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Substitution of tin catalyst in antifouling paint

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1. Foreword

The project “Substitution of tin catalysts in antifouling paint” was funded by the Danish Environmental Protection Agency’s program ‘MUDP’ and was carried out during the period from October 2017 to March 2019. The aim of the project was to develop a new silicone coating for antifouling paints without the need for tin catalysts.

This report describes the motivation for the project, the applied methodology, and the results achieved during the project. An introduction to the field is provided in chapter 3, while chapter 4 introduces the methods applied in the project. Hempel has already developed a tin-free solution, and an in-depth health and environmental investigation of cross linkers in this system is given in chapter 5. In addition to the solution analysed in chapter 5, the project team has been working on the development of a long-term solution. The main technical conclusions from this work are described in chapter 6, while chapters 7 and 8 provide more detailed descriptions and health and environmental considerations of these systems. Appendix 1 gives a list of abbreviations, and Appendix 2-4 report additional technical data.

The project was carried out in an interdisciplinary collaboration between Hempel A/S, Danish Technological Institute (DTI) and DHI. The project team consisted of Stefan M. Olsen, Maria Mikolajczak and Kim F. Sørensen (Hempel), Poul Bo Larsen and Henriette Christiansen (DHI), Søren S. Donau, and Lars H. Jepsen (DTI), where Lars was undertaking the project management. The project has been followed and approved first by Sidsel Dyekjær and subsequently by Maria T. Jensen on behalf of the Danish Environmental Protection Agency (EPA).

2. Conclusion and summary

This project deals with the substitution of tin-based catalysts in silicone antifouling coatings for marine vessel applications. During the past 10 years, Hempel has improved the environmental impact of their coatings significantly by developing new silicone-based topcoats. The development is ongoing, and Hempel is continuing to improve their products. Today, small amounts of tin-based catalysts (~0.5 wt%) are used to cure the silicone polymer network in the industrial antifouling products, and Hempel wants to phase out these small amounts completely.

One approach to tin-free curing involves the use of self-catalytic silane cross linkers, e.g. oxime-based cross linkers. The by-products of these cross linkers, for example 2-pentanone oxime, have been examined in depth with respect to their health and environmental profile. In short, the 2-pentanone oxime has a milder classification than butanone oxime, has no restrictions and is not found being in focus for further investigation or assessment by regulatory bodies, neither in the EU nor in the USA. This result is of high value as it allows Hempel to continue product development and commercialization along this track with components that have good performance and a minor impact on the environment.

The main focus in the project has been on the technical and chemical product development aiming at a 'long-term solution', i.e. a product that can remain compliant on the market until after 2030. Many technical learnings have been achieved in the project: areas that previously were considered the 'black box' have now become a 'tool box'. Thus, thanks to this project, today Hempel has the required knowledge to develop and formulate long-term sustainable solutions. Some of the main conclusions are listed below:

- Simple 1:1 substitution of tin-based catalysts is not possible.
- When developing the top-coat, it is also necessary to develop the underlying tiecoat to ensure adhesion under various conditions (temperatures and humidities).
- The inhibitor acetylacetone that is used today is registered under REACH as toxic by inhalation and in contact with skin. It may be substituted with ethyl acetoacetate which is a better alternative. The substance is not listed in Annex VI to CLP but has been registered under REACH as "Not classified". Ethyl acetoacetate gives rise to similar inhibition as acetylacetone, but approx. 3 times the amount is required as compared to acetylacetone.
- The most effective way to allow alternative catalysts (or to avoid the need for catalysts completely) is to select alternative cross linkers, as the curing speed is mainly determined by the cross linker. Several factors determine the reactivity of the cross linkers. The two main factors are:
  a) The pK_a value of the leaving group: Lower pK_a value (more acidic) leads to higher reactivity.
  b) The fourth substituent on the silanol cross linker plays a great role for the reactivity and both activating and deactivating substituents have been determined. No clear trend has been observed, but electron donation/attraction and steric hindrance are important factors.

Based on this project, Hempel believes that it is possible to obtain a solution that has superior performance and superior environmental profile. The important learnings are considered to be 'handles' or 'tools' that will guide Hempel in the ongoing development of solutions for antifouling application.

3. Introduction

Hempel is a global leading paint manufacturer of, among others, silicone-based antifouling paints for maritime vessels. Antifouling paints are used on maritime vessels to reduce the growth of algae and barnacles on the ship hull below water. The growth of underwater micro-organisms increases the vessel's water resistance, which leads to an increased consumption of fuel and has a great financial and environmental impact on the shipping industry.

Today, a conventional self-polishing paint is mainly used which emits biocides into the water environment. An alternative is the usage of silicone-paint with a lower environmental impact, which also prevents the growth of microorganisms.

In silicone-paints, small amounts (~0.5 %) of tin-based catalysts are added to ensure a sufficiently fast curing. Hempel aims at substituting these small amounts of catalysts due to primarily health, safety and environmental (HSE) concerns for paint applicators. Hence, the aim of this project is to phase out the usage of tin catalysts in silicone paints. Two strategies have been followed in the project focusing on a current tin-free solution and long-term solutions.

The main aim of this project has been to develop a new coating that would work as a long-term solution with a superior health/environmental profile. Additionally, the components in the current tin-free coating have been investigated in detail regarding health/environment to ensure that Hempel would develop a substitution into a better solution from a health/environmental perspective.

3.1 Technical introduction

In short, Hempel's antifouling coatings consist of 3 layers: a primer layer, a tie coat and a topcoat, see Figure 1. The primer ensures anticorrosion of the metal surface, the tie coat is bridging the primer and the topcoat, whereas the topcoat ensures the desired coating properties, e.g. antifouling properties.

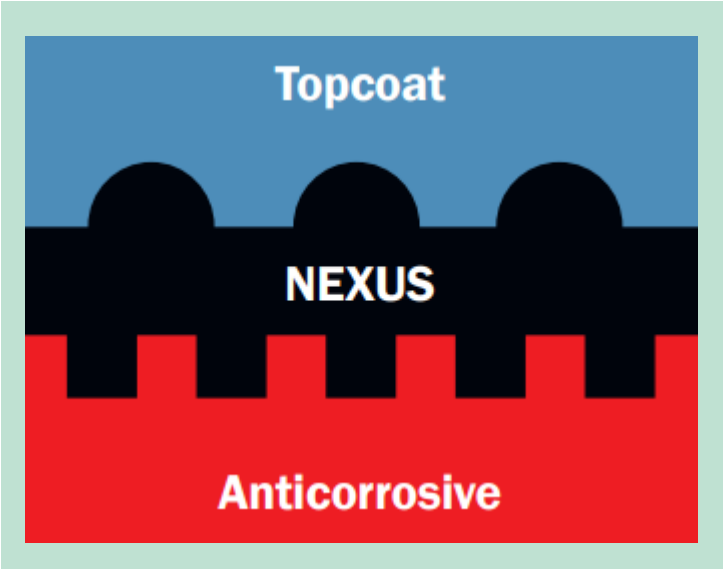


FIGURE 1 Schematic representation of a typical fouling release coating system, consisting of anticorrosive system towards the substrate and tie coat for facilitating adhesion of the silicone based topcoat.

The topcoat is the focus of this project and the main component in the topcoat is a silicone polymer, hydroxy-functionalized polydimethylsiloxane (PDMS-OH). To form the cured topcoat, PDMS reacts with a cross linker, and the reactions are today catalysed by a tin-based catalysator, see Figure 2. To control that the reaction takes place when applied on the hull surface and not in the paint container, an inhibitor may be added. Today, the inhibitor acetyl acetone is used which inhibits the tin-catalysts in the container but evaporates when applied.

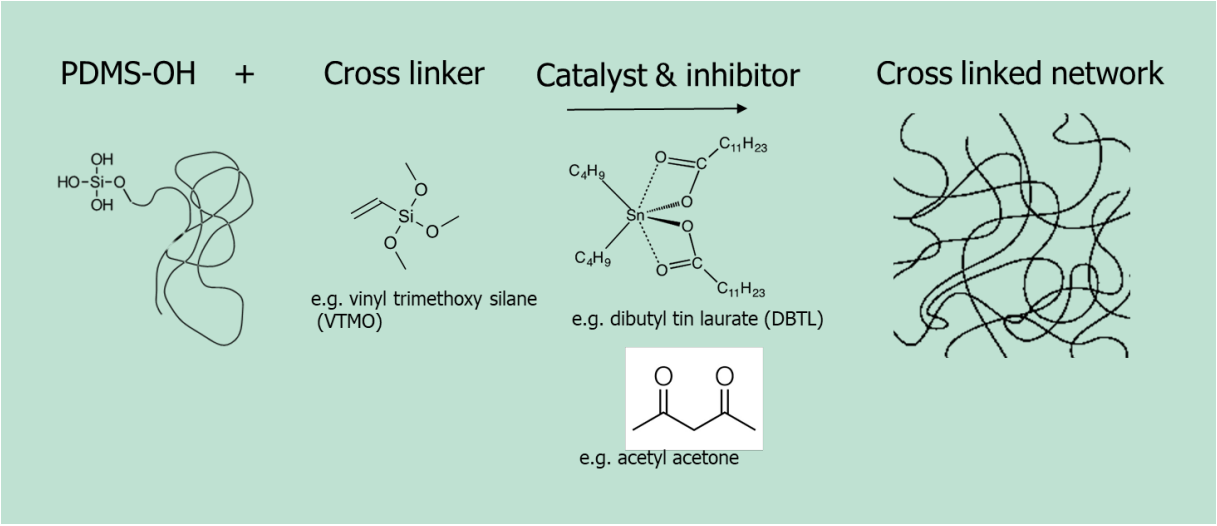


FIGURE 2 An illustration of the reaction scheme that takes place to form a cross linked silicone polymer network in the topcoat.

This reaction must cure within few hours when applied, and at the same time have a pot life of around one hour (pot life = be stable in container). Here, the challenge is to develop a topcoat that cures fast, but not *too* fast.

To substitute the tin catalyst, two approaches have been described:

a) Select and test other cross linkers.
b) Select and test other catalysts.

Practically, this is carried out by preparing new formulations, and subsequently testing their properties. The technical properties are tested via a “test-funnel”, see Figure 3, where the tests in the upper part of the funnel are the most critical and the least time-consuming.

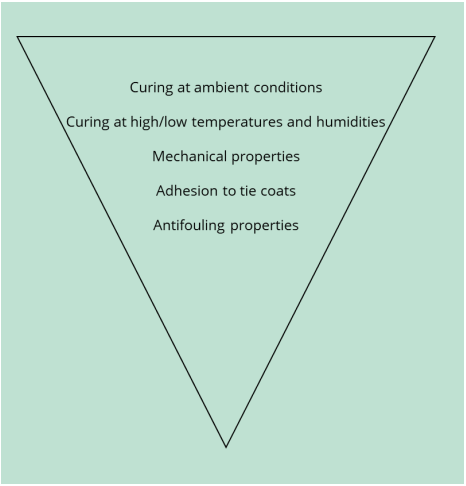


FIGURE 3 Illustration of the ‘test funnel’ used in the project.
A detailed description of all methods applied in this project is provided in the next chapter.

4. Methods

4.1 Application of coatings

The coatings in this project are mainly produced from an already finished base product. This way, all the coating properties normally needed such as coloration, thixotropy and reinforcement are already present. In some cases, the only changes carried out are replacing the cross linker only, as this is sometimes beneficial to evaluate, for instance miscibility, viscosity etc. The base is mixed with the curing agent, either as a mixture of all components or as single components, and then everything is stirred by hand in a small cup to a homogenous consistency.
The coatings are applied to a given flat substrate using a bar-type applicator. The applicator gap can then be varied to achieve the desired wet film thickness of the coating. Usually, a clearance in the range of 200-500 µm is used, as this typically will give a coating thickness in the range of 100-300 µm dry film.

4.2 Curing time and potlife

4.2.1 Curing time

In this project, the curing time measurements are one of the main characteristics for finding the best solution for tin substitution. The coating film is considered as cured, when it achieves a certain hardness, no markings are left when it is touched or when pressure is applied. Knowledge of curing time is important when developing the coating and for further applications. Curing time is needed to specify minimum overcoating interval, and when coating/coated area is fully cured and ready to be used.

FIGURE 4 A picture of the instrument used to measure the drying time.

