL / g). The meeting of experts concluded that adsorption in this study may have been overestimated due to the fact that experimental Koc values are simultaneously affected by degradation and volatilization during the experiment. The experts in the meeting considered that the adsorption study was not conducted in an appropriate manner for a low adsorbing substance with regard to the soil water ration and the OC content of the soil types used. Therefore, the meeting of experts proposed a data gap for a new soil adsorption desorption study conducted with consideration of the volatility and the low adsorption properties of MITC (eg. with shorter equilibration times, soil solution ratios of 1:1, high organic carbon soils).

After the meeting of experts, a new data gap has been identified by EFSA to address the mobility of impurity DMTU in soil in order to obtain adequate input parameters for ground water modelling.

A lysimeter study is available in the dossier of dazomet and summarized in the dazomet DAR. The meeting of experts discussed if the results of this study with respect to MITC could be used to address potential ground contamination by this active metabolite coming from metam.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Hydrolysis of metam in buffered aqueous solutions (pH 5, 7 and 9) at 25 °C was investigated in one acceptable study. Hydrolysis is relatively fast at any pH being slightly faster at the more acidic ones (pH 5: DT_{50} = 1.9 d; pH 7 DT_{50} = 2.2 d; pH 9 DT_{50} = 4.5 d). Major hydrolysis metabolites identified were MITC (max. 60 % AR after 5 d at pH 7 and max 20 % AR at pH 5 and 9) and MCDT (16 % AR at pH 9 after 5.4 d, end of the study). Hydrolysis of MITC in buffered aqueous solutions (pH 4, 7 and 9) at 15 °C 25 °C and 50 °C was investigated in one study that was considered acceptable as supportive information. At 25 °C half lives for MITC were ≈ 40 d (pH 4), 50 d (pH 7) and 11 d (pH 9). Major hydrolysis products of MITC were DMU, DMTU and MDTA (metam). The fact that one of the major metabolites of MITC is metam indicates that metam and MITC may be interconverted under these conditions.

The aqueous photolysis of metam was investigated in a study at pH 7 under artificially simulated sunlight. Degradation of metam in this experiment is very fast (DT_{50} = 12 min; equivalent to 27.8 min at 38 °N). The major degradation products in these experiments were N-methylthioformamide (max. 22 % AR after 25 min), MCDT[8] (sodium methylcarbamo(dithioperoxo)thioate; max. 14 % AR after 25 min), MITC (max. 16 % AR after 25 min), methylamine (18 % AR after 25 min; already detected at time 0 at 14 % AR).

No readily biodegradation study is available and therefore the substance is considered to be non readily biodegradable.

Degradation / dissipation of metam (potassium salt) in aquatic environment were investigated in a water sediment system (pH_{water} 7.4; pH_{sed} 6.7; OC 4.3 %; clay 10 %) under dark aerobic and anaerobic conditions at 25 °C. In the aerobic experiment metam degrades rapidly in the whole system ($DT_{50whole\ system}$ = 0.32 h). During the peer review the notifier was requested to calculate formation fraction and whole system degradation rates for the active metabolite MITC and to provide an evaluation of the effect of the temperature on the results of these studies with respect to the volatilization of MITC. Temperature used in this study was in the higher part of the range allowed by OECD guidance (10 - 30 °C). The experts in the meeting considered that the range is set to allow testing the most relevant worst case conditions. In this case, a lower temperature would result on a more representative worst case due to the high volatilisation of MITC. Studies used for EU risk assessment are generally performed at 20 °C and the meeting did not find any reason that justifies the use of a higher temperature. The meeting agreed that the information provided by the notifier did not allow any quantitative estimation of the effect of temperature on the volatilization. Since in the dossier vapour pressure measurements at 15 and 25 °C are available, a more quantitative assessment should be possible. Consequently, the meeting of experts identified a data gap to address the effect of temperature on the dissipation of MITC from water by volatilization. Depending on the results of the volatilization assessment, a new water sediment study at lower temperature may be necessary. The

[8] MCTD: sodium methylcarbamo(dithioperoxo)thioate

data from the anaerobic water sediment study was considered not relevant for the representative uses and to average dissipation rates form aerobic and anaerobic experiments was not found scientifically justified.

During the peer review a clarification was required with respect to metabolite DMTD. This metabolite reaches 24 % AR after 2 h, 13 % AR after 4 h and is not detected after 8 h. Since the metabolite is produced directly form metam and not from MITC the meeting agreed that it does no need to be addressed if significant direct exposure of surface water to metam may be precluded from the representative uses.

Due to the data gaps identified on the derivation of various key modelling input parameters and to the fact that FOCUS SW modelling does not considers volatilization-deposition route of entry in surface water, the available PEC_{SW} were not considered appropriate for the EU risk assessment. The meeting of experts identified a data gap for worst case PEC_{SW} estimations of MITC taking into consideration short range transport and deposition to surface water bodies and potential exposure via drainage with adequate input parameters. The experts also agreed that the observed dissipation of MITC in these experiments is due to volatilization and not to degradation. Therefore, they agreed that a kinetic formation fraction and degradation rate cannot be properly calculated. The half life for MITC resulting from the kinetic analysis presented in the addendum (June 2008) was reclassified by the meeting of experts as a dissipation half life from water phase.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

According the FOCUS GW modelling presented by the notifier the limit of 0.1 µg / L may be exceeded by MITC for the 80^{th} percentile concentration at 1 m depth in some ground water scenarios (up to a maximum of 8.97 µg / L for carrots use in Hamburg). Since data gaps have been identified during the peer review for half life and adsorption / desorption properties in soil of MITC the available PEC_{GW} calculations were not considered reliable by the meeting of experts. The meeting also agreed that FOCUS GW was probably not completely satisfactory for volatile compounds such as MITC, but considered that it is the best available tool at the moment.

The meeting of experts identified the need to recalculate MITC PEC GW with adequate input parameters (when available) using FOCUS GW or higher tier approach if appropriate.

After the meeting of experts, a new data gap has been identified by EFSA to address the potential ground water contamination of impurity DMTU.

4.3. FATE AND BEHAVIOUR IN AIR

MITC is a very volatile compound. Half life of MITC in the troposphere due to photochemical degradation was estimated to be 78.6 d by Atkinson calculation. Potential long range transport cannot be therefore precluded from available information. The meeting of experts identified a data gap to address the atmospheric fate and behaviour of MITC including global warming (ozone depletion), long range transport and deposition, and to address the potential contamination of surface water and soil by deposition in the vicinity of the applied areas.

5. Ecotoxicology

Metam-sodium was discussed at the PRAPeR experts' meeting for ecotoxicology (PRAPeR 53) in July 2008 on basis of the draft assessment report, the Addendum Vol 3 B.9 and subsequent Metam Revised Vol. 3 B .9.

The representative uses evaluated were the uses as a soil fumigant (nematicide, fungicide, herbicide, insecticide) in carrot (Field), corn salad (F), cucumber (Glasshouse), eggplant / aubergine (G), pepper (G), potato (F), strawberry (F) , tomato (F, G), grape (F) at the application rate of 153-612 kg a.s./ha (local application of 1020 kg a.s./ha in the case of grape).

Metam–sodium will rapidly degrade into Methylisothiocyanate (MITC), which is active on living organisms present in the soil and water.

DMTU (N,N'-dimethylthiourea) was an impurity applied together with the active ingredient at rates up to 1 – 7 kg / ha. DMTU was considered as a relevant impurity; however, ecotoxicological studies were not available in the original Draft Assessment Report. Therefore, a data gap was identified for submission of ecotoxicological information with the DMTU.

The risk assessment was conducted according to the following guidance documents: Risk Assessment for Birds and Mammals. SANCO/4145/2000 September 2002; Aquatic Ecotoxicology, SANCO/3268/2001 rev.4 final, October 2002; Terrestrial Ecotoxicology, SANCO/10329/2002 rev.2 final, October 2002; Risk Assessment for non-target arthropods, ESCORT 2, March 2000, SETAC.

"In view of the restrictions concerning the acceptance of new (i.e. newly submitted) studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007, the new studies could not be considered in the peer review".

5.1. Risk to terrestrial vertebrates

The acute and short-term endpoints for birds were obtained from *Colinus virginianus* and *Anas platyrhynchos* studies, respectively. The acute and short-term endpoints LC_{50}/LD_{50} for birds were 211 mg/kg bw and > 324 mg/kg bw/day, respectively. The lowest acute and long-term endpoints in mammals were observed in rat LD_{50} = 896 mg a.s./kg bw and NOAEL = 1.5 mg a.s./kg bw/day.

Application of metam–sodium was on bare soil; the product was incorporated into the soil (soil injection or drip irrigation) and thereafter, the soil was compressed with a roller to prevent evaporation. After a waiting period of two weeks, the soil would be cultivated. The notifier and the RMS proposed in the DAR that due to the method of application of metam-sodium, no contaminated food would be available for birds and mammals in the field (no contaminated crop or weeds, no contaminated earthworms or insects). RMS considers that the risk to birds was considered acceptable for the intended field uses. MS Experts at PRAPeR 53 discussed the risk assessment for the birds and mammals exposed to metam-sodium and to the main metabolite (MITC). Member States experts suggest that the most probable contaminated food items for birds and mammals would be the soil invertebrates (included earthworms). The experts agreed that even if the soil invertebrates were expected to be killed, birds and mammals may feed on them. Therefore, an acute risk assessment for insectivorous birds and mammals should be provided, A data gap was identified for the notifier to conduct an acute risk assessment to assess the effects of metam-sodium and its metabolite MITC to terrestrial vertebrates feeding on soil invertebrates.

Member States experts agreed that acute risk assessment was necessary for the metabolite MITC for mammals. The endpoint for MITC from dazomet DAR is lower than the endpoint used in the metam-sodium DAR. Member State experts agreed that lowest endpoint could be used in the risk assessment in accordance with previous assessment of active substance with common metabolite, unless scientific reasons suggest not to use it. Otherwise RMS should provided a risk assessment for the metabolite MITC using the lower endpoint of 100 mg / kg bw obtained from a mouse oral toxicity study in the dazomet DAR. Therefore, a new open point was identified during the PRAPeR 53 meeting, and the RMS was asked to check if the lowest endpoint could be used in the risk assessment with the metabolite MITC and to update the list of end points. The RMS did not provide the risk assessment with the lowest endpoint, therefore a new data gap was identified by EFSA after the PRAPeR 53 meeting for the submission of a new risk assessment to mammals based on the agreed endpoint of 100 mg/kg bw.

No risk assessment for secondary poisoning was triggered for the metam-sodium since the log $P_{OW} \leq - 2.91$.

Birds and mammals were not exposed to metam-sodium in the glasshouse uses, suggesting that risk to birds and mammals for the use of metam in glasshouse were low.

5.2. RISK TO AQUATIC ORGANISMS

Based on the available information metam-sodium was considered to be very toxic to aquatic organisms. The metabolite MITC was more toxic than metam-sodium. Application of metam-sodium is such that no drift exposure of the surface water was expected. The unique ways of exposure were through run-off and drainage and due to the rapid degradation of metam-sodium in soil (DT_{50} in soil between 4 and 17 minutes), surface water contamination with the parent molecule could be excluded. Aquatic organisms might be exposed to the metabolite MITC as result of the drainage and run-off. The lowest endpoints driving the aquatic risk assessment were obtained in studies with fish, daphnids and algae. The LC_{50}/EC_{50} for fish, *Daphnia*, higher acquatic plants and algae values were 0.0531, 0.076, 0.28 and 0.59 mg MITC/L, respectively. With regards to chronic toxicity fish was the most sensitive group. Results from the fish prolonged toxicity test with the metabolite MITC (Munk R., 1990) showed that at the three highest tests measured concentrations were <80 % of the nominal concentrations. Therefore, the experts in the PRAPeR 53 agreed that NOEC from this study should be

provided using the third highest concentration expressed in mean measured. The RMS presented the new NOEC = 0.004 mg MITC/L (mean measured concentrations) for *Oncorhynchus mykiss* in the Metam Revised Vol. 3 B.9 that was submitted in August 2008.
The RMS based the aquatic risk assessment on the estimation of the TER values for the metabolite MITC. The TERs values were calculated on basis of initial PECsw values from FOCUS step 3. The TERs showed that there were acceptable scenarios for carrot (2 out of 7 acceptable scenarios for fish and daphnids, 4 out of 7 acceptable scenarios for algae and 5 out of 7 acceptable scenarios for aquatic plants), for corn salad (7 out of 12 acceptable scenarios for fish and daphnids, 10 out of 12 acceptable scenarios for algae and 11 out of 12 acceptable scenarios for aquatic plants) and for tomatoes (1 out of 4 acceptable scenario for fish and daphnids, 2 out of 4 acceptable scenarios for algae and aquatic plants). However there were still some scenarios where the TERs were below the Annex VI trigger values.
The TER values were estimated, then, on basis of initial PECsw values from FOCUS sw Step 4, with a 20 m buffer zone. The TERs values were above the Annex VI trigger values for algae and aquatic plant for all evaluated uses. Furthermore, TERs values for fish and aquatic invertebrates were above the Annex VI trigger values in the following FOCUS scenarios for carrot (2 out of 5 scenarios for fish, 3 out of 5 scenarios for daphnids), for corn salad (5 out of 7 scenarios for fish and daphnids) and for tomatoes (1 out of 3 scenarios for fish and daphnids). However, there were some TERs values for some scenarios that were below the Annex VI trigger values, indicating a potential high risk of the MITC metabolite to fish and aquatic organism.
The experts in the Fate and Behaviour meeting agreed that the PECsw for the MITC evaluated uses could not be estimated with FOCUS SW, also that there was uncertainty with the soil DT_{50} value. The experts agreed that PECsw should be re-estimated by the notifier. As a consequence the aquatic risk assessment should be performed again, once the new PECsw would be available.
Experts at the PRAPeR 53 meeting agreed that due to the uncertainty from Fate section on the DT_{50} values in water, chronic exposure of the aquatic organisms should not be discarded. The experts also agreed on the use of the initial PECsw values in the TER estimation following the RMS proposal.
A new data gap was identified to the notifier to specify the initial PEC values and the reliability of a chronic exposure of the aquatic organisms. Once the PECsw would be available the risk assessment for aquatic organisms should be updated.

The greenhouse uses poses no concern for the surface water contamination. No bioconcentration study with fish is triggered since the log P_{ow} of metam is < 3.

5.3. RISK TO BEES

The application of metam- sodium was on bare soil; the product was incorporated into the soil (soil injection or drip irrigation) and thereafter the soil was compressed with a roller. After a waiting period of 2 weeks the soil would be cultivated. There was not direct application into plant material. Bees were not at risk in-field and off-field since no exposure to contaminated crops or weeds was expected. Consequently, the risk of metam-sodium and its metabolite MITC to bees was assessed as low.

The risk of metam-sodium to bees for the use in greenhouse was considered to be low, due to bees were not exposed in the greenhouse.

5.4. RISK TO OTHER ARTHROPOD SPECIES

The notifier proposed that due to the application method, there was no exposure to standard foliage dwelling arthropods, such *Typhlodromus pyri* and *Aphidius rhopalosiphi*. Therefore studies with standard foliage dwelling arthropods should not be required. Only the soil dwelling arthropods would be exposed to the metam fumigation. The notifier provided an extended laboratory study conducted with (soil dwelling) rove beetles (*Aloechara bilinaeta*). This aged residues study was performed with treated soil after 55 days of aging under field conditions. No biological relevant effects were observed for the reproduction (14.6%) at the application rate of 1 x 1200 L Sodium-metam/ha (608.4 kg a.s./ha). This aged residue study demonstrated that *A. bilienata* could recolonised the field after 55 days. The RMS proposed that the risk of metam-sodium and its metabolite MITC should be addressed in terms of recovery in the field. Extended laboratory study could be used to assess the potential for recolonisation, but not actual recovery. Therefore, the experts from the Member States agreed to propose a data gap for the notifier to provided a semi-field or field study to address the recovery potential of the non-target arthropods and soil non-target macro-organisms.

The risk of metam-sodium to non-target arthropods for the use in greenhouse was considered to be low, due to non-target arthropods were not exposed in the greenhouse.

5.5. RISK TO EARTHWORMS

An earthworm field study (Lurhs U. 2002) was conducted with two different concentrations 152.1 and 608.4 kg a.s./ha during one year. After this period the earthworm abundance and earthworm biomass were comparable to the agricultural controls. The abundance of juvenile earthworm was comparable to the agricultural control at the lowest test dose (152.1 kg a.s./ha); however, at the higher test treatment (608.4 kg a.s./ha) there was statistically significant difference with the agricultural controls. The experts agreed that after the application of the 608.4 kg a.s./ha, there was no clear indication of full recovery of earthworms after one year, therefore, some uncertainties of recovery in the field area still remained. A data gap was identified to the notifier to address concerns on the recovery/recolonisation of earthworms. This should include considerations on effects on recovery of different ecological groups as well as known data on migration distances.

EFSA noted while drafting the conclusion that there was some concern about the risk of metam-sodium to earthworm in the glasshouse uses. EFSA considers, for permanent glasshouse the risk was considered low but for temporary glasshouse tunnels that included natural soil (non-artificial substrate) member states might wish to ask for further data to clarify the risk to earthworms.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

As metam-sodium is used as soil fumigant, it was expected that metam-sodium would have effects on the entire soil flora and fauna including the Collembola populations. Therefore the risk of metam-sodium and its metabolite MITC should be addressed. An extended laboratory study was presented in the DAR (Meister A., 2002), however, the RMS did not consider this study to be valid.
Risk to metam and its metabolite should be addressed in terms of recovery in the field. RMS suggests that a semi-field or field study should demonstrate the recolonisation of the fields
The expert at the PRAPeR 53 agreed to propose a data gap for the notifier to provide a semi-field or field study to address the recovery potential of soil non-target macro-organisms.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No effects of >25 % on soil respiration and nitrification were observed in tests with metam-sodium up to concentration of 608.4 kg a.s./ha indicating a low risk to soil non-target micro-organisms for the representative uses evaluated.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

The application of metam –sodium was on bare soil; the product was incorporate into the soil and thereafter the soil was compressed with a roller. The mode of application excludes the off-field exposure by drift. In conclusion the risk of metam-sodium and its metabolite MITC to non-target terrestrial plants was expected to be low.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

Technical metam-sodium inhibit the respiration of activated sewage sludge at a concentration giving an EC_{50} (activate sludge, 3h) = 4.36 mg a.s./L. It is not expected that the concentrations of metam-sodium in biological sewage treatment plants would reach a concentration of more than 0.142 mg a.s./L if the product is applied according to the GAP and therefore the risk to biological methods of sewage treatment is considered to be low.

6. Residue definitions

Soil

Definition for risk assessment: metam-sodium, MITC, DMTU (impurity)

Definition for monitoring: MITC

Water

Ground water

Definition for exposure assessment: MITC, DMTU (impurity)

Definition for monitoring: MITC, DMTU (impurity) the inclusion of the impurity in the residue definition is provisional pending the finalization of the ground water exposure assessment.

Surface water

Definition for risk assessment: MITC

Definition for monitoring: MITC

Air

Definition for risk assessment: MITC

Definitions for monitoring: MITC

Food of plant origin

Definition for risk assessment: MITC[9]

Definition for monitoring: MITC (provisional)

Food of animal origin

Definition for risk assessment: Not currently required.

Definition for monitoring: Not currently required.

[9] MITC: methyl isothiocyanate

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
metam	very low persistent (DT_{50} = 9 – 17 min)	Further information was required to address the risk to earthworms and soil macro-organisms
MITC	data gap identified to consider available information in the public literature and to regulatory authorities	Further information was required to address the risk to earthworms and soil macro-organisms
DMTU (impurity applied together with the active ingredient at rates up to 4 – 6 Kg / ha)	data gap	data gap

Ground water

Compound (name and/or code)	**Mobility in soil**	**> 0.1 µg / L 1m depth for the representative uses** **(at least one FOCUS scenario or relevant lysimeter)**	**Pesticidal activity**	**Toxicological relevance**	**Ecotoxicological activity**
MITC	very high mobile data gap for a more appropriate study was identified	data gap	Yes	Yes	Very toxic to the aquatic organisms
DMTU (impurity applied together with the active ingredient at rates up to 4 – 6 Kg / ha)	data gap	data gap	Data gap	Data gap (agreed as relevant during PRAPeR 59 due to the lack of information)	Data gap

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
MITC	Data gap. New aquatic risk assessment will need to be submitted when the new PEC_{SW} become available.

Air

Compound (name and/or code)	Toxicology
MITC	Toxic via inhalation (R23 proposed)

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- Revised specification to include the relevant impurity MITC Taminco (relevant for all uses evaluated, data gap identified by EFSA August 2008, proposed submission date unknown, refer to chapter 1).
- Spectra for the relevant impurity DMTU (relevant for all uses evaluated, data gap identified by EFSA August 2008, proposed submission date unknown, refer to chapter 1).
- Flash point for metam-sodium TK (relevant for all uses evaluated, data gap identified by meeting of experts June 2008, proposed submission date unknown, refer to chapter 1).
- Storage stability data with analysis of the relevant impurities before and after storage (relevant for all uses evaluated, data gap identified by EFSA August 2008, proposed submission date unknown, refer to chapter 1).
- Information on operator, worker and bystander exposure during drip irrigation application in greenhouse is missing (relevant for greenhouse uses, data gap identified at the meeting of experts residues July 2008, proposed submission date unknown, refer to chapter 2.12)
- Further metabolism studies in plants. However, the need for these studies is dependant on the outcome of the data gaps identified for fate and behaviour. Should the fate studies confirm that there are no other significant metabolites in soil then further plant metabolism studies would not be required. (relevant for all uses evaluated, data gap identified at the meeting of experts residues July 2008, proposed submission date unknown, refer to chapter 3).
- The 2 significant organic impurities in the technical material should be addressed with regard to consumer exposure given the hi rate of application (relevant for all uses evaluated, data gap identified at the meeting of experts residues July 2008, proposed submission date unknown, refer to chapter 3).
- Sufficient residue trials according to GAP to support the non-residue situation have been identified as a data gap. A sufficiently sensitive method should be used and also given that MITC is volatile the samples should be analysed as soon as possible after harvest. (relevant for all uses evaluated, data gap identified at the meeting of experts residues July 2008, proposed submission date unknown, refer to chapter 3).
- A data gap has been identified by EFSA after the meeting of experts to address the fate of DMTU in soil in order to obtain adequate input parameters for ground water modelling (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.1.2).
- A data gap was identified by the meeting of experts to address the range of half-lives available for metam and MITC and whether they are applicable to metam EU risk assessment. The notifier should address the different variables that might impact on the degradation in soil, such as method of application dose rate and soil adaptation (relevant for all uses evaluated, data gap

identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.1.2).