A commonly used method for measuring drying and curing times for coatings is the Beck Koller method (BK method). In the BK method, a coating is applied on the strip panel with specific wet film thickness. The panel is set on the BK recorder where a special needle is set on the surface of the coating and which moves with the time set to 6, 12 or 24 hours (see Figure 4). There are 4 stages of the drying/curing process in BK method:
I – Set to touch; II – Tack-free; III – Dry-hard; IV – Dry-through

BK I: the coating is no longer liquid, and the needle starts to leave a line in the film; BKII: the needle leaves a clear marking, BKIII is when the needle starts to lift up and leave a broken marking , and the last stage where the needle does not leave any markings.
Generally, BKIII is used as the recorded result. Because silicone coatings form soft films, this method is not straightforward, in comparison to e.g. epoxy coatings. Therefore, for silicone, BKIII is often the same as BKIV as needle does not leave any light markings, especially in short curing times. On the other hand, the needle may stop leaving the marking of BKIII, but the film could still be not cured. The BK IV might also vary greatly from sample to sample tested, and the test should thus always be performed together with a reference coating.
An issue which often happens when using this method is the curing of very thin layers. When the coating is applied, the applicator leaves a very thin coating film on the edges. These often tend to be not cured, even if the normal layer coating is cured.

4.2.2 Pot life

Along with curing, pot life time is a basic parameter of a 2-component coating and is defined as the time where the coating can be successfully applied.
The methods for assessing the pot life are:

- Visual assessment: where the flow of the coating is assessed. This includes also noting down if the skin formation occurs on top of the mixed product, while the underlaying coating is still liquid.
- Application assessment: the coating is good as long as it can be well applied.
- Viscosity measurements: this method must be used together with application assessment to know the highest acceptable viscosity.

4.3 Adhesion test

topcoatTopcoating adhesion to its substrate is very important. The coatings must have a service life that lasts many years, and the adhesion must be present from the start to finish of service life.
Adhesion is tested and assessed on a scale from 0 to 5, with 0 being no adhesion and the ability to peel the silicone coating entirely from its substrate in one big piece, and 5 being perfect adhesion where some of the coating is left on the substrate when removed mechanically by scratching through the soft coating towards the substrate.
When the coating has grade 5, the adhesive strength exceeds the cohesive strength of the coating. Grade 4 is given when the coating has good adhesion, but the cohesive strength slightly exceeds the adhesive strength. This will be visible when scratching through the coating, and seeing the substrate exposed without any coating remaining on the substrate.
Grade 3 is given when it looks like grade 4 when scratching the coating it, but it is possible to rub the coating off the substrate with some force. Grades 2 and 1 are used to grade poor adhesion to no adhesion at all. Anything below grade 4-5 adhesion is not acceptable in any case.
The adhesion can be tested as part of other stress tests, e.g. during the time of a blister box test.

4.4 Mechanical properties

Silicone (PDMS) is a soft elastic material, and the topcoat main constituent is the PDMS binder. Therefore, the coating will always be soft and elastic, and it is complicated to define clearly the mechanical properties important to such coating. The two main properties that are assessed are: scratch resistance and tear strength. But also, properties like elasticity and general surface feel are possible parameters to look for. It is rather complicated to measure all these parameters, except tear strength. However, the uncertainty of tear strength measurements is problematic, and quite many repetitions are necessary for proper datasets, which is

thus very time-consuming. As a result, the mechanical properties are not quantified, but evaluated through experience in working with these types of coatings. Where necessary, the evaluation results are included in this report in the form of written explanations.

4.5 Blister box test – continuous condensation

The blister box test can be used to evaluate the following relevant failures of the silicone coatings: blistering, mechanical properties, adhesion and gloss retention. Water vapour is generated by heating water at the bottom of the test chamber. The test panels form the roof or walls of the chamber, so that the rear sides of the panels are exposed to the cooling effects of room temperature in the surrounding laboratory environment. The resulting heat transfer causes vapour to condense on the test panels as liquid water.
The test temperature and the room temperature control the amount and temperature of the condensate forming on the specimens. The test panels are inclined so that condensate runs off the test surface by gravity and is replaced by fresh condensate in a continuous process. Panels are exposed at an angle of 15°±5°. With the coated panel surface exposed to 38±2°C, saturated water vapour at an angle of 15° to the horizontal and the reverse side of the panel exposed to room temperature (23±2°C), a temperature gradient through the panel of approx. 5°C is obtained, when using a steel panel of 3 to 5 mm in thickness. Steel panels, 75 x 150 x 3 mm panels, are preferred.

4.6 Antifouling test

An acrylic test panel (150x200 mm), sandblasted on one side to facilitate adhesion of the coating, is coated with 100 µm dry film thickness (DFT) of a tie coat (HEMPASIL 27310) applied by airless spraying. After 16-30 hours of drying at room temperature, the topcoat composition is applied by a bar applicator of 400 µm clearance. The panels are dried for at least 72 hours before immersion on the raft.
In this test, the panels are immersed in seawater at a depth of at least 30 cm and at an average temperature in the range 29-31°C in Singapore or 17-18°C in the Mediterranean, Spain. Every 8 or 12 weeks, panels are inspected, and the antifouling performance is evaluated. Coverage of fouling is categorized according to types: “animals and long algae”, “short algae” and “slime”. An antifouling performance index is used to grade the performance, considering that animals are worse than slime. The performance is graded on a scale from 0 to 100, with 100 being fouling free. Also, visual appearance is stored in the form of pictures.

4.7 Raman spectroscopy

Raman spectroscopy is a strong tool for analysing surfaces and interfaces as these can be mapped in relation to the precedence of specific compounds. Such mappings can therefore show the presence of one compound in another compound matrix. Consequently, this can be used to characterize the distribution of the cross linker in the topcoat as well as the penetration of the cross linker into the tie coat.

4.8 Health and environmental evaluation of components

To obtain data for the assessment of specific chemical substances, initial reduced web-based data searches on the substances was performed from a series of relevant web-sites: European Chemicals Agency (ECHA), other national websites (e.g. US EPA, NICNAS Australia, BAUA Germany), toxicological databases such as the PubChem database and the TOXNET database covering 15 databases including TOXLINE. The search was supplemented with Google search using the substance CAS numbers.

For 3 specified chemicals described in chapter 5, these data were further supplemented by Quantitative Structure-Activity Relationship (QSAR) data on the substances. Here, predictions from the Danish QSAR database were used as this database is recommended by ECHA. As the database further makes predictions for each human health endpoint with up to three different recognized QSAR models, this enables predictions with high reliability.

5. Health and environmental evaluation of oxime-based cross linkers

Various oxime silanes may be used in the coating formulation, see Figure 5.

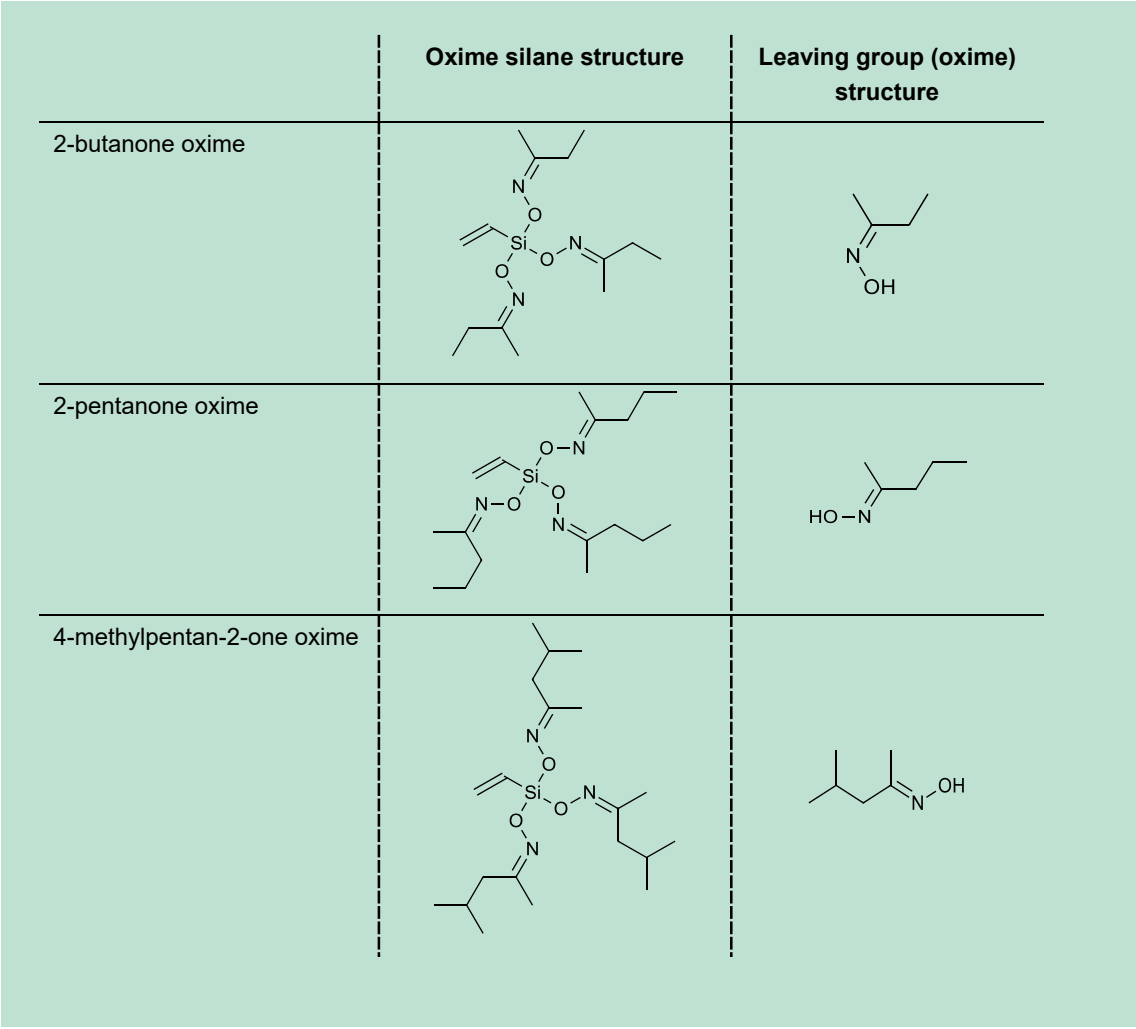


FIGURE 5 Structure of the cross linkers and the corresponding leaving groups in selected oxime-based cross linkers.

To ensure that the oxime silane with the best toxicological profile is selected, cross linkers with three different leaving groups were evaluated:

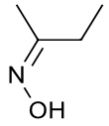
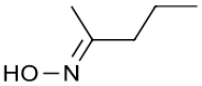
2-butanone oxime, CAS No.: 96-29-7;
2-pentanone oxime, CAS No.: 623-40-5;
4-methylpentan-2-one oxime, CAS No.: 105-44-2

The evaluation was conducted to describe the toxicological profile of the substances, i.e. which type of toxicological effects are relevant for the substances in relation to relevant exposure routes (oral, dermal or inhalation exposure) and at which exposure levels. Also, the aim was to compare the toxicological similarities and differences between the substances as this may provide a basis for identifying the least toxic substance among the leaving groups. A full report with data and analysis is found in Appendix 2.

5.1 Results

The toxicological data from the web-based search and the data from the QSAR predictions were analysed and conclusions could be made based on the data on butanone oxime and 2-pentanone oxime as for these substances most knowledge/data could be gathered, see Table 1. For 4-methylpentan-2-one oxime only QSAR data was found.

Table 1 Comparison of the toxicological potential of butanone oxime and 2-petanone oxime

	butanone oxime	**2-pentanone oxime**	**Comments**
CAS No	96-29-7	623-40-5	
Chemical formula	C_4H_9NO	$C_5H_{11}NO$	
Chemical structure			
Classification	*Currently:* Acute Tox. 4 H312 **Skin Sens. 1 H317** **Eye Dam. 1 H318** **Carc. 2 H351** *Proposed in ECHA:* Acute Tox. 3 H301 Acute Tox. 4 H312 **Skin Sens. 1B H317** **Eye Dam. 1 H318** **Carc. 1B H35**0 STOT SE 3 H336	Acute Tox. 4 H302; Eye Irrit. 2 H319; STOT RE2 H373 (blood and spleen) Aquatic Chronic 3 H412	Most restrictive classification for butanone oxime (**in bold**) compared to 2-pentanone oxime
Acute toxicity, oral	LD50, rats: 930-1620 mg/kg LD50, rabbits: < 160 mg/kg	LD50, rats: 1133 mg/kg (not tested in rabbits)	Similar toxicity
Acute toxicity, inhalation	LC50, rats > 10.5 mg/L (8h)	LC50, rats > 1.224 mg/L	No mortality for any of the substances
Acute toxicity, dermal	LD50, rabbits: 1848 mg/kg	No data	
Skin irritation	No/ mild irritation in rabbits	No/ mild irritation in rabbits	Similar toxicity
Eye irritation/ damage	Conjunctival **necrosis** in rabbits	Eye Irritation in rabbits	Butanone oxime having most severe effect

Skin sensitization	**Positive** in GPMT and Buehler test	**Negative** in LLNA and Buehler test	2-pentanone oxime not a skin sensitiser
Repeated dose toxicity, oral	28-day study rats: LOAEL 20 mg/kg bw/day anaemia effects on spleen. NOAEL: 4 mg/kg bw/day 90-day study, rats: LOAEL: 10 mg/kg bw/day (anaemia and neuro-behavioural effects)	28-day study rats: LOAEL: 50 mg/kg bw/day anaemia and effects on spleen NOAEL: 15 mg/kg bw/day	Similar toxicity
Repeated dose toxicity, inhalation	28-day study, rats: LOAEC 360 mg/m^3 anaemia **NOAEC: 90 mg/m^3** Chronic carc. study: LOAEC: 54 mg/m^3 (anaemia and effects on nasal epithelium)	28-day study, rats: NOAEC 1240 mg/m^3 90-day study, rats: **NOAEC 1249 mg/m^3** Slight effects on blood and relative organ weight observed at highest tested concentration. Considered as non-adverse by the registrant.	**Significant lower inhalation toxicity** of 2-pentanone oxime compared to butanone oxime (about a factor 14)
Genotoxicity	Sufficiently tested: Overall negative	Sufficiently tested: Overall negative	Both negative
Cancer	Malignant and benign tumours in both rats and mice by inhalation.	No data	Carcinogenic potential of butanone oxime.
Reproductive toxicity	No effects on fertility or development in two-generation study and in developmental toxicity studies.	No effects on fertility or development in OECD 422 screening test.	No concern for effects on fertility and development for any of the substances

In relation to the following hazard endpoints, the two substances (butanone oxime and 2-pentanone oxime) seems very comparable:

- *Acute toxicity (about same oral LD50 values in rats)*
- *Skin irritation (no / mild irritation)*
- *Genotoxicity/ mutagenicity (no concern)*
- *Reproductive toxicity, (no concern).*

With respect to *local eye effects,* butanone oxime has an eye damaging potential, whereas 2-pentanone oxime is only an eye irritant, indicating more severe effect of butanone oxime.

For *skin sensitisation,* butanone oxime was tested positive, while 2-pentanone oxime was tested negative. Here, a rapid hydrolysis of butanone oxime into 2-butanone and hydroxylamine may contribute to this, as hydroxylamine is skin sensitising. 2-petanone oxime has been shown to be stable towards hydrolysis.

From *repeated oral dose toxicity studies* (exposure period of 28 and 90 days) in experimental animals*,* a very similar pattern of toxicological effects was observed as both substances produced anaemia and effects on the spleen at comparable dose levels. The lowest exposure levels for causing toxicity for butanone oxime and for 2-petanone oxime have been determined to 10 mg/kg bw/day and 50 mg/kg bw/day, respectively.

For *repeated inhalation toxicity,* a very large difference exists between these two substances. Butanone oxime causes the same type of systemic effects as for oral exposure and in addition

induces effects in the nasal epithelium of rats and mice. The lowest exposure level for toxicity of 54 mg/m^3 was found for these effects for butanone oxime. For 2-pentanone oxime, on the other hand, a *no effect level* of 1249 mg/m^3 was achieved in a 90-day inhalation study in rats, i.e. no sign of toxicity was observed in this study.

There are no data that can explain why 2-pentanone oxime is far less toxic by inhalation compared to oral exposure or compared inhalation exposure to butanone oxime. It is unclear whether high stability towards hydrolysis and therefore no generation of hydroxylamine in the respiratory tract may play a role.

Carcinogenicity studies (chronic exposure for 2 years) are only available from butanone oxime, where inhalation exposure studies produced benign and malignant tumours primarily located in the liver of rats and mice.

Since no toxic effects at all occurred in the 90-day inhalation study with 2-pentanone oxime at a dose level of 1249 mg/m^3, it seems very unlikely that the substance would be carcinogenic by inhalation under an extended exposure period for up to 2 years.

Although no long-term oral studies have been conducted, 2-butanon oxime may be considered having a carcinogenic potential also by the oral exposure route, as other toxic effects on the target organs are very comparable as seen in the studies with repeated oral and inhalation exposure. Furthermore, the toxicological effects from oral exposure to butanone oxime are very comparable to the toxicological effects from oral exposure to 2-pentanone oxime. There may also be some concern for carcinogenic effects from 2-pentanone oxime in relation to oral exposure, although no specific data can document this.

Currently, 2-pentanone oxime is not found to be in focus for further investigation or assessment by regulatory bodies. In the EU, no initiatives have been taken by ECHA regarding the substance as to the CLP or REACH regulation. In the USA, neither U.S. EPA nor the U.S. Department of Health and Human Services (leading the National Toxicology Program that prioritizes and conducts cancer testing of chemicals in the U.S.) indicate any initiatives or prioritizations of the substance.

5.2 Conclusions

When comparing the cross linker, from which butanone oxime is a leaving group, with the cross linker, from which 2-petanone oxime is a leaving agent, the latter may be considered of less concern in relation to potential health risks in the working environment. This can be concluded for various reasons:

- *2-pentanone oxime is an eye irritant whereas butanone oxime may cause irreversible eye damage.*
- *2-pentanone oxime is not a skin sensitiser whereas butanone oxime is a skin sensitiser.*
- *2-pentanone has a lower vapour pressure than butanone oxime, and thus lower occupational levels would be expected.*
- *Furthermore, 2-pentanone oxime is considered being of significantly less toxicological concern by inhalation compared to inhalation of vapours from butanone oxime.*
- *As a non-genotoxic substance, the lack of toxicity by inhalation at high exposure level of 2-petanone oxime also indicates a lack of any carcinogenic potential by inhalation.*

As indicated above, a carcinogenic potential for 2-pentanone oxime by oral exposure route cannot be ruled out. As neither butanone oxime nor 2-petanone oxime have any genotoxic potential, a carcinogenic mode of action is considered as having a threshold level. For such non-genotoxic carcinogens, the induction of tumours is typically driven by sustained toxicity towards the target organs, and consequence is the development of tumours. Thus, if toxicity in the organs is avoided, then the carcinogenic potential is avoided as well. By keeping the exposure below the threshold for any sign of toxicity, there is no concern for carcinogenic effects.

For *4-methylpentan-2-one oxime* as a leaving group, no conclusions can be made based on specific experimental data on the substance or the data from the QSAR predictions. The toxicity often decreases with the increasing molecular size within a homologue group of chemicals, as the data on butanone oxime and 2-pentanone oxime also indicate. Although it could be tempting to conclude that *4-methylpentan-2-one oxime* would be even less toxic than 2-pentanone oxime, this would require further data to substantiate such a conclusion.

6. Technical results for a long-term solution

Chapter 6 focuses on the potential long-term solutions for replacing tin as a catalyst. Chapter 6 gives a summary of the technical conclusions, and shows a selection of the results from the experimental work performed during the project period.

A list of abbreviations is included in Appendix 1. Unless stated otherwise, the numbers given for formulations in the tables are indicated in grams of the given components.

6.1 Cross linker

To develop a long-term catalyst-free solution, it is necessary to understand the impact of the choice of the cross linker and catalyst. The crosslinker cures the coating by reacting with the polymers, resulting in a *cross-linked* network forming the final hardened coating. Conclusively, the first reactive group of the crosslinker only increases the molecular weight (MW) of the polymer by its own mass, whereas the second and third reaction initiates cross-linking and network formation. Conclusively, the reactivity of each individual functionality of the crosslinker has a direct impact on the curing rate or curing time, which in this project was primarily followed by measuring the drying time using the BK method as described previously in this report. Controlling the curing rate of the cross linker was primarily performed applying three approaches (see Figure 6):

- Choice of leaving group on the cross linker.
- Choice of "*activating functionality*" on the cross linker.
- Choice of size and numbers of functionalities on the cross linker.

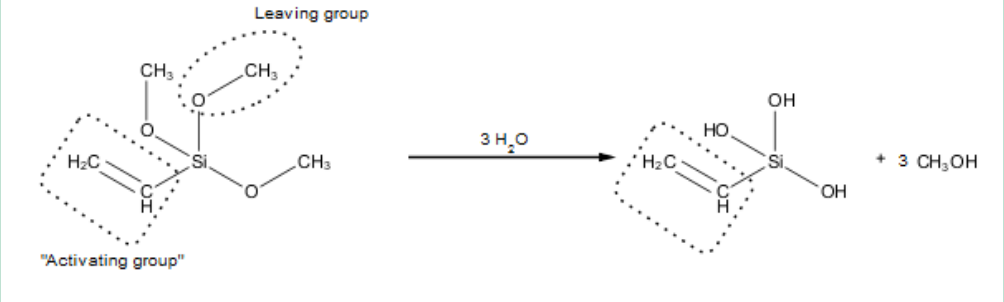


FIGURE 6 Illustration of the leaving group and the "*activation functionality*"

6.1.1 Impact of the leaving groups

Cross-linking from silanes involves two steps: an initial hydrolysis of the alkoxy silanes followed by a condensation, see Figure 6.

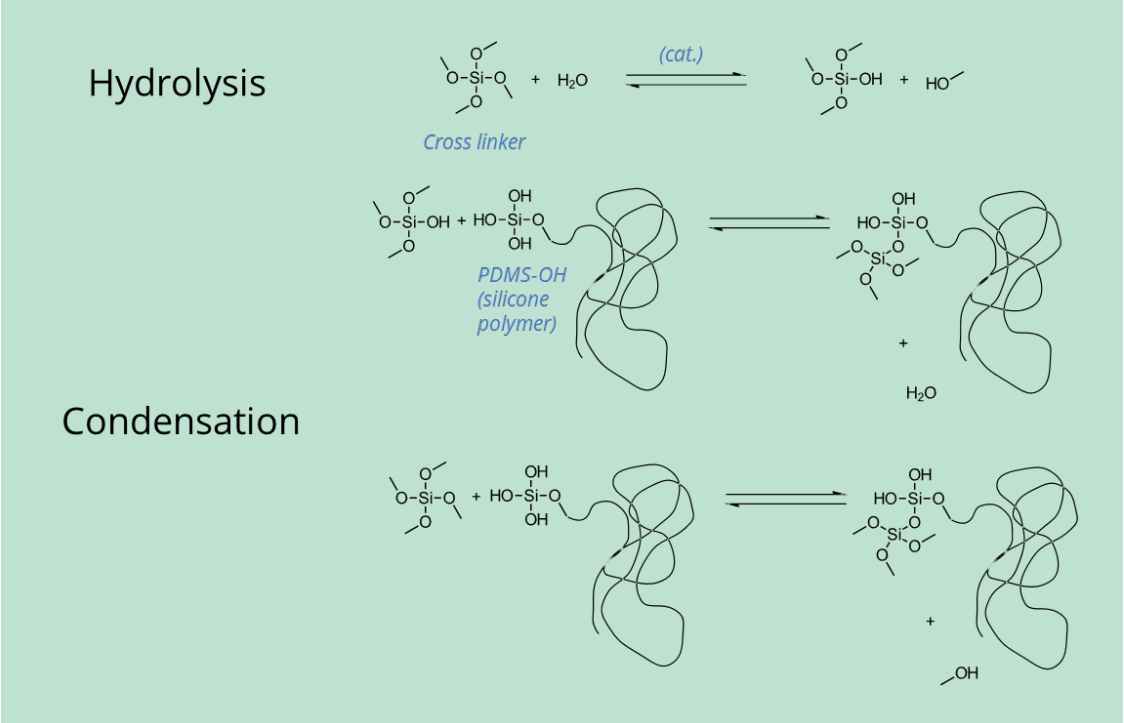


FIGURE 6 Illustration of the two reaction mechanisms taking place when forming a cross-linked silicone network, i.e. hydrolysis and condensation.

If the initial hydrolysis is the rate-limiting step with respect to the curing time, increasing the rate of hydrolysis will result in faster curing times. Consequently, better leaving groups will lower the activation energy for the hydrolysis and eventually increase the rate of the initial hydrolysis, thus decreasing the need for a catalyst.
General, pK_a values (acidity) is a good measure for the capability as leaving groups; the lower the pK_a (less basic), the better the leaving group. Often used cross linkers are based on methoxysilane or ethoxysilanes. The leaving groups of these-methoxide and ethoxide- are both strong bases with pK_a values of 15.5 and 15.9, respectively, making them relatively slow leaving groups, which requires catalysts to achieve sufficiently low curing times.