- The meeting of experts proposed a data gap for a new soil adsorption / desorption study conducted with consideration of the volatility and the low adsorption properties of MITC (eg. with shorter equilibration times, soil solution ratios of 1:1, high organic carbon soils) (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.1.3).
- A new data gap has been identified by EFSA after the meeting of experts to address the mobility of impurity DMTU in soil, in order to obtain adequate input parameters for ground water modelling (relevant for all uses evaluated, data gap identified after the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.1.3).
- A data gap was identified by the meeting of experts to address the effect of temperature on the dissipation of MITC from water by volatilization (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.2.1).
- A data gap for worst case PEC_{SW} estimations of MITC taking into consideration short range transport and deposition to surface water bodies and potential exposure via drainage with adequate input parameters was identified by the meeting of experts (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.2.1).
- A data gap was identified by the meeting of experts to recalculate MITC PEC_{GW} with adequate input parameters (when available) using FOCUS GW or higher tier approach if appropriate (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.2.2).
- A new data gap has been identified by EFSA after the meeting of experts, to address the potential ground water contamination of impurity DMTU (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.2.2).
- A data gap to address the atmospheric fate and behaviour of MITC including global warming ozone depletion, long range transport and deposition, and to address the potential contamination of surface water and soil by deposition in the vicinity of the applied areas was identified by the meeting of experts (relevant for all uses evaluated, data gap identified at the meeting of experts PRAPeR 52, proposed submission date unknown, refer to point 4.3.).
- Acute risk assessment for metam-sodium and MITC to birds and mammals that feed invertebrates is required (relevant for all out-door uses; submission date proposed by the notifier: unknown; data gap was identified during the PRAPeR 53; refer to point 5.1).
- A data gap for the submission of a new risk assessment to mammals based on the agreed endpoint of 100 mg/ kg bw has been identified (relevant for all representative uses evaluated;

submission date proposed by the notifier: unknown; data gap identified by EFSA after the PRAPeR 53 meeting refer to point 5.1).

- The aquatic risk assessment needs to be revised when the new PECsw will be available. The reliability of the chronic exposure of the aquatic organisms should be confirmed after data gaps in fate and behaviour are solved; in case MITC DT_{50} > 2 d, then the chronic risk assessment to aquatic organisms would have to be performed (relevant for all representative out-door uses evaluated; submission date proposed by the notifier: unknown; data gap was identified during the experts meeting; refer to point 5.2).
- Notifier to provided a semi-field or field study to address the recovery potential of the non-target arthropods after exposure to metam and MITC (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap was identified in the DAR by RMS refer to point 5.4)
- Notifier to address concerns on the recovery/recolonisation of earthworms this should include considerations on effects on recovery of different ecological groups as well kwon data on migration distances (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap was identified in the DAR by RMS; refer to point 5.5).
- A semi-field or field study to address the recovery potential of the soil non-target macro-organisms after exposure to metam and MITC (relevant for all representative uses evaluated; submission date proposed by the notifier: unknown; data gap was identified in the DAR by RMS; refer to point 5.6).
- A new data gap was identified by EFSA after the meeting of the experts, to provide ecotoxicological data to address the equivalence of the relevant impurity DMTU compare with metam-sodium.

Conclusions and Recommendations

Overall conclusions

This conclusion was reached on the basis of the evaluation of the representative uses as a nematicide, fungicide, herbicide and insecticide by soil fumigation prior to the planting of carrot, lamb’s lettuce, cucumber, aubergine, pepper, potato, strawberry, tomato and grapes. Full details of the GAP can be found in the attached list of end points.

The representative formulated product for the evaluation was “Metam sodium 510 g/L”, soluble concentrate (SL), registered under different trade names in Europe.

Adequate methods are available to monitor all compounds given in the respective residue definition. However, it should be noted that the residue definition for plants and ground water are provisional.

Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. There is a data gap for the flash point of the TK. Storage stability data where the relevant impurities are analysed for was also identified as a data gap. Spectra are available for the relevant impurity MITC[10] but not for the other relevant impurity DMTU[11] so this has also to be a data gap. As MITC is currently not specified in the technical specification a new specification is needed.

As for mammalian toxicology, metam sodium is harmful by oral ingestion and inhalation (R22 and R20 proposed). In irritation tests, metam sodium was not irritant to eyes but was corrosive to skin, therefore R34 ("Causes burns") was proposed. Metam sodium is a skin sensitiser (R43 "May cause sensitisation by skin contact" proposed). The relevant short term No Observed Adverse Effect Levels (NOAELs) are 0.1, 0.5 and 0.8 mg/kg bw/day in dogs, rats and mice, respectively. In particular, the occurrence of severe hepatotoxicity in dogs was considered to support the proposal of R48/22 ("Danger of serious damage to health by prolonged exposure if swallowed") to the European Chemicals Agency (EChA). Metam did not show any genotoxic potential, but caused angiosarcomas in mice (therefore R40 "Limited evidence of a carcinogenic effect" was proposed). The relevant long term NOAEL was 1.5 mg/kg bw/day based reduced bodyweight gain, specific lesion within the nasal passages, and changes in some haematology and spleen (haemosiderin depots) parameters in rats. In multigeneration tests, the relevant parental, reproductive and offspring NOAELs were 4, 12 and 4 mg/kg bw/day, respectively. Tested in developmental toxicity studies, metam sodium caused an increased incidence of variations and retardations at maternally toxic dose in rats and decreased number of live foetuses, increased number of dead implants in rabbits, with relevant maternal and developmental NOAEL in rats of 5 mg/kg bw/day and of 5 and 10 mg/kg bw/day, respectively, in rabbits. The malformations occurred at low incidences (sometimes in singularity), but in a consistent manner, at the top-doses, in the presence of quite severe maternal toxicity. Effects were clearly treatment related and associated with maternal toxicity: the classification as R63 ("Possible risk of harm to the unborn child") was proposed for consideration to the EChA. The Acceptable Daily Intake (ADI) and Acceptable Operator Exposure Level (AOEL) are 0.001 mg/kg bw/day, based on the 1-year dog study NOAEL with a Safety Factor (SF) 100; the Acute Reference Dose (ARfD) is 0.1 mg/kg bw based on an overall rat developmental toxicity NOAEL and supported by rabbit developmental study.
MITC is toxic via ingestion (R25 proposed) and via inhalation (R23 proposed). It is harmful in contact with skin (R21 proposed). In skin irritation tests it was corrosive to skin (R34 proposed). It was also irritative to the respiratory system (R37 proposed). It is a skin sensitiser (R43 proposed).

[10] MITC: methyl isothiocyanate
[11] DMTU: N,N-dimethylthiourea

The relevant NOAEL for short term exposure to MITC is 0.04 mg/kg bw/day, based on the thymus involution and liver vacuolation at 0.4 mg/kg bw/day. MITC did not show any genotoxic, carcinogenic, reproductive and developmental toxicity potential. The relevant NOAEL for long term toxicity is 0.44 mg/kg bw/day based on haematological changes in rats; the relevant parental NOAEL is 0.7 mg/kg bw/day, the reproductive and offspring NOAEL is >3.6 mg/kg bw/day. The relevant maternal and developmental toxicity NOAELs in rats are 3 and 10 mg/kg bw/day. The ADI and AOEL are 0.004 mg/kg bw/day based on the 1 year and 90-day studies in dog, respectively; the ARfD is 0.03 mg/kg bw based on NOAEL for rat maternal toxicity with SF 100. The operator exposure in open field is below the AOEL with the use of Respiratory Protective Equipment (RPE); the bystander and worker exposure in the open field is below the AOEL without the use of Personal Protective Equipment (PPE).
The PRAPeR meeting of experts considered the impurity DMTU as relevant, due to the lack of toxicological information.

Metabolism studies were supplied but no metabolites were identified. It was noted that the majority of the metabolism studies were under dosed. The meeting of experts considered the under dosing and lack of identification. It was concluded that as long as fate and behaviour had not identified any significant metabolites in soil then the metabolism data could be accepted. At this time fate and behaviour are unable to conclude on this issue and therefore a data gap has been set to address this. As some of the impurities in the technical material are applied at significant levels the consumer risk for the impurities still has to be addressed. A data gap for new residue trials was identified. Currently the need for processing studies, rotational crops and livestock studies are not triggered. However, this is subject to the data gaps. The risk assessment can not be finalised and MRLs can not be proposed at this time as the residue trials data are a data gap

Degradation of metam and its known active metabolite MITC in soil was investigated in four soils under dark aerobic conditions at 20 °C. The experts in the meeting were not confident that these experiments provided a realistic representation of the fate and behaviour of metam and MITC in soil mainly due to the mode of application used in the study with respect to the application in field where volatilization is minimized by compacting soil or with plastic films. However, the meeting noted that a number of scientific studies investigating the persistence of metam and MITC are available in the public domain and to regulatory authorities. Consequently, a data gap was identified by the meeting of experts to address the range of half-lives available for metam and MITC and whether they are applicable to metam EU risk assessment. The notifier should address the different variables that might impact on the degradation in soil, such as method of application dose rate and soil adaptation.
Taking into consideration the application rates of metam (306 – 612 kg / ha), during the peer review it was considered that impurities need to be addressed for the potential environmental and ground water contamination. The notifier submitted an overview of the main impurities present in the technical material that was summarized by the RMS in the addendum (June 2008). The meeting of experts in

toxicology agreed that the impurity DMTU should be regarded as toxicological relevant and therefore will need a ground water exposure assessment.

PEC soil for metam and MITC were calculated for the worst case use in field tomato (612 kg a.s. / ha) assuming 15 cm incorporation. Time dependent PEC soil need to be updated once the data gaps identified for persistence in soil are solved. Initial PECs in soil may be used for the EU risk assessment.

Mobility of metam was investigated by the HPLC method. According this experiment metam may be considered to be very high mobile in soil. A batch adsorption / desorption study is available for MITC in four soils. This compound was very high mobile in these soils (K_{foc} = 27 – 46 mL / g). The meeting of experts concluded that adsorption in this study may have been overestimated due to the fact that experimental Koc values are simultaneously affected by degradation and volatilization during the experiment. Therefore, the meeting of experts proposed a data gap for a new soil adsorption desorption study conducted with consideration of the volatility and the low adsorption properties of MITC (e.g. with shorter equilibration times, soil solution ratios of 1:1, high organic carbon soils).

After the meeting of experts, a new data gap has been identified by EFSA to address the mobility of impurity DMTU in soil in order to obtain adequate input parameters for ground water modelling.

Hydrolysis of metam is relatively fast at any pH. Hydrolysis of MITC at 25 °C occurs with half-lives of ≈ 40 d (pH 4), 50 d (pH 7) and 11 d (pH 9). Major hydrolysis products of MITC were DMU, DMTU and MDTA (metam). The fact that one of the major metabolites of MITC is metam indicates that in water metam and MITC are in equilibrium.

Aqueous photolysis of metam under simulated sunlight is very fast (DT_{50} = 12 min; equivalent to 27.8 min at 38 °N). No readily biodegradation study is available and therefore the substance is considered to be non readily biodegradable.