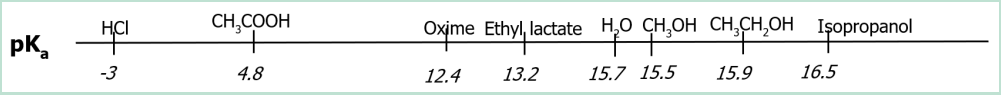


FIGURE 7 pK_a values for selected compounds

The curing rates of +10 cross-linkers with different leavinggroups were tested. A good correlation between the reactivity and pK_a-values of the leaving group was found, see Table 2.

Table 2 Curing times and pK_a values of leaving groups for selected cross linkers

Cross linker	Corresponding leaving group	pK_a of leaving group	Curing time at ambient conditions
Chloro silane	HCl	-3	Very fast (explosive)
Acetoxy silane	CH3COOH	4.8	<30 min.

Butanone oxime silane	C_4H_9NO	12.4	2-3 hours
Ethoxy silane	CH3CH2OH	15.9	Do not cure

The leaving group itself can also have a catalytic effect on the curing system. For acetoxy functional silanes, the leaving group, being acetic acid, has a catalytic effect on its own by making the entire system acidic.

A range of different tests were performed on glass substrate, using methyltriacetoxy (MTAC) and vinyltriacetoxy (VTAC) silanes to cure the base component. The temperature and humidity has been varied to try to map the response on curing properties, see Table 3.

Table 3 Curing times (BK3) for MTAC and VTAC at different conditions on glass substrate.

	Base material	MTAC	VTAC	Climate	Cure time (h)	Notes
MTAC	88	5.9		23°C/14%RH	0.5	Fully cured
	88	5.9		24°C/18%RH	0.5	Fully cured
	88	5		25°C/27%RH	0.5	Fully cured
	88	5		25°C/34%RH	0.5	Fully cured
	88	5.9		10°C/55%RH	no cure	sticky film
	88	5.9		5°C/60%RH	no cure	sticky film
	88	5.9		5°C/95%RH	no cure	sticky film
VTAC	88		5.9	24°C/18%RH	3	matt, long to BK4
	88		5	25°C/27%RH	1.5	sticky after cure
	88		5	25°C/34%RH	2	sticky after cure
	88		5	25°C/35%RH	0.75	not sticky
	88		5.9	10°C/55%RH	no cure	sticky film
	88		5.9	5°C/60%RH	no cure	sticky film

MTAC generally cures to a satisfactory coating film at room temperature and low humidity. It gives predictable cure speed, with repetitive tests showing the same results. This is, however, not the case for VTAC. Four different experiments with same or very similar formulation, at room temperature and low humidity, give varying results in curing time. In one out of the four experiments, it cured to a satisfactory film.

At low temperature and high humidity, neither MTAC or VTAC cured properly in any of the performed experiment.

When it comes to pot life, the VTAC indicates problems. Its skin-over time is as short as 15 min. at room temperature and low humidity. Under these conditions, thin coating film typically does not cure. In the mixing cup, the thin layer on the sides (which will have similar thickness as the drawdown) cures to a proper non-sticky film for VTAC. It is suspected that this is due to a very fast hydrolysis rate. If it is a thin film in open air, all the acetic acid is quickly hydrolysed off the silane and can evaporate freely, whereas, the atmosphere inside the mixing cup will be saturated by acetic acid from the bulk in the bottom of the cup. With the acetic acid released too fast in a drawdown, it will not be able to cure to a fully cured film.

The MTAC has much better pot life properties compared to VTAC. However, the pot life still relatively short: 30-45 min. at room temperature and low humidity. If the relative humidity is low, it seems to have a suitable hydrolysis rate, since it can cure to a non-sticky film. When the

relative humidity is higher, it starts behaving in the same manner as the VTAC. Again, it is suspected that this is caused by a too fast hydrolysis rate, and consequently the acetic acid will evaporate.

6.1.2 Activation functionality

Popular crosslinkers are tetra methoxy or ethoxy silanes, Compound **1** in Figure 8. Eventually, tri alkoxy versions of these compounds are used instead, where the fourth alkoxy group has been replaced by a non-leaving group (typically a vinyl), Compound **2** in Figure 8. Even though these tri alkoxy silanes have one less "cross-linking" capability compared to its tetra alkoxy derivative (**1**), they have enhanced curing properties.

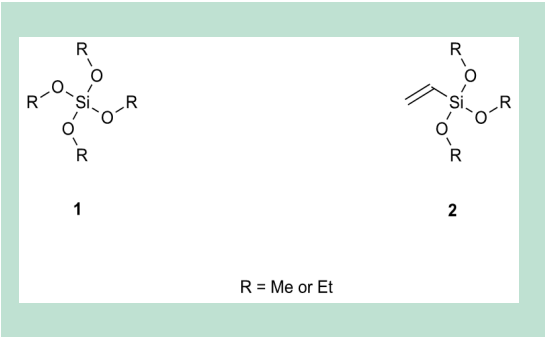


FIGURE 8 Illustration of typical cross linkers, where compound **2** has a vinyl group as "activation group".

Exchanging one of the leaving groups with a non-leaving substitute ("*fourth substituent*") allows finetuning the reactivity of crosslinker. Several properties of the fourth substituent influence the reactivity as mesomericand inductive effects and capability of coordination to the silicon atom. Generally, it was found that for methoxy-silanes, the amount of catalyst required for acceptable curing rates were lower for the vinyl- and significantly lower for methyl butanoate silane derivative compared to the methyl silane derivative, see Figure 9.

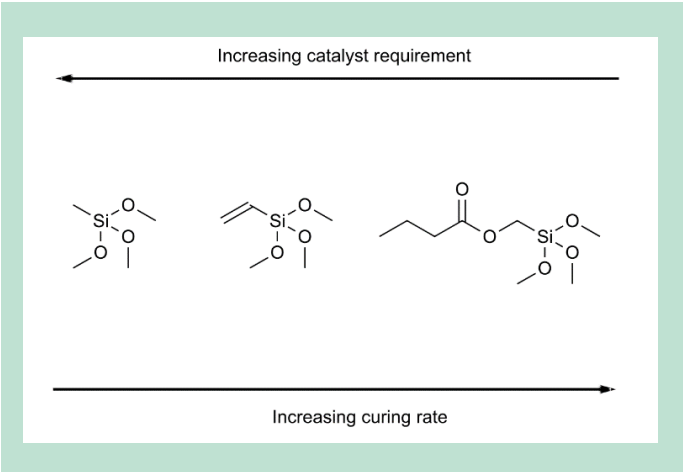


FIGURE 9 Changing the "*activation group*" on the fourth position has an impact on the curing times (e.g. satisfying curing times can be achieved with lower amounts of catalyst)

6.1.2.1 Vinyl functional alkoxy silanes

Vinyl-activated silanes of various kinds were tested against each other to evaluate the curing time (Table 4). The ethoxy functional types, vinyl triethoxy silane (VTEO) and 1,2-Bis(triethoxysilyl)ethylene (Bis-VTEO), were given slightly higher amounts of catalyst, as these are typically less reactive than the methoxy types, vinyl trimethoxy silane (VTMO) and allyl trimethoxy silane (ATMO).

Cure speed was evaluated on glass substrate, and no cure was observed for all but the bis-triethoxy functional SIB1820.0. Surprisingly, VTMO shows no cure with 0.25g of tin-catalyst. On the other hand, Bis-VTEO shows satisfactory cure at 1.75 h and 2.25 h for BK3 and BK4, respectively.

6.1.2.2 Highly activated alkoxy silanes

Higher activity silanes with activating groups in the alpha position require much less catalyst compared to the vinyl activated ones. A test was performed for formulations using methacrylic and acetoxymethyl activated silanes with organotin catalyst. In general, it was found that these types of highly activated silanes needed in the range of 10-15% of the catalyst amount needed to cure a corresponding vinyl activated silane.

These coatings were tested on both glass and tie coat (Table 6). The tie coat slows the curing in all cases. For methacroyloxy trimethoxy silane (XL33) and acetoxymethyl trimethoxy silane (SIA0055.0), thin layers showed cure issues on tie coat but cured on glass. For acetoxymethyl triethoxy silane (SIA0050.0), thin layers did not cure neither on glass or tie coat.

Table 6 Curing time results (h) on glass and tie coat at 22°C/20-25%RH

Silane	XL33		SIA0050.0		SIA0055.0	
	BK3	BK4	BK3	BK4	BK3	BK4
Glass (20%RH)	1	1.5	2.5	3	0.75	1.25
Tie coat (25%RH)	2.25	3.75	6+	N/A	1.25	2.25

6.1.2.3 XL33 – further testing

Coatings cured by XL33 on tie coat and glass were examined by Raman spectroscopy. Among the tested coatings, this analysis proved to be possible for XL33 only, since the significant signal originated from the acrylate part of the silane. However, XL33 has a unique Raman signal from the ester functionality making the Raman map possible.
Surprisingly, it was found that the reason for the inhibited cure on tie coat was due to a high affinity of the XL33 silane towards the tie coat. This tendency was not present on glass, where cure with XL33 performed perfectly. Various attempts to solve the challenge were performed.

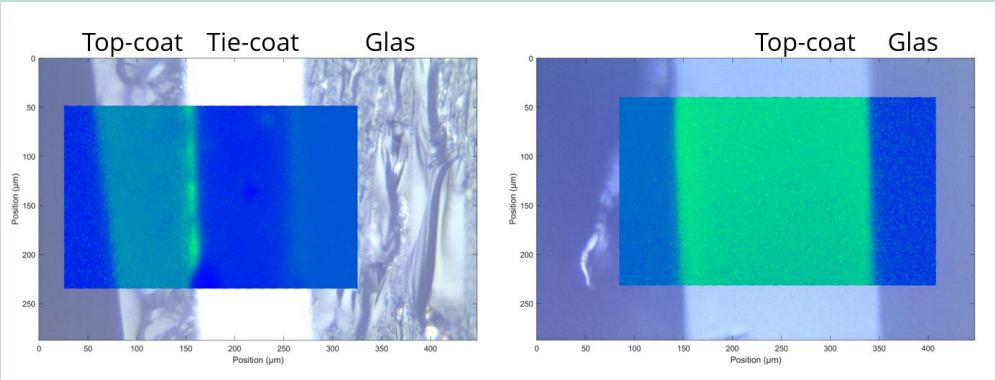


FIGURE 12 Images showing the results of Raman spectroscopy mapping of coating cross sections. The signal from XL33 is in green colour, clearly showing that there is a high concentration at the interface between tie coat and topcoat (left), whereas fully homogeneous distribution is seen through the coating on glass substrate (right)

A test of induction time influence was performed for XL33, since this could be a possible solution to the thin layer issues. By leaving the silane with the silanol PDMS for some time, a pre-reaction of the two could take place.

Tests were performed on a siloxane-epoxy based tie coat and on glass. Evaluation was performed by manually evaluating the properties for a drawdown performed 2, 10 and 25 min. after mixing the components. All showed the same cure tendency irrespective of induction time, with fast cure on glass and slow cure on tie coat.

6.2 Catalysts

As described, the curing rate of silicone highly depends on the leaving group of the cross linker, and not all room temperature vulcanization (RTV) types of silicone require a catalyst. However, high reactivity also involves such impracticalities as stability, safety and short pot life. One way to overcome this is to use a catalyst, enabling the use of otherwise slower reacting cross linkers and achieving proper curing profiles and mechanical properties of the film. Catalysts that are well known for silicone systems are: acids, bases and metallic-based (Sn, Bi, Ti, etc.).
In this project, it is shown that none of the available catalysts have proven to be capable of a direct 1:1 substitution of the organotin catalysts. However, it is shown that it may be possible to develop a high-performance coating by combining new cross linkers and catalysts. Therefore, it is important to have knowhow about environmentally benign catalysts for RTV silicones. In total, more than ten different catalysts have been tested in several different coating formulations and cured under various conditions, both as stand-alone and in combinations.

6.2.1 Alternative organo-metallic catalyst

An example of an alternative catalyst, Zn-cat, comprising a zinc carboxylate complex, was tested with a range of high reactivity alkoxy silanes (Table 17).

The Zn-cat proved to work fine with a range of different curing agents on glass at room temperature and low humidity.