In the aerobic water /sediment experiment (25 °C) metam degrades rapidly in the whole system ($DT_{50\text{whole system}}$ = 0.32 h). The meeting agreed that the information provided by the notifier did not allow any quantitative estimation of the effect of temperature on the volatilization. Consequently, the meeting of experts identified a data gap to address the effect of temperature on the dissipation of MITC from water by volatilization. Depending on the results of the volatilization assessment, a new water sediment study at lower temperature may be necessary. The data from the anaerobic water sediment study was considered not relevant for the representative uses and it was not considered scientifically justified to average dissipation rates from aerobic and anaerobic experiments.

Due to the data gaps identified on the derivation of various key modelling input parameters and to the fact that FOCUS SW modelling does not considers volatilization-deposition route of entry in surface water, the available PEC_{SW} were not considered appropriate for the EU risk assessment. The meeting of experts identified a data gap for worst case PEC_{SW} estimations of MITC taking into consideration short range transport and deposition to surface water bodies and potential exposure via drainage with adequate input parameters.

The meeting of experts identified the need to recalculate MITC PEC_{GW} values with adequate input parameters (when available) using FOCUS GW or higher tier approach if appropriate.

After the meeting of experts, a new data gap has been identified by EFSA to address the potential ground water contamination of impurity DMTU.
The meeting of experts identified a data gap to address the atmospheric fate and behaviour of MITC including global warming (ozone depletion), long range transport and deposition, and to address the potential contamination of surface water and soil by deposition in the vicinity of the applied areas.

No risk assessment for terrestrial vertebrates was presented in the DAR.. Experts suggested that the most probable contaminated food items for birds and mammals would be the soil invertebrates (included earthworms). The experts in the PRAPeR 53 agreed that the risk to birds and mammals should be addressed by the notifier. Acute risk assessment should be also done for the metabolite MITC using the lowest endpoint available of 100 mg a.s./kg bw agreed during the meeting. Metam-sodium and its relevant metabolite MITC are very toxic to aquatic organisms. Due to the rapid degradation of metam-sodium in soil, surface water contamination with the parent molecule can be excluded. Aquatic organisms may be exposed to the metabolite MITC as result of the drainage and run-off. The experts in the fate and behaviour meeting agreed that the PECsw should be re-estimated by the notifier. As a consequence the aquatic risk assessment should be performed again, once the new PECsw will be available. An extended laboratory study was conducted with *Aloechara bilineata* and this aged residue study demonstrated that *A. bilineata* was able to re-colonise the field after 55 days. From an extended laboratory study it was only possible to assess the potential for recolonisation, but not the actual recovery. Therefore, the experts agreed that further refinement is required to address the recovery potential of the non-target arthropods and soil macro-organisms.
An earthworm field study was conducted with the metam-sodium. The experts agreed that after the application of the 608.4 kg a.s./ha, there was no clear indication of full recovery after one year. A further refinement was required to the notifier to address concerns on the recovery/re-colonisation of earthworms this should include considerations on effects on recovery of different ecological groups as well as known data on migration distances.
The risk of metam and its metabolite MITC to other soil macro-organisms should be addressed. The risk of metam and its metabolite MITC to bees, soil micro-organisms, non-target plants and biological method of sewage treatment were assessed as low in out-doors uses.
The risk of metam and its metabolite MITC to terrestrial vertebrates, aquatic organisms, bees and non-target arthropods were assessed to be low in greenhouse uses.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- Use of respiratory protective equipment (RPE) to be considered for operator exposure to MITC during field applications (soil injection)
- EFSA noted while drafting the conclusion that there was some concern about the risk of metam-sodium to earthworm in the glasshouse uses. EFSA considers, for permanent glasshouse the risk was considered low but for temporary glasshouse tunnels that included natural soil

(non-artificial substrate) Member States might wish to ask for further data to clarification the risk to earthworms.(refer to point 5.5).

Critical areas of concern

- The risk assessment for operators and workers in greenhouses can not be concluded on.
- The consumer risk assessment can not be concluded on.
- Environmental exposure assessment (including potential ground water contamination) can not be finalised. The preliminary assessment indicates that active metabolite MITC may exceed 0.1 µg/L. Relevant impurity DMTU (4-6 Kg/ ha) needs to be addressed for potential ground water contamination.
- Active metabolite MITC is volatile and has an estimated half life in the atmosphere of 78 days, long range transport and potential effects on the atmosphere need to be addressed.
- The acute risk to birds and mammals needs to be addressed.
- MITC; a high risk to aquatic organisms was identified. Further information is required to address the risk for aquatic organisms.
- Further information is required to address the recovery potential of the non-target arthropods.
- Further information is required to address the risk of metam-sodium to earthworms.
- Further information is required to address the risk of non-target soil macro-organisms.

Appendix 1 – list of end points

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Metam (The given data belong to the variant metam-sodium, unless specified otherwise)
Function (*e.g.* fungicide)	Nematicide, fungicide, herbicide, insecticide

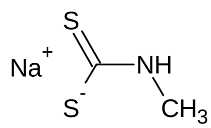
Rapporteur Member State	Belgium
Co-rapporteur Member State	Not applicable

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	N-methyldithiocarbamic acid Variant: sodium N-methyldithiocarbamate
Chemical name (CA) ‡	methylcarbamodithioic acid Variant : Methylcarbamodithioic acid sodium salt
CIPAC No ‡	20 Variant : 20.011
CAS No ‡	144-54-7 Variant : 137-42-8
EC No (EINECS or ELINCS) ‡	Metam-sodium: 205-293-0
FAO Specification (including year of publication) ‡	20.1Na/13/S/15, published in AGP:CP/82 (1979): *“The metam-sodium content shall be declared (g/L at 20°C or % w/w). When the combined carbon disulphide is determined and expressed as metam-sodium the content obtained shall not differ from that declared by more than ± 5% of the declared content.”*
Minimum purity of the active substance as manufactured ‡	Technical concentrates (TK): Metam-sodium TK: min. 400 g/kg – max. 442 g/kg Dry weight basis (calculated): Metam-sodium: min. 983 g/kg

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Methylisothiocyanate MITC maximum content OPEN N,N'-dimethylthiourea (DMTU) Maximum content 23 g/kg on a dry weight basis
Molecular formula ‡	$C_2H_5NS_2$ Variant : $C_2H_4NNaS_2$
Molecular mass ‡	107.2 u Variant: 129.2 u
Structural formula ‡	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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Physical and chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	86.5 – 90.5 °C (99.9%)
Boiling point (state purity) ‡	Not applicable
Temperature of decomposition (state purity)	150 °C (97%)
Appearance (state purity) ‡	(97.0%): white crystalline powder; (510 g/L aqueous solution): yellow clear solution;
Vapour pressure (state temperature, state purity) ‡	5,75 .10^{-2} Pa at 25°C (99.9%)
Henry's law constant ‡	8.34 x 10^{-6} Pa.m³.mol^{-1}
Solubility in water (state temperature, state purity and pH) ‡	578.29 g/L at 20°C (distilled water; pH increases to 9.2 - 9.3) (99.9%) 734 g/L at 20°C (pH 9 buffer; pH increases to 10.1) (99.2%)
	Water solubility is not significantly affected by pH
Solubility in organic solvents ‡ (state temperature, state purity)	Solubility at 20°C in g/L (99.9%)

	solubility at 20°C (g/L)
n-heptane	< 0.2126
Xylene	< 0.2611
1,2-dichloroethane	< 0.2620
ethyl acetate	< 0.2032
acetone	< 0.2188
methanol	33 – 40

Surface tension ‡ (state concentration and temperature, state purity)	72.0 mN/m at 21°C (1 g/L) (97.0%)
Partition co-efficient ‡ (state temperature, pH and purity)	log $P_{O/W}$ ≤ - 2.91 at 20 °C (pH 6.9) (99.9%)
	No significant pH-effect expected (cfr. dissociation constants)
Dissociation constant (state purity) ‡	pKa_I = 2.99; pKa_{II} = 11.06 (99.2%)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	<table><tr><td></td><td>λ_{max} (nm)</td><td>ε ($L.mol^{-1}.cm^{-1}$)</td></tr><tr><td rowspan="4">Neutral (distilled water)</td><td>205.0</td><td>7502.8</td></tr><tr><td>248.0</td><td>7942.3</td></tr><tr><td>280.0</td><td>9924.0</td></tr><tr><td>at λ 290 nm</td><td>> 10</td></tr><tr><td rowspan="3">Alkaline (0.1 M NaOH)</td><td>248.0</td><td>8042.5</td></tr><tr><td>280.0</td><td>9796.8</td></tr><tr><td>at λ 290 nm</td><td>> 10</td></tr><tr><td>Acidic (0.1M HCl)</td><td colspan="2">Metam-sodium hydrolysed too fast to measure accurately</td></tr></table>
Flammability ‡ (state purity)	Not auto-flammable (510 g/L aqueous solution, i.e. TK) Flash point:Open
Explosive properties ‡ (state purity)	Not explosive (statement)
Oxidising properties ‡ (state purity)	Not oxidising (statement)

Physical and chemical properties of the relevant metabolite methylisothiocyanate (MITC)

Appearance (state purity) ‡	Colourless crystalline solid (97.0%)
Vapour pressure (state temperature, state purity) ‡	1739 Pa (20°C, 99.4%)
Henry's law constant ‡	$H = 14.2\ Pa.m^3.mol^{-1}$
Solubility in water (state temperature, state purity and pH) ‡	8.94 g/L at 20°C (97.0%, pH 7.5)
Partition co-efficient ‡ (state temperature, pH and purity)	log P_{ow} at 20°C: 1.05 (pH 7.5, 97.0%)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

UV/VIS absorption (max.) incl. ε ‡
(state purity, pH)

97.0% pure:

	λ_{max} (nm)	ε ($L.mol^{-1}.cm^{-1}$)
Neutral (distilled water)	235	635
	283	65
	321	17
Alkaline (0.1 M NaOH)	276	46
	320	5
	at λ 290 nm	Not reported, but > 10 based on spectrum
Acidic (0.1M HCl)	235	635
	283	23
	324	6
	at λ 290 nm	Not reported, but > 10 based on spectrum

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Summary of representative uses evaluated (metam-sodium)

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Carrot	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Soil injection + incorporation at 25 cm by rotavation	April-June	1	n.a.	n.a.	No dilution	408	n.a.	(One application every two years in carrot) [1] [3] [4] [5] [6] [7] [8]
Carrot	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Soil injection + incorporation at 25 cm by rotavation	Oct-Dec	1	n.a.	n.a.	No dilution	408	n.a.	(One application every two years in carrot) [1] [3] [4] [5] [6] [7] [8]

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Corn salad (=lamb's lettuce)	France, Spain, Belgium, Germany, Italy	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Soil injection + incorporation at 15 cm by rotavation	April-Aug	1	n.a.	n.a.	No dilution	306	n.a.	[1] [3] [4] [5] [6] [7] [8]
Cucumber	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	G	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Drip-irrigation on the planting row	June-Aug	1	n.a.	n.a.	No dilution	459	n.a.	[1] [3]
Eggplant / aubergine	Cyprus, Spain, France, Greece, Italy, Malta, Netherlands, Portugal	*	G	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Drip-irrigation on the planting row	June-Aug	1	n.a.	n.a.	No dilution	612	n.a.	[1] [3]
Pepper	Belgium, Cyprus, Spain, France, Greece, Hungary, Italy, Malta, Netherlands, Poland, Portugal, United Kingdom	*	G	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Drip-irrigation on the planting row	June-Aug	1	n.a.	n.a.	No dilution	612	n.a.	[1] [3]

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Potato	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Soil injection + incorporation at 25 cm by rotavation	Sept-Nov	1	n.a.	No dilution		153	n.a.	[1] [3] [4] [5] [6] [7] [8]
Strawberry	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Drip irrigation under a plastic film on the planting row	Jul-Oct	1	n.a.	n.a.	No dilution	612	n.a.	[1] [3] [4] [5] [6] [7] [8]
Tomato	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	G	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Drip irrigation on the planting row	Feb-Aug	1	n.a.	n.a.	No dilution	612	n.a.	[1] [2] [3]

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Tomato	Germany, Belgium, Cyprus, Spain, France, Malta, Greece, Poland, Hungary, Ireland, Italy, Netherlands, Portugal, United Kingdom	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Soil injection at 5 cm + coverage by 10 cm of soil	March	1	n.a.	n.a.	No dilution	612	n.a.	[1] [3] [4] [5] [6] [7] [8]
Grape	France, Italy, Germany, Spain, Greece, Hungary, Portugal	*	F	Nematodes Soil fungi Weeds Insects	SL	510 g/l	Soil injection at 40 cm at the site of the de-rooted vine (0,2 l/m²)	Autumn. Before replanting	1	n.a.	n.a.	No dilution	1020	n.a.	Spot treatment [1] [3] [4] [5] [6] [7] [8]

[1] The consumer risk assessment can not be finalized.