Table 17 Curing time (h) on glass substrate at 24°C/30%RH

	BK3	BK4
SIA0055.0 with 0.03g Zn-cat	1	2
SIA0055.0 with 0.06g Zn-cat	0.5	1
SIA0055.0 with 0.1g Zn-cat	0.33	0.66
SIB1820.0 with 0.3g Zn-cat	0.25	0.5

When tests with similar formulations were performed on tie coat, the substrate influence became obvious, showing a deactivating effect (Table 18). Curing at room temperature is almost fully deactivated by application on a silicone-based tie coat.

Table 18 curing time (h) on silicone tie coat vs glass, 24°C/23%RH

		SIA0055.0 with 0.05g Zn-cat	SIB1820.0 with 0.1g Zn-cat
Glass	BK3	0.75	0.75
	BK4	1.25	1.25
Silicone tie coat	BK3	6h+	6h+
	BK4	very sticky@24h (still slightly sticky after 5 days)	wet@24h (no sign of curing after 5 days)

Also, there seems to be issues at low temperature and high humidity. Formulations, which cures at room temperature on glass, have an extensively prolonged curing time and is unable to cure to a fully cured film. Generally, there are issues with thin layers and the surface tends to stay sticky in most cases.

Table 19 Curing time (h) of Zn-cat with different curing agents, tested at high and low temperature. Performed on glass substrate. Thin layer issues for all low temperature, and no problems at room temperature.

		SIA0050.0	SIA0055.0	SIB1820.0
Zn-cat (wt%)		0.1	0.05	0.2
10°C/ 90%RH	BK3	4.5	4	1.5
	BK4	6h+	6h+	2.5
23°C/ 40%RH	BK3	0.67		0.42
	BK4	1.25		0.75

6.2.2 Inhibitors

A typical downside of fast curing rates is the short pot life. To ensure enough pot life, the added catalyst is subdued by the addition of an inhibitor. Once the coating mixture has been applied, the inhibitor evaporates from the film, reenabling the catalytic behaviour of the catalyst, and the curing takes place. A popular inhibitor for the metal-based catalysts is acetylacetone. However, due to safety reasons, it would be preferable to substitute acetylacetone. During the project, the ethyl acetoacetate was tested as a substitute for the acetylacetone inhibitor and in some systems, this proved possible, though higher concentration was needed to achieve sufficient inhibition.

6.2.2.1 Pot life testing with ethyl acetoacetate

One of Hempel's commercial topcoats, Hempaguard X7 was used to test inhibiting behaviour of ethyl acetoacetate, EAA. Pot life was evaluated by viscosity change within a period of time. When the viscosity is low, the curing is inhibited by the inhibitor. The viscosity change over time is measured for a range of different concentrations of EAA and compared to Hempaguard X7 (see Figure 11). More data is shown in Appendix 2.

As it is seen, in both cases the tendency of viscosity change is similar to standard and does not differ from each other. Within a period of 1.5 hours, EAA containing samples provide almost the same viscosity profile, and after a longer time viscosity increases above standard. The period where viscosity change overlaps is satisfying. It means that EAA in concentration that is 3 times higher than current concentration of standard inhibitor can be used as an alternative.

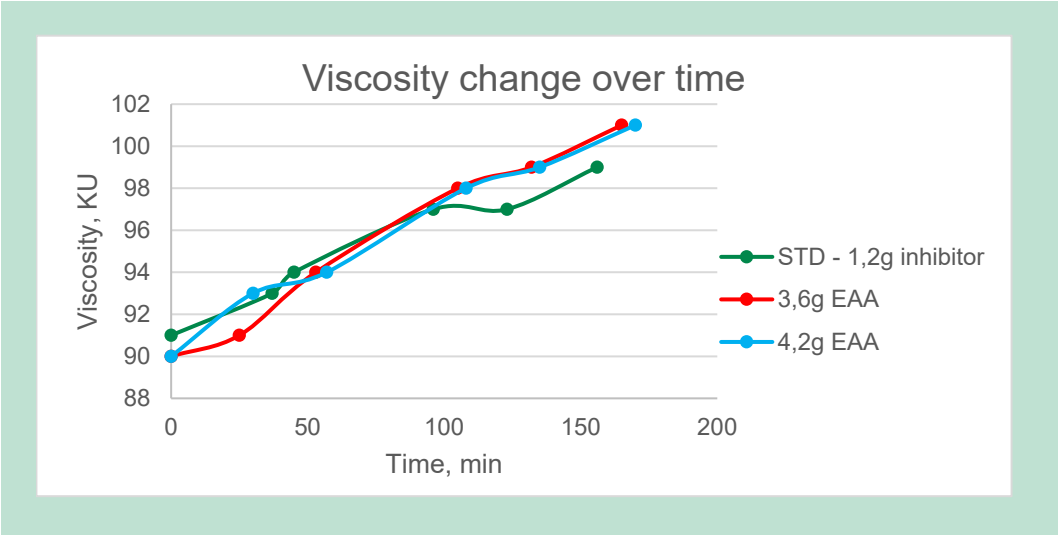


FIGURE 11 Substitution of acetyl acetone with EAA is tested by measuring viscosity changes and compared to a reference sample denoted STD. The data shows that EAA is a viable substitute.

6.2.3 Co-catalysts / adhesion promoters

In general, the type of catalyst was found not only to affect the curing of the film, but also the adhesion of the final film to the substrate, complicating the design of a stable performing RTV silicone coating. One strategy to overcome poor adhesion of the coating is to use two catalysts; one known for its curing properties and one for its adhesion promoting properties. The curing properties were determined by numerous curing experiments on several substrates and under varying conditions.

6.2.3.1 Amine co-catalyst

As an approach to solving the possible curing problems of a highly activated silane, SIA0050.0, a co-catalyst could be added. The effect of adding a series of amines to a tin catalysed system was tested. The selected amines were ethylenediamine (EDA), dibutylamine (DBA) and triethylenediamine (TEDA), which is then representing a primary, a secondary and a tertiary amine. A reference without amine could then be compared to the various types in different concentrations.

Table 15 Content of added amines (in wt %) and corresponding curing times on glass at 22°C/16%RH

	SIA-0050.0	+0.1 EDA	+0.1 TEDA	+0.1 DBA	+0.01 EDA	+0.05 EDA	+1 TEDA
SIA0050.0	6	6	6	6	6	6	6
ethylenediamine		0.1			0.01	0.05	
triethylenediamine			0.1				1
dibutylamine				0.1			
BK3 (h)	3.25	1.5	1.25	1	2	1.25	no cure
BK4 (h)	4	2	1.5	1.25	2.5	1.75	no cure

In all cases, an addition of a small amount of amine gives faster curing of the coatings when comparing to the reference without addition of amine as a co-catalyst. After comparing the addition of EDA in different concentrations (0.01, 0.05 or 0.1 g), the results indicate that an optimum concentration might exist, since fastest cure is observed for 0.05 g. This is further supported by the fact that increasing addition of TEDA from 0.1g to 1g makes a change from

something that cures faster than the reference without amine to something that does not cure at all.

7. Curing systems

This chapter provides a detailed account of technical data and results for some selected curing systems of specific interest. In the project, much more data is obtained, but only selected parts are presented in this chapter. The remaining data is stored at Hempel.

A list of abbreviations is provided in Appendix 1. Unless stated otherwise, the numbers in the tables indicated for formulations of the given components are in grams.

7.1 Bismuth carboxylate catalysed system

Specific curing agent #1 (SCA#1) in combination with bismuth carboxylate catalyst gave promising results. The SCA#1 is relatively high reactivity, so small amounts of a neodecanoic acid bismuth complex catalyst (Bi-cat) gave good curing properties in many conditions.

7.1.1 Initial testing

Initial trial for testing of curing a silicone binder with SCA#1 in presence of Bi-cat was performed, and the results are shown as Figure 13.

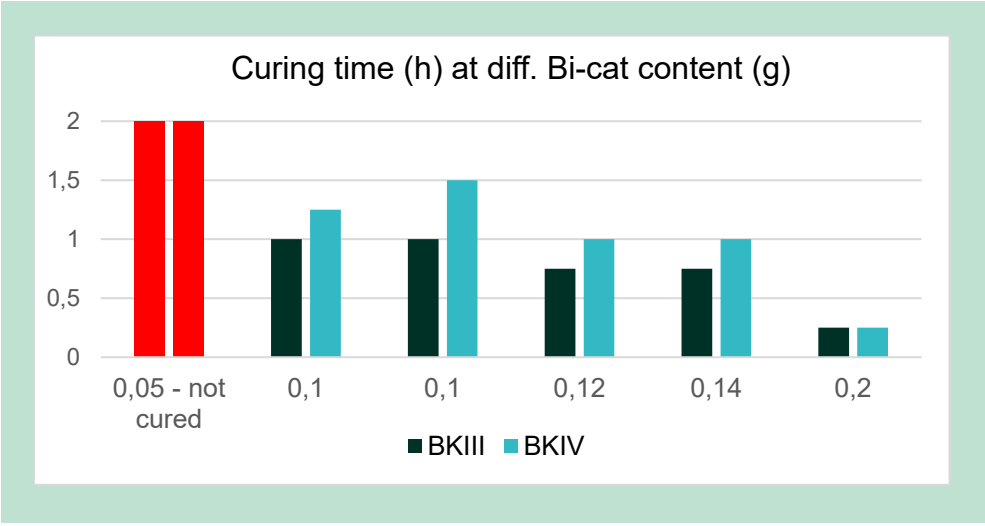


FIGURE 13 Curing time results for silicone binder with SCA#1 and varying amount of Bi-cat on glass substrate

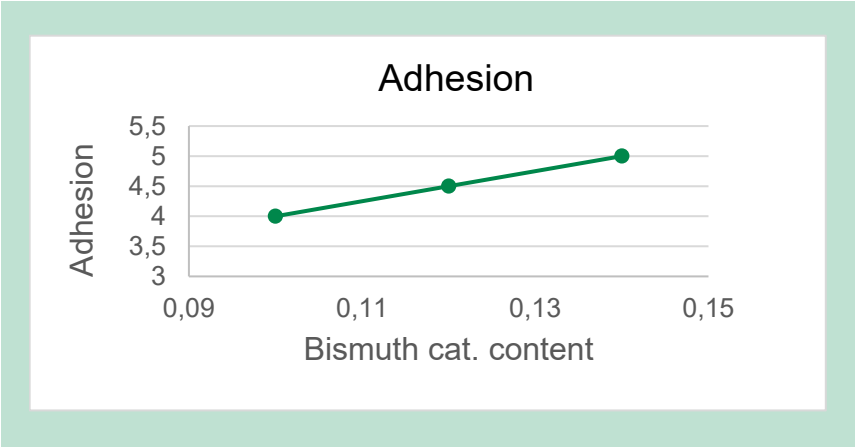


FIGURE 14 Adhesion results on silicone-based tie coat for silicone binder cured with SCA#1 and varying amount of Bi-cat. (0 to 5 scale, with 5 being perfect adhesion)

Curing with 0,2 g of Bi-cat is too fast, while with 0.05g of catalyst, system with SCA#1 is not curing at all. Bi-cat in concentrations of 0.1 to 0.14 is fine with reasonable curing times. The less catalyst needed the better, but tests of adhesion (Figure 14) show that more catalyst improves adhesion. Therefore 0.14g for 6g of SCA#1 can be good combination. However, in the entire range of tested catalyst content pot life is an issue (Table 21).

Table 21 SCA#1 with Bi-cat tested on tie coat. Curing time in lab conditions: 28°C/55%RH

Formula				Curing time, h		Pot life
Base material	**SCA# 1**	**Bi-cat**	**Oil additive**	**on glass**	**on silicone tie coat**	
88	6	0.14	-	1	2,5	less than 1 hour/skin formation seen at 1h
88	6	0.14	3	-	>6	skin after 1 hour

Curing on tie coat is slower than on glass. Addition of generic oil additive commonly used in these coatings caused longer curing time on tie coat. Skin formation within an hour is not satisfactory, therefore addition of inhibitors was tested.

7.1.2 Testing of inhibitors

The inhibitors acetylacetone (AA) and ethyl acetoacetate (EAA) were tested to prolong pot life and prevent a too fast skin formation (Table 22).

Table 22 Curing results with inhibitors and oils, tested at lab. conditions: 28°C/40-55%RH

Formula						Curing time, h	
Base material	**SCA#1**	**Bi-cat**	**AA**	**EAA**	**Oil additive**	**on glass**	**on silicone tie coat**
88	6	0.14	1.5	-	-	1	1,5 (BKIV-1,75)
			3	-	-	1.5*	-
			1.5	-	3	2.5	>6
			1.5	-	1.5	2.5	-
			-	1.5	-	1.5	2.5 (BK IV > 6h)

Addition of inhibitor improved the pot life for all of the above-mentioned formulas. Curing tests were performed in laboratory conditions where humidity varied from day to day. Curing time BKIII is similar regardless the humidity, but formulas cured slower on the silicone-based tie coat. However, films remained sticky, and fingerprints appeared when touched, which may be related to higher humidity. A similar result occurred after adding oil. The formula with AA cures

well; film is not sticky, whereas oil addition causes fingerprints even after a day of curing. On the silicone-based tie coat, the formula with AA did not cure in the presence of oil. Formula with EAA on tie coat was not fully cured, but the test was only performed under higher humidity, and was thus tested further also by adding oil. Higher amount of catalyst gives no pot life but might help curing in higher humidity, so an increased content of catalyst together with an increased amount of inhibitor will be tested later.

7.1.2.1 Testing at low temperature

Initial testing of inhibitor behaviour at low temperature was tested (Table 23).

Table 23 Curing at 10C/60%RH on glass

Formula						Curing time, h
Base material	SCA#1	Bi-cat	AA	EAA	Oil additive	on glass
88	6	0.14	3	-	-	1.75
			1.5	-	1.5	3
			-	1.5	-	1.5
			-	-	-	1.25

All films in the presence of inhibitor leave fingerprints, but are not sticky. No inhibitor in the formula ensures a fully cured film in low temperature, which is why Bi-cat might be deactivated in low temperature.

7.1.2.2 Testing different amounts of Bi-cat and EAA

Testing of various amount of Bi-cat was carried out at a low temperature and high humidity, with reference in laboratory conditions (Table 24).

Table 24 Results for varying amounts of EAA (*-sticky films)

	Formula				Curing time
Conditions	Base material	SCA#1	Bi-cat	EAA	on glass
23C/27%RH	88	6	0.14	1.5	35min
			0.2	1.5	30min
			0.2	3	35min
			0.3	3	20min
5C/95%RH	88	6	0.14	1.5	2h*
			0.2	1.5	1.25h*
			0.2	3	1.5h*
			0.3	3	45min*

Curing at low temperature and high humidity gives a sticky film in the range of 0.14-0.3g catalyst, whereas the systems cure well in room temperature. A double amount of inhibitor per amount of catalyst does not influence the curing time significantly, but pot life is affected significantly by higher concentrations (higher than 0.14g) of catalyst. A higher amount of inhibitor could solve the problem of a short pot life. More tests were performed to see how high humidity can affect the curing when performed at room temperature and low temperature (Table 25). These tests also included the effect of adding oil.

Table 25 Curing time under different climatic conditions

	Formula					Curing time	
Conditions	Base material	SCA#1	Bi-cat	EAA	Oil additive	on glass	Comments
5°C/ 60%RH	88	6	0.14	1.5	-	1.75h	slightly sticky
			0.2		-	1.25h	slightly sticky
			0.2		1.5	2h	slightly sticky
23°C/ 60%RH			0.14		-	45min	
			0.2		-	30min	
			0.2		1.5	45min	
23°C/ 22%RH			0.14			30min	45min ok, later skin
			0.2		-	20min	45min - skin
			0.2		1.5	30min	45min - skin

The system with both concentration levels of Bi-cat cures well at 60%RH and RT as well as in laboratory conditions with or without oil. However, curing at this humidity and at lower temperature equal to 5 °C gives sticky film, even in the absence of oil. Pot life could be improved; therefore, the next step was the addition of more EAA and Bi-cat to achieve both pot life and non-sticky film.

Table 26 Curing of system: 88g base material + 6g SCA#1 with different Bi-cat and EAA concentrations

	Amount, g			Curing time	Comments	Pot life
Conditions	Bi-cat	EAA	Oil additive	on glass		
5°C/60%RH	0.2	1.5	1.5	1.75h	slightly tacky	
	0.2	4.5	1.5	1.75h	slightly tacky	
	0.3	4.5	1.5	1.5h	non-sticky	
	0.3	4.5	-	1h	non-sticky	
	0.3	9	-	1.5h	non-sticky	
22°C/60%RH	0.2	1.5	1.5	40min	slightly sticky	
	0.2	4.5	1.5	45min	slightly sticky	
	0.3	4.5	1.5	30min	slight fingerprints	
	0.3	4.5	-	25min	non-sticky	
	0.3	9	-	30min	non-sticky	
22°C/20%RH	0.2	1.5	1.5	28min	non-sticky	at 1h-skin
	0.2	4.5	1.5	45min	non-sticky	1.5h -OK
	0.3	4.5	1.5	30min	non-sticky	at 1h - skin
	0.3	4.5	-	28min	non-sticky	45min - skin
	0.3	9	-	40min	non-sticky	1.5h - OK

By increasing the catalyst amount to 0.3 g, it provided a well-cured film in RT and low temperature as well as higher humidity (60%RH). The formula with this catalyst concentration and inhibitor amount equal to 9 g or less, but more than 4.5 g due to satisfactory pot life, where no skin formed on the top of the wet paint within an hour will be tested further for adhesion.

7.1.2.3 Testing of adhesion to substrate and curing of model formula

The trials were performed in the laboratory conditions and under higher humidity (85%RH), and both at low and ambient temperature (Table 27).

Table 27 Adhesion and curing results on model SCA#1/Bi cat. formula

Formula tested: **Base material - 88g; SCA#1 - 6g; Bi-cat - 0.3g; EAA - 9g**			
Conditions	**Substrate**	**Curing time**	**Adhesion**
5°C/85%RH	Glass	1.5	N/A
	Silicone tie coat	2	weak adhesion 2-3
	Epoxy tie coat	not cured	gelly, sticky
	Silicone tie coat with amines	not cured	gelly, sticky
25°C/85%RH	Glass	30min	N/A
	Silicone tie coat	45min	weak adhesion 2-3
	Epoxy tie coat	not cured	-
	Silicone tie coat with amines	not cured	-
22°C/33%RH	Glass	50min	N/A
	Silicone tie coat	1	weak adhesion 2-3
	Epoxy tie coat	not cured	-
	Silicone tie coat with amines	not cured	kind of gelly film

The tested formulas cure well at high humidity and both at low and ambient temperature. The issue occurs when curing on tie coat. While it can cure well on a pure silicone tie coat, it cannot cure on neither epoxy-based tie coat nor a silicone-based tie coat with amino silanes. Amines may be involved in the deactivation of the catalyst. Adhesion to the pure silicone tie coat-coat is insufficient, which is why Bi-cat for SCA#1 cross linker is not an optimal solution for being topcoat formula.

7.2 Titanium catalysed system

The curing of silanol functional silicones by alkoxy-functional silanes can be catalysed by adding titanium-based catalysts. This is a well-known system, which can be formulated as both one- and two-component systems. Adding the titanium catalyst directly to a silanol functional PDMS gives a gel-effect when the amount of catalyst gets sufficiently high. This effect can be slightly hindered by adding acetyl acetone to the titanium catalyst before the addition to the silanol-containing base. However, there is still an upper limit to the amount of catalyst that can be added even when inhibited by acetyl acetone. The reactivity of the specific curing agent #2 (SCA#2) is high enough for the amount of catalyst to be kept low enough to avoid having the gelling problem. This would, for instance, not be the case for methyl-trimethoxy silane, where close to the triple amount of catalyst would be necessary when compared to SCA#2.

In general, the coatings cured with SCA#2 and titanium catalysts have poor adhesion to certain types of commercial tie coats. This problem can be solved by adding a separate adhesion promoter. The reactivity of the adhesion promoter under catalysis must be similar to the rest of the curing system, otherwise problems with pot life or delayed/no adhesion would appear.

Several silanes were tested, and a suitable adhesion promoter #1 (SAP#1) was found to have adequate properties. It has a catalytic effect but does not shorten the pot life too much when added in the desired concentration. In addition to solving the adhesion problems, it also significantly improved the mechanical properties of the cured film.

The system with SCA#2 as a curing agent, Titanium ethyl acetoacetate complex as catalyst and SPA#1 as adhesion promoter, was tested more systematically on various substrates (Table 31).

Table 31 Formulations with SCA#2 and titanium catalyst for testing on various substrates.

Panel No.	1	2	3
Base material	88.2	88.2	88.2
SCA#2	8	8	8
Silicone oil additive	2	2	2
Extra solvent	2	1	1
AA	0.5	0.5	0.5
TEAA	0.2	0.2	0.2
SAP#1		1	2

The system without SAP#1 does not give proper adhesion to all the substrates, but it works on all types of tie coats (Table 32) when adding SAP#1. The adhesion is stable after being immersed in tap water for several days.

Table 32 Adhesion results from SCA#2 test with titanium catalyst on various substrates. Numbers refer to a score from 0-5, where 5 is the best.

	Substrate	1	2	3
1-day cure	Glass	5	5	5
	Epoxy siloxane	5	5	5
	Epoxy tie coat	0	4-5	3-4
	Silicone tie coat	0	4-5	5
	Substrate			
4 days in tap water	Glass	5	2-4	5
	Epoxy siloxane	5	5	5
	Epoxy tie coat	0-1	5	5
	Silicone tie coat	0	5	5

Two of the formulations were selected for further testing in blister box. This test will stress the coatings further and accelerate identification of possible issues. Only formulations containing SAP#1 were of interest since the mechanical properties were not satisfactory without the addition of this component (Table 33).

Table 33 Adhesion results from blister box test for SCA#2 with titanium catalyst and SAP#1. Numbers refer to a score from 0-5, where 5 is the best.

Adhesion after curing			Adhesion after blister box test		
Substrate	2	3	Substrate	2	3
Epoxy siloxane	5	5	Epoxy siloxane	5	5
Epoxy tie coat	5	5	Epoxy tie coat	4-5	4-5
Silicone tie coat with amines	5	5	Silicone tie coat with amines	5	5
Silicone tie coat	5	5	Silicone tie coat	5	5

A raft test was performed to check the antifouling properties of the coating cured by SCA#2 (Figure 18). When applied to an epoxy siloxane tie coat as substrate, the adhesion is good, and for a static raft test the mechanical properties of the coating films are satisfactory. It was tested against a commercially available reference, Hempasil X3, and showed a good short-term performance compared to the commercial product.

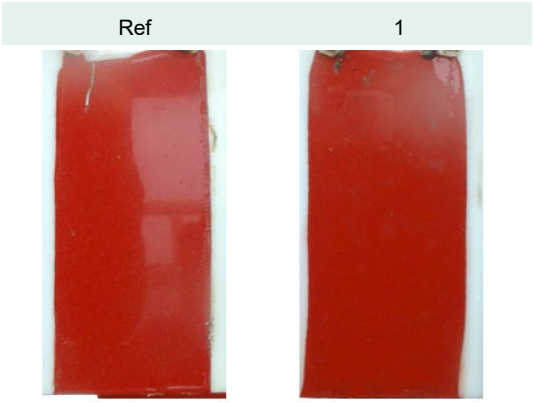


Figure 18 Raft test results for SCA#2 cured coating after 8 weeks in Singapore, showing performance comparable to Hempasil X3 as a commercial reference.

7.3 Pentanone oxime curing agent system

2-Pentanone oxime vinyl silane is already used as a curing agent in Hempel's Silic One coating system for pleasure boats. This curing agent has the advantage of not needing a catalyst to cure. However, these formulations are created as one component, and for this reason are not directly transferrable for use as formulations for professional industrial marine use. In this case, a two-component system would be preferred, which would require some reformulation of the product, and consequently additional testing.

In the project, three different oxime silanes have been considered and used. The size of the leaving group generally seems to have little to no influence on the curing time (Table 37).

Table 37 Curing time results comparing 3 different types of vinyl oximinosilanes with different leaving groups.

	2-pentanone oxime	Methyl-isobutyl oxime	Methyl-ethyl oxime
Silicone binder	60	60	60
Vinyl tri(methyl propyl ketoxime) silane	4		
Vinyl tri(methyl isobutyl ketoxime) silane		4	
Vinyl tri(methyl ethyl ketoxime) silane			4
BKIII (h)	3	2.75	3

Early in the project, a series of panels with 2-pentanone oxime silane cured standard product were sent to the raft for antifouling performance testing. This was done by simply using the already existing base component in combination with a curing agent containing 2-pentanone oxime silane and the additives needed for performance. This formulation is effective with good adhesion to existing tie coats. There are, however, some issues when trying to spray the product on the raft as tested.

The raft test shows very similar performance compared to the standard product as reference. In this particular test, a slightly better performance is observed in Singapore, and slightly worse performance is observed in Spain.