[2] The operator, worker and bystander risk assessment cannot be finalized

[3] Environmental exposure assessment, including potential ground water contamination by active metabolite MITC and relevant impurity DMTU, cannot be finalized

- [4] The acute risk to birds and mammals needs to be addressed.
- [5] High risk to aquatic organisms was identified for MITC. Further information is required to address the risk for aquatic organisms.
- [6] Further information is required to address the recovery potential of the non-target arthropods.

[7] Further information is required to address the risk of metam-sodium to earthworms

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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- [8] Further information is required to address the risk of non-target soil macro-organisms.

* : The preparation is identical to the technical active substance. Different tradenames are used in different EU member states.
Solasan, Terrasan, Monam, Nemasol, Traitam Sol, Metam sodio, etc.

* For uses where the column "Remarks" is marked in grey further consideration is necessary. Uses should be crossed out when the notifier no longer supports this use(s). (a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure) (b) Outdoor or field use (F), greenhouse application (G) or indoor application (I) (c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds (d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR) (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989 (f) All abbreviations used must be explained (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench (h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plant- type of equipment used must be indicated	(i) g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application (k) Indicate the minimum and maximum number of application possible under practical conditions of use (l) The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200 000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha (m) PHI - minimum pre-harvest interval

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	CS_2-evolution method (CIPAC method 20/13/M/1.3)
Impurities in technical as (analytical technique)	HPLC-UV, titration, ion chromatography
Plant protection product (analytical technique)	CS_2-evolution method (CIPAC method 20/13/M/1.3)

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		MITC (provisional)
Food of animal origin		None
Soil		MITC
Water	surface	MITC
	drinking/ground	MITC and DMTU (provisional)
Air		MITC

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	GC-MS (ILV available): Food commodities of plant origin with high water content and with high acid content: LOQ = 0.01 mg/kg (MITC)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Not required, as no MRL's are proposed.
Soil (analytical technique and LOQ)	GC-NPD (conf. technique: column of different polarity): LOQ = 0.02 mg/kg (MITC)
Water (analytical technique and LOQ)	GC-NPD (conf. technique: column of different polarity): LOQ = 0.1µg/L (MITC) Open for ground water for the compound DMTU
Air (analytical technique and LOQ)	GC-NPD (conf. technique: column of different polarity): LOQ = 0.5 µg/m³ (MITC)

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Body fluids and tissues (analytical technique and LOQ)	HPLC-MS (conf. technique: HPLC-MS-MS): *blood plasma, urine:* LOQ = 0.05 mg/L (N-acetyl-S-[(methylamino)carbothioyl]cysteine, i.e. appropriate target analyte from a toxicological point of view) GC-NPD (conf. technique: column of different polarity): *liver:* LOQ = 0.1 mg/kg (MITC, i.e. appropriate target analyte from a toxicological point of view)

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

	RMS/peer review proposal
Active substance	R31

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1) metam and MITC

Rate and extent of oral absorption ‡	85 % (based on urinary (50%) and expired air (35%) excretion within 48 h)
Distribution ‡	Uniformly distributed
Potential for accumulation ‡	Slight potential for accumulation in thyroid
Rate and extent of excretion ‡	Rapid and extensive (app. 85 %) within 48 h, mainly via urine (50 %) within 24 h, 4 % via faeces, 35 % via expired air
Metabolism in animals ‡	Extensive degradation of metam into MITC which is further conjugated with GSH or decomposes into MIC, COS and CO_2. Another important metabolic pathway is formation of CS_2 which is related to acidic conditions of stomach
Toxicologically relevant compounds ‡ (animals and plants)	Parent compound and metabolites: Methylisothiocyanate (MITC) , methylisocyanate (MIC), COS, CS_2
Toxicologically relevant compounds ‡ (environment)	Methylisothiocyanate (MITC), methylisocyanate (MIC), COS, CS_2

Acute toxicity (Annex IIA, point 5.2) metam sodium

Rat LD_{50} oral ‡	896 mg/kg bw	**R22**
Rat LD_{50} dermal ‡	> 2000 mg/kg bw	**-**
Rat LC_{50} inhalation ‡	2.54 mg/L air /4h (whole body)	**R20**
Skin irritation ‡	Corrosive	**R34**
Eye irritation ‡	Non-irritant	**-**
Skin sensitisation ‡	Sensitising (M & K)	**R43**

Acute toxicity (Annex IIA, point 5.2) MITC

Rat LD_{50} oral ‡	147 mg/kg bw	**R25**
Rat LD_{50} dermal ‡	1290 mg/kg bw	**R21**
Rat LC_{50} inhalation ‡	0.54 mg/L air /4h (whole body)	**R23** **R37**
Skin irritation ‡	Corrosive	**R34**
Eye irritation ‡	No study required	**-**
Skin sensitisation ‡	Sensitising (M & K)	**R43**

Short term toxicity (Annex IIA, point 5.3) metam sodium

Target / critical effect ‡	Nasal cavity (rat), urinary bladder(mice), liver(dog)	
Relevant oral NOAEL ‡	1-year, dog 0.1 mg/kg bw/day 90-day rat: 0.5 mg/kg bw/day 90-day mice: 0.8 mg/kg bw/day	**R48/22**
Relevant dermal NOAEL ‡	21-day, rabbit: 31.2 mg/kg bw/day	
Relevant inhalation NOAEL ‡	90-day rat: 6.5 mg/m^3 corresponding to	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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	1.75 mg/kg bw/d	

Short term toxicity (Annex IIA, point 5.3) MITC

Target / critical effect ‡	Nasal cavity (rat), liver (dog)	
Relevant oral NOAEL ‡	90-day, dog 0.04 mg/kg bw/day	
Relevant dermal NOAEL ‡	No data - not required	
Relevant inhalation NOAEL ‡	28-day rat : 5 mg/m^3 (1.35 mg/kg bw/d)	

Genotoxicity ‡ (Annex IIA, point 5.4)

	Metam and MITC are unlikely to be genotoxic	

Long term toxicity and carcinogenicity (Annex IIA, point 5.5) Metam sodium

Target/critical effect ‡	Nasal cavity (rat) urinary bladder (mice)	
Relevant NOAEL ‡	1.5 mg/kg bw/day; 2-year, rat 1.9 mg/kg bw/day; 24-month, mouse	
Carcinogenicity ‡	Angiosarcomas in mice	**R40**

Long term toxicity and carcinogenicity (Annex IIA, point 5.5) MITC

Target/critical effect ‡	Changes in some WBC parameters	
Relevant NOAEL ‡	0.44 mg/kg bw/day; 2-year, rat 3.3 mg/kg bw/day; 24-month, mouse	
Carcinogenicity ‡	MITC is unlikely to pose a risk to humans	

Reproductive toxicity (Annex IIA, point 5.6) Metam sodium

Reproduction toxicity

Reproduction target / critical effect ‡	Decreased pup and litter weight at the parental toxic dose in the rat	
Relevant parental NOAEL ‡	0.03 mg/L (4 mg/kg bw/day)	
Relevant reproductive NOAEL ‡	>0.1 mg/L (12 mg/kg bw/day)	
Relevant offspring NOAEL ‡	0.03mg/L(4 mg/kg bw/day)	

Developmental toxicity

Developmental target / critical effect ‡	Increased incidence of variations and retardations at maternally toxic dose in rats; decreased number live foetuses and increased incidence of dead implants at maternal toxic doses in rabbits	**R63 (R61 ?)**
Relevant maternal NOAEL ‡	Rat: 5 mg/kg bw/day Rabbit: 5 mg/kg bw/day	
Relevant developmental NOAEL ‡	Rat: 5 mg/kg bw/day Rabbit: 10 mg/kg bw/day	

Reproductive toxicity (Annex IIA, point 5.6) MITC

Reproduction toxicity

Reproduction target / critical effect ‡	Reproduction parameters not significantly	

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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	altered	
Relevant parental NOAEL ‡	0.7 mg/kg bw/day	
Relevant reproductive NOAEL ‡	>3.6 mg/kg bw/day	
Relevant offspring NOAEL ‡	>3.6 mg/kg bw/day	

Developmental toxicity

Developmental target / critical effect ‡	Decreased fetal weight at maternal toxic doses in rabbits	
Relevant maternal NOAEL ‡	Rat: 3 mg/kg bw/day Rabbit: 3 mg/kg bw/day	
Relevant developmental NOAEL ‡	Rat: 10 mg/kg bw/day Rabbit: 10 mg/kg bw/day	

Neurotoxicity (Annex IIA, point 5.7) metam sodium

Acute neurotoxicity ‡	NOAEL> 1500 mg/kg bw	
Repeated neurotoxicity ‡	NOAEL = 14.7 mg/kg bw/d	
Delayed neurotoxicity ‡	No data-not required	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	No studies performed
Studies performed on metabolites or impurities ‡	No further studies performed

Medical data ‡ (Annex IIA, point 5.9) metam sodium

	no medical surveillance data for manufacturing plant personnel was found for metam sodium

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡metam sodium	0.001 mg/kg bw/day	dog, 1-year gavage study	100
ADI MITC	0.004	dog, 90-d drinking water study	100
AOEL ‡ metam sodium	0.001 mg/kg bw/day	dog, 1-year gavage	100
AOEL MITC	0.004 mg/kg bw	dog, 90-d drinking water study	100
ARfD ‡ metam sodium	0.1 mg/kg bw	rat, overall developmental toxicity	100

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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ARfD MITC	0.03 mg/kg bw/day	rat, developmental study	100

Dermal absorption ‡ (Annex IIIA, point 7.3)

Formulation (e.g. name 50 % ECMonam)	Concentrate: 1 %; 12% : for the dilution ŧ Rat *in vivo* and comparative *in vitro* (human/rat skin)

Exposure scenarios (Annex IIIA, point 7.2)

Operator exposure to metam sodium	Not relevant: metam sodium decomposes very rapidly into MITC.
Operator exposure to MITC	Measurements under realistic open field conditions ; values as % of AOEL of MITC (0.004 mg/kg b.w./d) ; RPE (operator, worker) : combination filter A1P2, 2% penetration **Operator exposure** (personal measurements); -Study1, soil injection: 450% of AOEL w/o RPE and 9.0% with RPE -Study 2, soil fumigation, 229% of AOEL w/o RPE and 4.6% with RPE -Study 3, soil injection: 239% of AOEL w/o RPE and 4.8% with RPE Greenhouse use: data gap
Workers exposure to metam sodium	Not relevant: metam sodium decomposes very rapidly into MITC.
Workers exposure to MITC	**Worker exposure** ; 14-17 day after soil injection, *0-2 hr after breaking seal, personal measurements:* -Preparation of soil:14-19% of AOEL w/o RPE and 0.3-0.4% with RPE -Plastic film opening: 37% of AOEL w/o RPE and 0.74% with RPE -Volatilisation from field, *18h post application*, 1 m height: 27% of AOEL w/o RPE and 0.54% with RPE Greenhouse use: data gap
Bystanders exposure to metam sodium	Not relevant: metam sodium decomposes very rapidly into MITC.

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

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Bystanders exposure to MITC	**Bystander exposure** (no RPE assumed)**:** -soil injection, distance of 100 m, during application: 18.7% of AOEL -soil injection, MITC in air 6 hour after application: 3.1% of AOEL - soil injection, 1.1-9 days after application, 1.5 m height: 7.3% of AOEL Greenhouse use: data gap

Classification and proposed labeling with regard to toxicological data (Annex IIA, point 10)

	RMS/peer review proposal
Substance classified (metam sodium)	Repr.Cat 3; R63 (R61?): Carc. Cat 3; R 40: Xn, R48/22 : Xn; R20/22: C;:R34: R43

	RMS/peer review proposal
Substance classified (MITC)	C ; R34 : T; R23/25: Xn ; R21 : R43

‡ End point identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of end points

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	OPEN
Rotational crops	OPEN
Metabolism in rotational crops similar to metabolism in primary crops?	OPEN
Processed commodities	OPEN
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not relevant.
Plant residue definition for monitoring	MITC (provisional)
Plant residue definition for risk assessment	MITC (provisional)
Conversion factor (monitoring to risk assessment)	None.

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	OPEN
Time needed to reach a plateau concentration in milk and eggs	-
Animal residue definition for monitoring	-
Animal residue definition for risk assessment	-
Conversion factor (monitoring to risk assessment)	-
Metabolism in rat and ruminant similar (yes/no)	-
Fat soluble residue: (yes/no)	No (Log P*o/w*: -2.9 at 20 °C).

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

	OPEN subject to the primary crop metabolism being concluded on.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

	OPEN

Appendix 1 – list of end points

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	-	-	-
Potential for accumulation (yes/no):	-	-	-
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	-	-	-
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle	-	-	-
Liver	-	-	-
Kidney	-	-	-
Fat	-	-	-
Milk	-		
Eggs		-	

Appendix 1 – list of end points

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
OPEN						
A sufficient number of acceptable residue trials using the validated BASF analytical method 234/2 has to be provided in order to confirm the situation of no residue for all the intended uses.						

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use

Appendix 1 – list of end points

(c) Highest residue

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Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.004 mg/kg b.w./day for MITC.
TMDI (% ADI) according to WHO European diet	OPEN
TMDI (% ADI) according to national (to be specified) diets	OPEN
IEDI (WHO European Diet) (% ADI)	OPEN
NEDI (specify diet) (% ADI)	OPEN
Factors included in IEDI and NEDI	OPEN
ARfD	0.03 mg/kg bw/day (based on a rat developmental study)
IESTI (% ARfD)	OPEN
NESTI (% ARfD) according to national (to be specified) large portion consumption data	OPEN
Factors included in IESTI and NESTI	OPEN
The risk assessment calculation cannot be finalised pending the results of the new residue database for each supported crop.	

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
OPEN				

Appendix 1 – list of end points

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Expression of the residue	Crops	MRLs (mg/kg)
		OPEN. No proposal. Further residue trials are required for all the supported uses.

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Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	(MITC as test substance) 45.96-86.25 % after 21 d (study termination), [^{14}C-thiocarbonyl]-label (n = 4). Amount found in the NaOH trap.
Non-extractable residues after 100 days ‡	(MITC as test substance) 9.88-38.38% after 21 d (study termination), [^{14}C-thiocarbonyl]-label (n = 4)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	(metam-sodium as test substance) Methyl isothiocyanate (MITC) : 82.9 % at 1-2 d (n= 1) Recovered as volatile

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡	
Mineralization after 100 days	No acceptable data available. Not required for the representative uses.
Non-extractable residues after 100 days	No acceptable data available. Not required for the representative uses.
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	No acceptable data available. Not required for the representative uses.
Soil photolysis ‡	
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	No acceptable data available. Not required for the representative uses.

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Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	X[12]	PH (water)	t. °C / % MWHC	DT_{50} /DT_{90} (minutes)	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam	-	5.4	20°C, 50% MWHC	17/57	-	0.87	Linear regression, first order
Sandy loam	-	5.7	20°C, 50% MWHC	4/13	-	1.00	
Silt loam	-	7.1	20°C, 50% MWHC	11/36	-	0.86	
Clay loam	-	7.7	20°C, 50% MWHC	9/30	-	0.99	
Sandy loam	-	5.4	10°C, 50% MWHC	22/72	-	0.70	
Geometric mean				10.8			

MITC	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20 °C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam	-	5.2	20°C, 50% MWHC	2.78/9.23	-	-	0.9908	Linear regression, first order
Sandy loam	-	4.5	20°C, 50% MWHC	2.94/9.77	-	-	0.9917	
Silt loam	-	6.1	20°C, 50% MWHC	0.97/3.21	-	-	0.9898	
Clay loam	-	7.6	20°C, 50% MWHC	1.91/6.35	-	-	0.9995	
Sandy loam	-	5.2	10°C, 50% MWHC	8.31/27.61	-	-	0.9449	
Geometric mean				2.63 d				

[12] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

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Data gap identified to consider data available in the public scientific literature and to other regulatory authorities (MITC DT_{50} = 5 – 13.6 d).

Field studies ‡

Parent	Aerobic conditions
The field studies do not reflect the mode of application relevant for the uses supported in Europe (Application into the soil by direct injection or through drip-irrigation system). The application was made by overhead-sprinkler system. The formulation was injected in the sprinkler irrigation pipeline while water was applied to the plot. Incorporation of the a.s. in soil was achieved by post-application spray irrigation in some experiments.	

pH dependence ‡ (yes / no) (if yes type of dependence)	-
Soil accumulation and plateau concentration ‡	Not required

Laboratory studies ‡

Parent, MITC	Anaerobic conditions
Not required	

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡
HPLC determination: Koc < 17.8 mL/g at pH 4 and 9

Metabolite MITC ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	Kf (mL/g)	Kfoc (mL/g)	1/n
Hokkaido Tokachi	2.56	6.2	-	-	0.68	27	1.12
Fukushima	1.08	7.6	-	-	nv	nv	nv
Okayama	0.69	6.7	-	-	nv	nv	nv
Miyazaki	1.50	7.2	-	-	nv	nv	nv
Arithmetic mean						na	na
pH dependence (yes or no)			no				

n.v. not valid; n.a. not applicable. Data gap for an additional study identified by the meeting of experts.

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Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Not required
Aged residues leaching ‡	Not required
Lysimeter/ field leaching studies ‡	Not required

PEC (soil) (Annex IIIA, point 9.1.3)

Parent Method of calculation	DT_{50} (metam-sodium): 0.0118 days (17 minutes) Kinetics: 1st order Representative worst case from laboratory study.
Application data	Crop: field tomato Depth of soil layer: 15 cm Soil bulk density: 1.5 g/cm^3 % plant interception: 0% Number of applications: 1 Interval (d): - Application rate(s): 612 kg as/ha

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		272	-	-	-
Short term	24h	<0.0001	4.630	-	-
	2d	<0.0001	2.315		
	4d	<0.0001	1.158		
Long term	7d	<0.0001	0.661	-	-
	28d	<0.0001	0.165		
	50d	<0.0001	0.092		
	100d	<0.0001	0.046		

MITC Method of calculation	Molecular weight relative to the parent: 0.566 = 73.11/129.17 DT_{50} (d): 2.94 days Kinetics: first order kinetics Field or Lab: representative worst case from lab

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	study.
Application data	Crop: field tomato 0 % plant interception: 15 cm soil incorporation Number of applications: 1 Interval (d): - Application rate assumed: 346 kg MITC/ha (assumed MITC is formed at a maximum of 100 % of the applied dose)

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	153.778	-	-	-

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 5: DT50 a.s. : 1.9 d at 25 °C (1st order, r^2=0.98) MITC: 20 % AR (1.8 d)
	pH 7: DT50 a.s. : 2.2 d at 25 °C (1st order, r^2=0.92) MITC: 60 % AR (5 d)
	pH 9: DT50 a.s. : 4.5 d at 25 °C (1st order, r^2=0.98) MITC: 20 % AR (5.4 d)
	pH 5: DT50 MITC : ~ 40 d at 25 °C (1st order)
	pH 7: DT50 MITC : 50 d at 25 °C (1st order)
	pH 9: DT50 MITC : 11 d at 25 °C (1st order)

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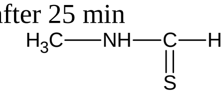
Photolytic degradation of active substance and metabolites above 10 % ‡	DT_{50} = 12 min (equivalent to 27.8 min of natural summer sunlight at latitude 38° N) *Major degradation products (≥ 10% of applied radioactivity AR):* - N-methylthioformamide (*syn*- and *anti*-rotamer): 22% of AR after 25 min  - MCDT (sodium methylcarbamo(dithioperoxo)thioate): 14% of AR after 25 min - MITC (methylisothiocyanate): 16% of AR after 25 min - Methylamine: 18% of AR after 25 min (zero-time sample contained 14% methylamine)
Quantum yield of direct phototransformation in water at ☒ > 290 nm	Not required
Readily biodegradable ‡ (yes/no)	No information available; considered to be **not readily biodegradable.**

Degradation in water / sediment

Metam-potassium	Distribution (less than 1%AR after 1 day in whole system)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} Water	St. (r^2)	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
Non-sterile aerobic	7.4	6.7	25	0.32/1.09 h	0.946	-	-	-	-	Linear 1st ord.
Sterile anaerobic	7.4	6.7	25	1.59/5.28 h	0.928	-	-	-	-	Linear 1st ord.
Non-sterile anaerobic	7.4	6.7	25	2.87/9.53 h	0.976	-	-	-	-	Linear 1st ord.
Geometric mean/median										

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MITC	Distribution 3.2-8.5% AR as in water at study termination (8-72 hours) 3.2-7.2% AR in sediment at study termination (8-72 hours) 58.2-79.4% AR as volatile at study termination (8-72 hours)

Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} Water *	r^2	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
Non-sterile aerobic	7.4	6.7	25	-	0.906	2.65/8.79 h	0.906	-	-	Linear 1st ord.
Sterile anaerobic	7.4	6.7	25	-	0.973	10.60/35.22 h	0.973	-	-	Non-lin 1st ord.
Non-sterile anaerobic	7.4	6.7	25	-	0.995	13.44/44.65 h	0.995	-	-	Non-lin 1st ord.
Geometric mean				-		Not relevant				