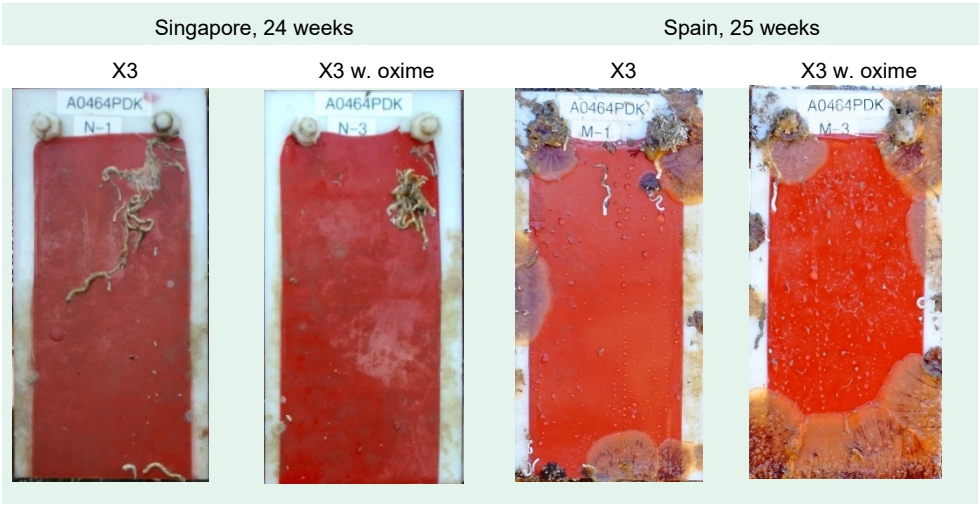


Figure 20 Raft results in Singapore and Spain showing the performance of a 2-pentanone oxime vinyl silane cured coating compared to the commercially available reference.

During this project, the focus has been on trying to solve the problems with the spray properties and in connection to this developing a base component which is suitable in terms of production and storage stability.

8. Health and environmental evaluation of components in long-term solution

The initial health and environmental assessment have been carried out for selected components that may have relevance for the long-term solution. These components are compared with components used commercially today, and the results are described in this chapter.

8.1 Catalysts

Dibutylbis(pentane-2,4-dionato-O,O')tin (DBTL)
Used today in commercial products.
Dibutylbis(pentane-2,4-dionato-O,O')tin, CAS no. 22673-19-4, is not currently listed in Annex VI to the CLP regulation, but the proposed harmonised classification as toxic to reproduction, category 1B and STOT RE1 (inhalation) was adopted by RAC in December 2017 and awaits final approval from the Commission before inclusion in Annex VI. Substances with a classification as toxic to reproduction, category 1A or 1B have the potential to be identified as an SVHC substance.

Tris(pentane-2,4-dionato)iron(II)
Tris(pentane-2,4-dionato)iron(II), CAS no. 14024-18-1, is a better alternative, with a ”milder” classification. The substance is not listed in Annex VI to CLP but has been registered under REACH with a classification as harmful by ingestion, inhalation and in contact with skin and as causing serious eye damage. Currently, there are no restrictions on use in the EU and no proposed harmonised classification.

Bismuth neodecanoate
With regards to Bismuth neodecanoate, no CAS no. was provided, so the data search was performed for CAS no. 34364-26-6. The substance is not listed in Annex VI but is listed in the C&L Inventory with several different classifications including “Not classified”. The non-classification has been submitted under REACH registration. However, other notifications suggest hazards to the environment, which is confirmed in various databases.

8.2 Inhibitors

Acetyl acetone, CAS no. 123-54-6, is used today in commercial products. It is included in Annex VI with a classification as flammable liquid and harmful by ingestion, the latter being a minimum classification that the manufacturers or suppliers must apply unless they have data resulting in a more severe hazard category. The substance has been registered under REACH with a more severe acute toxicity classification: toxic by inhalation and in contact with skin.

Ethyl acetoacetate, CAS no. 141-07-9, is a better alternative. The substance is not listed in Annex VI to CLP but has been registered under REACH as “Not classified”. The substance has been notified to the C&L Inventory with a few classifications, but these are “milder” classifications such as irritant to skin, eyes or the respiratory system. The skin, eye and respiratory irritations are also the data found after searching the TOXNET database. Currently, there are no restrictions on use in the EU and no proposed harmonised classification.

8.3 Cross linkers

Pentanone oxime vinylsilane (CAS-No. 58190-62-8)
Used today in commercial products.
It is not listed in Annex VI but has been registered under REACH with a classification as harmful by ingestion and an eye irritant. Currently, there are no restrictions on use in the EU.

Acetoxymethyltrimethoxysilane
CAS-No.: 65625-39-0 is not listed in the C&L Inventory nor the TOXNET database, but a Safety Data Sheet has been supplied with the classification as flammable liquid and causes serious eye irritation. Silanes may release methanol causing a potential concern with regards to work environment. Currently, there are no restrictions on use in the EU.

1,2-bis(triethoxysilyl)ethylene
CAS-No.: 87061-56-1 is not listed in Annex VI but has been notified to the C&L Inventory with a classification as eye irritant, corresponding to the classification used in the Safety Data Sheet from the current supplier. However, there is one notified classification as toxic by ingestion. Currently, there are no restrictions on use in the EU.

9. Next step

In conclusion, due to the mild evaluation of the leaving group 2-pentanone oxime described in chapter 5, it can be concluded that oxime-based curing is a viable tin-free silicone curing mechanism. The results are highly valuable, and Hempel will continue following the course of this development.

Many important technical learnings have been obtained on the generic catalysis process of condensation-based curing of silicone coatings. All these learnings are considered valuable tools, which Hempel believes will make it possible to develop a long-term solution with a superior environmental profile. Hempel will select the most promising systems and continue the development work after the completion of this project and will continue their work throughout 2019.

Appendix 1

Explanatory list of abbreviations, product codes etc.:

Materials:

MTAC	Methyltriacetoxy silane
VTAC	Vinyltriacetoxy silane
AA	Acetyl acetone
VTEO	Vinyl triethoxy silane
VTMO	Vinyl trimethoxy silane
SIB1820.0	1,2-Bis(triethoxysilyl)ethylene
SIA0540.0	Allyl trimethoxy silane
XL33	Methacroyloxy trimethoxy silane
SIA0050.0	Methylacetoxy triethoxy silane
SIA0055.0	Methacroyloxy trimethoxy silane
EDA	ethylenediamine
TEDA	triethylenediamine
DBA	dibutylamine
Zn-cat	Zinc carboxylate catalyst
EAA	ethyl acetoacetate
SCA#1	Specific curing agent #1
Bi-cat	Bismuth neodecanoic acid catalyst
SCA#2	Specific curing agent #2
TEAA	Titanium ethyl acetoacetate complex
SAP#1	Specific adhesion promoter

Appendix 2

Toxicological assessments of three leaving group substances from antifouling agents

The expert in WATER ENVIRONMENTS

Report
February 2019

This report has been prepared under the DHI Business Management System certified by Bureau Veritas to comply with ISO 9001 (Quality Management)

Approved by

19-02-2019

X Dorthe Nørgaard Andersen

Approved by

Signed by: Dorthe Nørgaard Andersen

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Environment and Toxicology

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Toxicological assessments of three leaving group substances from antifouling agents

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Toxicological assessments of three leaving group substances from antifouling agents

Objective and methodology
Toxicological assessments of the three different leaving groups:

butanone oxime, CAS No.: 96-29-7;
2-pentanone oxime, CAS No.: 623-40-5;
4-methylpentan-2-one oxime, CAS No.: 105-44-2

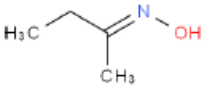
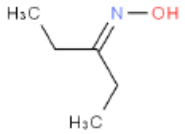
were conducted in order to describe the toxicological profile of the substances, i.e. which type of toxicological effects are relevant for the substances in relation to relevant exposure routes (oral, dermal or inhalation exposure) and at with exposure levels. Also, the aim was to compare the toxicological similarities and differences between the substances as this may provide a basis for identifying the least toxic substance among the leaving groups.

For obtaining data for the assessment web-based data searches for the substances was performed from a series of relevant web-sites: the web site of the European Chemicals Agency (ECHA), other national web sites (e.g. US EPA, NICNAS Australia, BAUA Germany), toxicological databases such as the PubChem database and the TOXNET database covering 15 databases including TOXLINE. The search was supplemented with Google search using the CAS numbers of the substances.

These data were further supplemented by Quantitative Structure-Activity Relationship (QSAR) data on the substances. Here, predictions from the Danish QSAR database were used as this database is recommended by ECHA. As the database further makes predictions for each human health endpoint with up to three different recognised QSAR models this enables predictions with high reliability.

Findings
The toxicological data from the web-based search and the data from the QSAR predictions were analysed and conclusions could be made based on the data on butanone oxime and 2-pentanone oxime as for these substances most knowledge/data could be gathered. For 4-methylpentan-2-one oxime only QSAR data was found.

Comparison of the toxicological potential of butanone oxime and 2-petanone oxime

	butanone oxime	2-pentanone oxime	Comments
CAS No	96-29-7	623-40-5	
Chemical formula	C_4H_9NO	$C_5H_{11}NO$	
Chemical structure			

	butanone oxime	2-pentanone oxime	Comments
Classification	*Currently:* Acute Tox. 4 H312 **Skin Sens. 1 H317** **Eye Dam. 1 H318** **Carc. 2 H351** *Proposed in ECHA:* Acute Tox. 3 H301 Acute Tox. 4 H312 **Skin Sens. 1B H317** **Eye Dam. 1 H318** **Carc. 1B H350** STOT SE 3 H336	Acute Tox. 4 H302; Eye Irrit. 2 H319; STOT RE2 H373 (blood and spleen) Aquatic Chronic 3 H412	Most restrictive classification for butanone oxime (**in bold**) compared to 2-pentanone oxime
Acute toxicity, oral	LD50, rats: 930-1620 mg/kg LD50, rabbits: < 160 mg/kg	LD50, rats: 1133 mg/kg(not tested in rabbits)	Similar toxicity
Acute toxicity, inhalation	LC50, rats > 10.5 mg/L (8h)	LC50, rats > 1.224 mg/L	No mortality for any of the substances
Acute toxicity, dermal	LD50, rabbits: 1848 mg/kg	No data	
Skin Irritation	No/ mild irritation in rabbits	No/ mild irritation in rabbits	Similar toxicity
Eye irritation/ damage	Conjunctival **necrosis** in rabbits	Eye Irritation in rabbits	Butanone oxime having most severe effect
Skin Sensitisation	**Positive** in GPMT and Buehler test	**Negative** in LLNA and Buehler test	2-pentanone oxime not a skin sensitiser
Repeated dose toxicity, oral	28-day study rats: LOAEL 20 mg/kg bw/day anaemia effects on spleen. NOAEL: 4 mg/kg bw/day 90-day study, rats: LOAEL: 10 mg/kg bw/day (anaemia and neurobehavioral effects)	28-day study rats: LOAEL: 50 mg/kg bw/day anaemia and effects on spleen NOAEL: 15 mg/kg bw/day	Similar toxicity
Repeated dose toxicity, inhalation	28-day study, rats: LOAEC 360 mg/m^3 anaemia **NOAEC: 90 mg/m^3** Chronic carc. study: LOAEC: 54 mg/m^3 (anaemia and effects on nasal epithelium)	28-day study, rats: NOAEC 1240 mg/m^3 90-day study, rats: **NOAEC 1249 mg/m^3** Slight effects on blood and relative organ weight observed at highest tested concentration. Considered as non-adverse by the registrant	**Significant lower inhalation toxicity** of 2-pentanone oxime compared to butanone oxime (about a factor 14)

	butanone oxime	2-pentanone oxime	Comments
Genotoxicity	Sufficiently tested: Overall negative	Sufficiently tested: Overall negative	Both negative
Cancer	Malignant and benign tumours in both rats and mice by inhalation.	No data	Carcinogenic potential of butanone oxime.
Reproductive toxicity	No effects on fertility or development in two-generation study and in developmental toxicity studies.	No effects on fertility or development in OECD 422 screening test.	No concern for effects on fertility and development for any of the substances

In relation to the following hazard endpoints, the two substances (butanone oxime and 2-pentanone oxime) seems very comparable:

- *Acute toxicity (about same oral LD50 values in rats)*
- *Skin irritation (no / mild irritation)*
- *Genotoxicity/ mutagenicity (no concern)*
- *Reproductive toxicity, (no concern)*

With respect to *local eye effects,* butanone oxime has an eye damaging potential, whereas 2-pentanone oxime is only an eye irritant, indicating more severe effect of butanone oxime.