Mineralization and non extractable residues

Water / sediment system	pH water phase	pH sed	Mineralization x % after n d. (end of the study).	Non-extractable residues in sed. max x % after n d	Non-extractable residues in sed at end of the study)
Non sterile aerobic	7.4	6.7	Not measured	33% after 7 min	14.4% after 8 hours
sterile anaerobic	7.4	6.7	Not measured	21.9% after 8 hours	21.1% after 72 hours
Non sterile anaerobic	7.4	6.7	Not measured	16.5% after 48 hours	13.3% after 72 hours

*** DT50 water includes dissipation due to volatilisation**

PEC (surface water) and PEC sediment (Annex IIIA, point 9.2.3)

Parent Parameters used in FOCUSsw step 1 and 2	Not required, since metam-sodium itself is subject to rapid degradation (laboratory DT_{50}'s ranged from 4 - 23 minutes) and is not expected to reach surface water
Parameters used in FOCUSsw step 3 (if performed)	Not required
Application rate	Not required

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Metabolite MITC Parameters used in FOCUSsw step 3	PRZM, MACRO and TOXSWA 2.2.1.F1 Molecular Mass (g mol^{-1}):73.11 Vapour Pressure (Pa):1739 Aqueous Solubility (mg/L):8940 Soil Adsorption Coefficient (K_{om}) (ml/g):data gap Freundlich Exponent (1/n):1 DT_{50} (days): data gap Plant Uptake Coefficient: 0 Dissipation rate in sediment: Dissipation rate in water: Metabolite kinetically generated in simulation :no
Parameters used in FOCUSsw step 4	
Application rate	Carrot (root vegetables) Application rate: 229 kg MITC/ha. (*) No. of applications: 1/year Time of application (month or season): 30 Sept to 31 Oct Incorporation (cm): 25 cm for PRZM (CAM4), default for MACRO Corn salad (leafy vegetables) Application rate: 172 kg MITC/ha. (*) No. of applications: 1/year Time of application (month or season): 1 Feb to 3 Mar for R2, R3, R4 (all 1st applications). 1 April to 1 May for D4 as well as D3 and R1 (both first applications). 1 June to 1 July for D6 as well as D3, R1, R2, R3, R4 (all second applications) Incorporation (cm): 15 cm for PRZM (CAM4), default for MACRO Tomatoes (fruiting vegetables) Application rate: 344 kg MITC/ha. (*) No. of applications: 1/year Time of application (month or season): 1 March to 31 March Incorporation (cm): 15 cm for PRZM (CAM5), default for MACRO * : The dose rate of MITC is based on 100% conversion from metam-sodium and a molecular weight conversion of 73.11/129.19.

Appendix 1 – list of end points

Main routes of entry	Run-off, drainage

Data gap identified during the peer review for new calculations with adequate input parameters

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	Metam-sodium Not required , since the a.s. itself is subject to rapid degradation (laboratory DT_{50}'s ranged from 4 - 23 minutes) and is not expected to reach groundwater MITC For FOCUS gw modelling, values used – Modelling using FOCUS model(s), with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model(s) used: PEARL 3.3.3 Scenarios : Chateaudun, Hamburg, Jokioinen, Kremsmunster, Porto, Sevilla, Thiva, Piacenza Crop: carrot, cabbage (surrogate for corn salad), tomato Molecular Mass (g mol^{-1}): 73.11 Vapour Pressure (Pa): 1739 at 20ºC Aqueous Solubility (mg/L):8940 at 20ºC Soil Adsorption Coefficient (mean K_{oc}) (ml/g): 36 (Kom = 21) Freundlich Exponent ($^{1}/_{n}$): 1.07 Arithmetic mean $DT_{50\ laboratory}$ (days): 2.15 at 20ºC and pF2 Plant Uptake Coefficient: 0
Application rate	Carrot Application rate: 229 kg MITC/ha. No. of applications: 1/year Time of application (month or season): 1 Oct (or 16 Oct after harvest of carrots at Porto) for PEARL Incorporation (cm): 25 Cabbage (surrogate for corn salad) Application rate: 172 kg MITC/ha. No. of applications: 1/year Time of application (month or season): 10 day before 2nd (or only) crop transplant Incorporation (cm): 15 Tomato

Appendix 1 – list of end points

	Application rate: 344 kg MITC/ha. No. of applications: 1/year Time of application (month or season): 10 March Incorporation (cm): 15

PEC(gw) - FOCUS modelling results (80^{th} percentile annual average concentration at 1m)
Data gap for calculation with adequate input parameters identified during the peer review.

Data gap for the calculation of potential ground water contamination by relevant impurity DMTU

PEC$_{(gw)}$ From lysimeter / field studies

Parent	1^{st} year	2^{nd} year	3^{rd} year
Annual average (µg/L)	Not available	Not available	Not available

MITC	1^{st} year	2^{nd} year	3^{rd} year
Annual average (µg/L)	Not available	Not available	Not available

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	Not required
Photochemical oxidative degradation in air ‡	DT_{50} of metam 1.997 hours based on 24h-day derived by the Atkinson model (version v1.90). OH concentration assumed = 1.5 x10^6 OH/cm³ DT_{50} of MITC = 78.6 days based on 12 h-day derived by the Atkinson model (version v1.92). OH concentration assumed = 1.5 x10^6 OH/cm³
Volatilisation ‡	from plant surfaces (BBA guideline): not available
	from soil surfaces (BBA guideline): not avaialble
Metabolites	MITC

PEC (air)

Method of calculation	Based on monitoring results

Appendix 1 – list of end points

PEC(a)

Maximum concentration	MITC air concentrations are proposed for the operator/worker/ bystander exposure risk assessment. These concentrations have not been peer reviewed by fate and behavior experts.

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil: metam-sodium, MITC Surface Water: MITC Sediment: MITC Ground water: MITC Air: MITC

Residue definition for monitoring

	Soil: MITC Surface Water: MITC Sediment: MITC Ground water: MITC Air: MITC

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	Not required
Surface water (indicate location and type of study)	Not required
Ground water (indicate location and type of study)	The Netherlands, around 1990-1995. In shallow groundwater, 2-3 samples out of 126 were in the range 0.1-2.5 µg MITC/L. All other samples were below 0.1 µg MITC/L. In the deeper groundwater, MITC was one of the compounds that was analyzed by drinking water companies in the period 1992-1995, but not detected Germany, in 1985-1986. MITC was analyzed in the program, but not found

	in any of the sampling points.
Air (indicate location and type of study)	See table below

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

R53 (by default, No acceptable study; new study required)

Appendix 1 – list of end points

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	End point (mg/kg b.w./day)	End point (mg/kg feed)
Birds ‡				
Colinus virginianus	metam-sodium	Acute	LD_{50} = 211	-
Colinus virginianus	metam-sodium	Short-term	LC_{50} > 448	> 5000
Anas platyrhynchos	metam-sodium	Short-term	LC_{50} > 324	> 5000
Mammals ‡				
rat	metam-sodium	Acute	LD_{50} = 896	-
	MITC	Acute	LD_{50} = 147	-
rat	metam-sodium	Long-term	NOAEL = 1.5	-
	MITC	Long-term	NOAEL = 0.44	-
Additional higher tier studies ‡				
Not required.				

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Metam-sodium is a soil fumigant, formulated as an aqueous solution. Metam-sodium is rapidly degraded into Methylisothiocyanate (MITC), which is active on living organisms present in the soil at the time of the application.

The intended uses of metam-sodium are :

- carrot : 1 x 408 kg a.s./ha, field, soil injection + incorporation at 25 cm by rotavation
- corn salad : 1 x 306 kg a.s./ha, field, soil injection + incorporation at 15 cm by rotavation
- cucumber : 1 x 459 kg a.s./ha, greenhouse, drip-irrigation on the planting row
- eggplant/aubergine : 1 x 612 kg a.s./ha, greenhouse, drip-irrigation on the planting row
- pepper : 1 x 612 kg a.s./ha, greenhouse, drip-irrigation on the planting row
- potato : 1 x 153 kg a.s./ha, field, soil injection + incorporation at 25 cm by rotavation
- strawberry : 1 x 612 kg a.s./ha, field, drip-irrigation under a plastic film on the planting row
- tomato : 1 x 612 kg a.s./ha, greenhouse, drip-irrigation on the planting row
- tomato : 1 x 612 kg a.s./ha, field, soil injection at 5 cm + coverage by 10 cm of soil
- grape : 1 x 1020 kg a.s./ha, field, soil injection at 40 cm at the site of the de-rooted vine (0.2 L/m²)

The application of metam-sodium is on bare soil; the product is incorporated into the soil (soil injection or drip irrigation) and thereafter the soil is compressed with a roller. After a waiting period of 2 to 4 weeks, the soil is cultivated to allow the non-mineralised gasses to disperse.
Member States experts at PRAPeR 53 discussed the risk assessment for the birds and mammals exposed to metam-sodium and to the main metabolite (MITC). Experts suggest that the most probable contaminated food items for birds and mammals would be the soil invertebrates (included earthworms). The experts agreed that an acute risk assessment for insectivorous birds and mammals

should be provided, even if the soil invertebrates were expected to be killed. A data gap was identified for the applicant to conduct an acute risk assessment to assess the effects of metam-sodium and its metabolite MITC to terrestrial vertebrates feeding on soil invertebrates.

Member States experts agreed that acute risk assessment was necessary for the metabolite MITC for mammals. Experts agreed that lowest endpoint could be used in the risk assessment in accordance with previous assessment of active substance with common metabolite, unless scientific reasons suggest not do it. Otherwise RMS should provided a risk assessment for the metabolite MITC using the lower endpoint of 100 mg / kg bw obtained from a mouse oral toxicity study in the dazomet DAR. New data gap was identified by EFSA for the submission of a new risk assessment for MITC to mammals based on the agreed endpoint of 100 mg/ kg bw.

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Laboratory tests ‡				
Fish				
Lepomis macrochirus	metam-sodium	96 h (static)	Mortality, LC_{50}	> 0.175 mg a.s./L (measured at 96 h)
Oncorhynchus mykiss	Vapam	96 h (static)	Mortality, LC_{50}	0.24 mg form/L (0.078 mg a.s./L) (nom)
Lepomis macrochirus	Vapam	96 h (static)	Mortality, LC_{50}	1.19 mg form/L (0.389 mg a.s./L) (nom)
Cyprinodon variegatus	Vapam	96 h (static)	Mortality, LC_{50}	1.3 mg form/L (0.425 mg a.s./L) (nom)
Striped *Majatis*	Vapam	96 h (static)	Mortality, LC_{50}	1.5 mg form/L (0.491 mg a.s./L) (nom)
Oncorhynchus mykiss	MITC	96 h (semi-static)	Mortality, LC_{50}	**0.0531 mg/L** (mm)
Oncorhynchus mykiss	MITC	96 h (flow-through)	Mortality, LC_{50}	0.094 mg/L (mm)
Lepomis macrochirus	MITC	96 h (flow-through)	Mortality, LC_{50}	0.142 mg/L (mm)
Oncorhynchus mykiss	MITC	28 d (flow-through)	Growth NOEC	0.004 mg/L (mm)

Appendix 1 – list of end points

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Aquatic invertebrate				
Daphnia magna	Metam-Fluid 510 g/L	48 h (static)	Mortality, EC_{50}	2.34 mg form/L (0.99 mg a.s./L) (nom)
Daphnia magna	MITC	48 h (semi-static)	Mortality, EC_{50}	**0.076 mg/L** (mm)
Daphnia magna	MITC	21 d (semi-static)	Reproduction, NOEC	0.00625 mg/L (nom)
Sediment dwelling organisms				
Not required. The assessment of the risk to sediment dwelling organisms is not justified since the properties of MITC (low Koc, high solubility in water) exclude exposure of the sediment organisms. Moreover, a low level of MITC was observed transiently in the sediment phase of the w/s study (1.5-4.5 % AR in the sediment after 72 h).				
Algae				
Pseudokirchneriella subcapitata	Metam-Sodium 510 g/L	96 h (static)	Biomass: E_bC_{50} (72 h) Growth rate: E_rC_{50} (72 h)	0.556 mg a.s./L 1.08 mg a.s./L (initially measured)
Pseudokirchneriella subcapitata	MITC	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	**0.28 mg/L** 0.58 mg/L (initially measured)
Anabaena flos-aquae	MITC	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	2.12 mg/L 3.72 mg/L (initially measured)
Higher plant				
Lemna gibba	MITC	7 d (semi-static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	**0.59 mg/L** 1.18 mg/L (mean measured initial)
Microcosm or mesocosm tests				
Not required. An acceptable risk of metam-sodium and its metabolite MITC has been proven for the intended uses with a no-spray zone of 20 m.				

Appendix 1 – list of end points

[1] indicate whether based on nominal ($_{nom}$) or mean measured concentrations ($_{mm}$). In the case of preparations indicate whether end points are presented as units of preparation or a.s.

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

The indoor uses pose no concern for surface water contamination. (e.g. cucumber, eggplant/aubergine, pepper and tomato) whilst the outdoor uses on strawberries occur under a plastic film, thus also preventing connectivity between soil and run-off water. Therefore no MITC contamination of surface water bodies via run-off is possible for this use. The uses on grapes are as a spot treatment and are very localized. Hence the overall application rate (for instance over an entire hectare) will be much lower than the application rate stated by m².

As already mentioned in the section on fate and behaviour, the PEC_{SW} values should be used with precaution. The FOCUS sw models were not developed with soil fumigants in mind. The models do not properly consider the volatilisation of MITC and therefore highly overestimate the actual surface water contamination.

EFSA: the risk assessment of MITC to the aquatic organisms should be addressed when the new PECsw values would be available.

Bioconcentration				
	metam-sodium	MITC	Metabolite 2	Metabolite 3
$\log P_{O/W}$	- 2.91	1.05	-	-
Bioconcentration factor (BCF)[1] ‡	Not required.			
Annex VI Trigger for the bioconcentration factor	-	-	-	-
Clearance time (days) (CT_{50})	-	-	-	-
(CT_{90})	-	-	-	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	-	-	-	-

[1] only required if log $P_{O/W}$ >3.

* based on total ^{14}C or on specific compounds

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Hazard quotients for honey bees (Annex IIIA, point 10.4)

The application of metam-sodium is on bare soil; the product is incorporated into the soil (soil injection or drip irrigation) and thereafter the soil is compressed with a roller. After a waiting period

of 2 to 4 weeks, the soil is cultivated to allow the non-mineralised gasses to disperse. Since the product is phytotoxic, it is advisable to perform a germination test (Cress-test) on samples of soils collected from the treated field, before planting.
There is no direct spraying on plant material. The germination test proofs that there is no concern of residues of metam-sodium or MITC in the planted crops. Therefore, bees are not at risk in-field and off-field since they are not exposed to contaminated crops or weeds. Bees are not exposed to the uses in greenhouse.
In conclusion, the risk of metam-sodium and its metabolite MITC to bees is acceptable for the intended uses.

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Laboratory tests with standard sensitive species

Not required.

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (kg a.s./ha)[1,2]	End point	% effect[3]	Trigger value
Aleochara bilineata	adults	Metam-Sodium 507 g a.s./L, aged field soil, 28 d	608.4 kg a.s./ha, aged for 55 days	Reproduction	14.6 %	50 %

[1] indicate whether initial or aged residues
[2] for preparations indicate whether dose is expressed in units of a.s. or preparation
[3] indicate if positive percentages relate to adverse effects or not

effect on reproduction : negative values : adverse effects; positive values : no adverse effects

Field or semi-field tests
Required. The risk of metam-sodium and its metabolite MITC should be addressed in terms of recovery in the field. An extended laboratory study is only able to assess the potential for recolonisation, but not actual recovery. Therefore, a semi-field or field study should demonstrate that the field can be recolonised with non-target arthropods from the border stripes (off-field). In this new study, several species should be tested (*Aleochara bilineata*, *Pardosa*, *Folsomia candida*, *Hypoaspis aculeifer*, …).

Appendix 1 – list of end points

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point[1]
Earthworms			
An earthworm field study (Lührs U., 2002) was performed with the formulation Metam-Sodium 507 g a.s./L.			
Other soil macro-organisms			
Required. The risk of metam-sodium and its metabolite MITC should be addressed in terms of recovery in the field. An extended laboratory study is only able to assess the potential for recolonisation, but not the actual recovery. Therefore, a semi-field or field study should demonstrate that the field can be recolonised with Collembola from the border stripes (off-field) or underlying soil layers (in-field). This new field study can be integrated with the requested semi-field or field study for the non-target arthropods.			
Soil micro-organisms			
A soil microflora laboratory test (Reis K.H., 2002) was conducted with soil samples from the earthworm field study with application rates of 300 and 1200 L Metam-Sodium/ha (equivalent to 152.1 and 608.4 kg a.s./ha). The effects of metam-sodium and its metabolite MITC on nitrogen and carbon transformation were transient and the processes were not drastically impaired.			
Field studies[2]			

Appendix 1 – list of end points

Test organism	Test substance	Time scale	End point[1]
An earthworm field study (Lührs U., 2002) was conducted from May 31, 2001 until May 22, 2002. The assessment of the effects of metam-sodium and its metabolite MITC should be done in comparison with the agricultural control only (same soil cultivation). One year after treatment of 300 and 1200 L Metam-Sodium/ha (equivalent to 152.1 and 608.4 kg a.s./ha), the earthworm abundance was 103.5 % and 85.2 % respectively of the agricultural control. The earthworm biomass was 123.7 % and 85.8 % one year after application of 300 and 1200 L Metam-Sodium/ha (equivalent to 152.1 and 608.4 kg a.s./ha) respectively. Amongst the collected earthworms, the most abundant species was *Aporrectodea caliginosa*. $4^{1/2}$ months after treatment with 300 and 1200 L Metam-Sodium/ha (equivalent to 152.1 and 608.4 kg a.s./ha), the abundance of *Aporrectodea caliginosa* was comparable to that in the agricultural control. The abundance of juvenile earthworms one year after application of 300 L Metam-Sodium/ha (equivalent to 152.1 kg a.s./ha) was comparable to the agricultural control, whereas at 1200 L Metam-Sodium/ha (equivalent to 608.4 kg a.s./ha) it was still statistically significantly lower. In conclusion, one year after application of 152.1 kg a.s./ha, the earthworm population in the field has recovered. One year after application of 608.4 kg a.s./ha, there is a clear indication of an almost completed process of recovery. **EFSA: The experts agreed that after the application of the 608.4 kg a.s./ha, there was no clear indications of the full recovery of earthworms after one year, therefore, some uncertainties of recovery in the field area still remained. A data gap was identified to the applicant to address concerns rest on the recovery/recolonisation of earthworms.**			

[1] indicate where end point has been corrected due to log Pow >2.0 (e.g. LC_{50corr})
[2] litter bag, field arthropod studies not included at 8.3.2/10.5 above, and earthworm field studies

Toxicity/exposure ratios for soil organisms

The application of metam-sodium is on bare soil; the product is incorporated into the soil (soil injection or drip irrigation) and thereafter the soil is compressed with a roller. After a waiting period of 2 to 4 weeks, the soil is cultivated to allow the non-mineralised gasses to disperse. Since the product is phytotoxic, it is advisable to perform a germination test (Cress-test) on samples of soils collected from the treated field, before planting.

The experts agreed that after the application of the 608.4 kg a.s./ha, there was no clear indications of the full recovery of earthworms after one year, therefore, some uncertainties of recovery in the field area still remained. A data gap was identified to the applicant to address concerns rest on the recovery/recolonisation of earthworms.
Risk to metam and its metabolite should be addressed in terms of recovery in the field. RMS suggests that a semi-field or field study should demonstrate the recolonisation of the fields
The expert at the PRAPeR 53 agreed to propose a data gap for the applicant to provide a semi-field or field study to address the recovery potential of soil non-target macro-organisms.
EFSA noted while drafting the conclusion that there was some concern about the risk of metam-sodium to earthworm in the glasshouse uses. EFSA considers, for permanent glasshouse the risk was

Appendix 1 – list of end points

considered low but for temporary glasshouse tunnels that included natural soil (non-artificial substrate) member states might wish to ask for further data to clarification the risk to earthworms.

Appendix 1 – list of end points

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

The application of metam-sodium is on bare soil; the product is incorporated into the soil (soil injection or drip irrigation) and thereafter the soil is compressed with a roller. The mode of application excludes the off-field exposure.
In conclusion, the risk of metam-sodium and its metabolite MITC to non-target terrestrial plants is acceptable for the intended uses.

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	Endpoint
Activated sludge	EC_{50} (3 hours) = 4.36 mg a.s./L

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

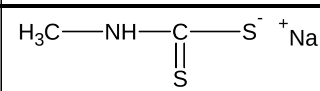
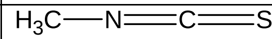
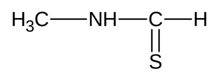
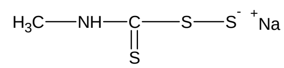
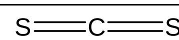
Compartment	
soil	metam-sodium, MITC
water	MITC
sediment	MITC
groundwater	MITC

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance	metam-sodium : N, R50
Metabolite	MITC : N, R50

	RMS/peer review proposal
Preparation	Not required. The formulated product is equivalent to the active substance.

Appendix 1 – list of end points

Code/Trivial name	Chemical name	Structural formula
Metam-sodium	sodium N-methyldithiocarbamate	
MITC	Methylisothiocyanate	
MIC	Methylisocyanate	$H_3C–N=C=O$
	N-methylthioformamide	
MCDT	sodium methylcarbamo(dithioperoxo)thioate	
	Carbon disulphide	
	methylamine	H_3C-NH_2

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
G	glasshouse
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient

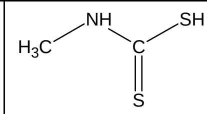
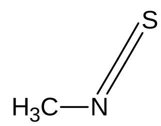
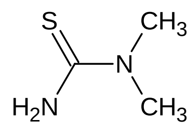
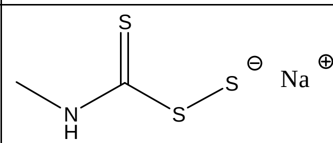
Appendix 2 – abbreviations used in the list of endpoints

kg	kilogram
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
pH	pH-value
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between n-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet

Appendix 2 – abbreviations used in the list of endpoints

WHO	World Health Organisation
WG	water dispersible granule
yr	year

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
MDTA	Methyldithiocarbamic acid, i.e metam	
MITC	methyl isothiocyanate	
DMTU Dimethyl thiourea	N,N'-dimethylthiourea	
MCDT	Sodium methylcarbamo(dithioperoxo)thioate	
DMU	dimethylurea