For *skin sensitisation,* butanone oxime was tested positive, while 2-pentanone oxime was tested negative. Here, a rapid hydrolysis of butanone oxime into 2-butanone and hydroxylamine may contribute to this, as hydroxylamine is skin sensitising. 2-petanone oxime has been shown to be stable towards hydrolysis.

From *repeated oral dose toxicity studies* (exposure period of 28 and 90 days) in experimental animals, a very similar pattern of toxicological effects was observed as both substances produced anaemia and effects on the spleen at comparable dose levels. The lowest exposure levels for causing toxicity for butanone oxime and for 2-petanone oxime have been determined to 10 mg/kg bw/day and 50 mg/kg bw/day, respectively.

For *repeated inhalation toxicity,* a very big difference exists between the two substances. Butanone oxime causes the same type of systemic effects as for oral exposure and in addition induces effects in the nasal epithelium of rats and mice. A lowest exposure level for toxicity of 54 mg/m^3 was found for these effects for butanone oxime. For 2-pentanone oxime on the other hand a *no effect level* of 1249 mg/m^3 was achieved in a 90-day inhalation study in rats i.e. no sign of toxicity was observed in this study.

There are no data that can explain why 2-pentanone oxime is far less toxic by inhalation compared to oral exposure or compared inhalation exposure to butanone oxime. It is unclear whether a high stability towards hydrolysis and therefore no generation of hydroxylamine in the respiratory tract may play a rule.

Carcinogenicity studies (chronic exposure for 2 years) are only available from butanone oxime, where inhalation exposure studies produced benign and malignant tumours primarily located in the liver in rats and mice.

As no toxic effects at all occurred in the 90-day inhalation study with 2-pentanone oxime at a dose level of 1249 mg/m^3, it seems very unlikely that the substance would be carcinogenic by inhalation using an extended exposure period up to 2 years.

2-butanon oxime may - although no long-term oral studies have been conducted - be considered as having a carcinogenic potential by the oral exposure route as well, as other toxic effects on the target organs are very comparable as seen in the studies with repeated oral and inhalation exposure. As further the toxicological effects from oral exposure to butanone oxime is very comparable to the toxicological effects from oral exposure to 2-pentanone oxime, there may also be some concern for carcinogenic effects from 2-pentanone oxime in relation to oral exposure, although no specific data can document this.

Currently, 2-pentanone oxime is not found to be in focus for further investigation or assessment of regulatory bodies. In EU, no initiatives are indicated by ECHA for the substance with regard to the CLP or REACH regulation. In the U.S. neither U.S. EPA nor the U.S. Department of Health and Human Services (leading the National Toxicology Program that prioritizes and conduct cancer testing of chemicals in the U.S.) indicate any initiatives or prioritizations of the substance.

Overall Conclusions
When comparing the antifouling agent, from which butanone oxime is a leaving group, with the antifouling agent, from which 2-petanone oxime is a leaving agent, the latter may be considered of less concern in relation to potential health risks in the working environment. This can be concluded for various reasons:

- *2-pentanone oxime is an eye irritant whereas butanone oxime may cause irreversible eye damage*
- *2-pentanone oxime is not a skin sensitiser whereas butanone oxime is a skin sensitiser*
- *2-pentanone has a lower vapour pressure than butanone oxime, and thus lower occupational levels would be expected*
- *Further, 2-pentanone oxime is considered of significantly less toxicological concern by inhalation compared to inhalation of vapours from butanone oxime*
- *As a non-genotoxic substance, the lack of toxicity by inhalation at high exposure level of 2-petanone oxime also indicates a lack of any carcinogenic potential by inhalation.*

As indicated above, a carcinogenic potential for 2-pentanone oxime by oral exposure route cannot be ruled out. As neither butanone oxime nor 2-petanone oxime have any genotoxic potential a carcinogenic mode of action is considered as having a threshold level. For such non-genotoxic carcinogens, the induction of tumours is typically driven by sustained toxicity towards the target organs and the development of tumours are a follow of this. Thus, if toxicity in the organs is avoided the carcinogenic potential is avoided as well. So, if exposure is kept below the threshold for any sign of toxicity then no concern for carcinogenic effects applies. (what is the threshold?)

For *4-methylpentan-2-one oxime* as a leaving group no conclusion can be made based on specific experimental data on the substance or the data from the QSAR predictions. The toxicity often decreases with increasing molecular size within a homologue group of chemicals as the data on butanone oxime and 2-pentanone oxime also indicate. Although it could be tempting to conclude that *4-methylpentan-2-one oxime* would be even less toxic than 2-pentanone oxime this would warrant further data to substantiate such a conclusion.

1 Introduction and scope

Hempel A/S is a large-scale manufacturer of antifouling agents. During development of new agents, Hempel A/S would like to obtain toxicological information on three chemical leaving groups from a new antifouling agent to evaluate whether there might be a toxicological concern when working with the antifouling agent.

The leaving groups are:

butanone oxime, CAS No.: 96-29-7;
2-pentanone oxime, CAS No.: 623-40-5;
4-methylpentan-2-one oxime, CAS No.: 105-44-2

Hempel A/S has asked DHI, Department of Environment and Toxicology, to perform literature search for toxicological data in relation to human health and, if necessary, to perform QSAR (Quantitative Structure-Activity Relationship) analyses of the substances and provide an overall toxicological assessment of the substances.

2 Methodology

In the following, data search for toxicological data for the three leaving groups will be performed, and an extract of the toxicological data will be given.

As toxicological data may not be available for all three substances QSAR (Quantitative Structure-Activity Relationship) predictions on toxicological effects will be performed using relevant QSAR tools.

An overall assessment of the gathered data will be made and the toxicological profiles and similarities and differences between the substances will be discussed.

Finally, it will – as far as possible – be concluded to which extent one or several of the substances should be considered of special concern and whether some of the substances could be prioritised as least problematic in the occupational environment.

3 Data Search

3.1 Search strategy

Data search for the substances was performed from the web site of the European Chemicals Agency (ECHA), other national web sites (e.g. US EPA, NICNAS Australia, BAUA Germany) and toxicological databases, e.g. the PubChem database and the TOXNET database covering 15 databases including TOXLINE. The search was supplemented with google search using the CAS numbers of the substances.

3.2 Overall findings

Toxicological data on *butanone oxime* could be found in a web-based search, in the TOXNET database, and in the REACH-registration of the substance. However, the most updated expert assessment was available from the ECHA-web site in a classification proposal for the substance where the toxicological data have been gathered and critically evaluated (ECHA 2017).

For *2-pentanone oxime* toxicological data were only found in the REACH-registration dossier of the substance.

No toxicological data were found on *4-methylpentan-2-one oxime*.

3.3 ECHA database

3.3.1 Classification

2-butanone oxime is registered under REACH in the tonnage band of 1000 – 10 000 tonnes per year. The substance has a harmonised EU-classification as:

Acute Tox. 4 H312
Skin Sens. 1 H317
Eye Dam. 1 H318
Carc. 2 H351

However, a current proposal is under discussion in ECHA for a harmonised EU-classification (ECHA 2017) as:

Acute Tox. 3 H301
Acute Tox. 4 H312
Skin Sens. 1B H317
Eye Dam. 1 H318
Carc. 1B H350
STOT SE 3 H336

2-pentanone oxime (also named *(E)-N-(pentan-2-ylidene)hydroxylamine* or *N-pentan-2-ylidenehydroxylamine*) is registered under REACH at the tonnage level of 100 – 1000 tonnes per year. The substance is not subject to harmonised EU-classification. In the registration dossier the substance is classified by the registrant as:

Acute Tox. 4 H302;
Eye Irrit. 2 H319;
STOT RE2 H373 (blood and spleen)
Aquatic Chronic 3 H412

4-methylpentan-2-one oxime **is not registered** under REACH. The substance is not subject to harmonised EU-classification, however, the substance is notified in the ECHA classification database with the classification:

Acute Tox. 4 H302;
Skin Irrit. 2 H315;
Eye Irrit. 2 H319

3.4 2-butanone oxime

The below data for 2-butanone oxime are from the proposal for a harmonized classification currently under discussion in ECHA (ECHA 2017). These data are considered more updated than the data given in the REACH registration, and the data have further been subject to expert assessment by the German Competent Authority BAuA (Federal Institute for Occupational Safety and Health).

3.4.1 Acute toxicity

Oral

Based on the lowest oral LD50 values (930 mg/kg bw (males) - 1620 mg/kg bw (females)) from studies with rats, butanone oxime would fulfil the criteria for classification for acute oral toxicity Category 4. However, the data from a preliminary dose range-finding study to a developmental toxicity study in rabbits have shown that butanone oxime induces acute lethality in this specie at lower doses. For the rabbits, LD50 was estimated to be below 160 mg/kg and a classification as Acute Tox. 3, H301 is fulfilled.

Inhalation

No LC50 value for inhalation could be established for butanone oxime as no deaths occurred in rats in an inhalation hazard test up to a concentration of 10.5 mg/L/8h.

Dermal

The dermal LD50 in rabbits was found to be 1848 mg/kg bw. Based on this, a classification as Acute tox. 4 was concluded.

Further, data from acute oral, inhalation and dermal toxicity testing in rats and rabbits have shown a strong transient narcotic effect in both sexes following single exposure to butanone oxime. Based on these effects, a classification as STOT RE (narcotic effect) was concluded.

3.4.2 Irritation/corrosion

No sign of irritation was observed in a guideline-confirming study on rabbits following a 4-hour application to butanone oxime. In another study, the primary dermal irritation index was 1.5 after exposure over 24 hours, which is below the mean scores that may require classification.

The available eye irritation study in rabbits showed that butanone oxime caused serious damage to the eyes. Butanone oxime caused corneal opacity, iritis and hyperemia of the conjunctivae. These lesions were observed 24, 48, and 72 hours post exposure (average scores 2 or above) in 6/6 animals. In addition, irreversible effects on the eye were observed in 2/6 rabbits. Conjunctival necrosis was observed in these rabbits which was not reversible at the end of observation period. A classification as Eye Dam 1 H318 was concluded.

3.4.3 Skin sensitisation

In two Guinea Pig Maximisation tests (GPMT) and a Buehler assay, guinea pigs exhibited positive results. From these data, butanone oxime fulfils the criteria for classification in the hazard class as skin sensitiser Sub-category 1B, H317, because a skin sensitisation response of ≥ 30 % at > 1.0 % intradermal induction dose was observed in the adjuvant type test method (GPMT); and of ≥ 15 % at > 20 % topical induction dose in the non-adjuvant type test method (Buehler assay).

3.4.4 Repeated dose toxicity

Oral exposure

There are several available oral repeated dose toxicity studies of butanone oxime with different time durations. Butanone oxime caused dose-related increased **effects on blood** parameters indicative of haemolytic anaemia and compensatory medullary haematopoiesis, as well as extramedullary haematopoiesis in the spleen and liver. In studies with rats and mice, the effects on the blood increased regarding incidence and severity observed at doses ≥ 10 mg/kg bw/d,

serious effects were seen in male and female rats at ≥ 175/215 mg/kg bw/d, and in male and female mice at ≥ 755/1010 mg/kg bw/d.

In developmental toxicity studies in rats and rabbits, oral administration of butanone oxime to dams by gavage produced clear evidence of maternal toxicity in both species which showed effects indicative of anaemia. The effects on the blood occurred at ≥ 25 mg/kg bw/d in rats and at ≥ 10 mg/kg bw/d in rabbits. Findings of extramedullary haematopoiesis and hemosiderosis in liver and spleen, unaccompanied by any other indications of blood toxicity were also seen in FI male and female rats receiving 10 mg/kg bw/d. Increased spleen weights and splenic and hepatic extramedullary haematopoiesis (haematopoietic cell proliferation) and hemosiderosis (pigment deposition from haemoglobin breakdown products) observed at ≥ 100 mg/kg bw/d. Mortalities that occurred in pregnant rabbits after treatment with two oral doses of 80 mg/kg bw/d butanone oxime during the gestation phase, i.e. methaemoglobin formation within the first 48 hours, were considered to be covered by classification for acute oral toxicity.

Overall, the effects observed at 100 mg/kg bw/day (the cut-off level for STOT RE 2 classification) were not considered sufficiently adverse as to warrant a STOT RE classification as the observed increases in hemosiderosis in the spleen, liver or kidney were not combined with severe morphological changes like necrosis, fibrosis or cirrhosis.

Inhalation

The lowest LOAEC value for effects of butanone oxime indicative of anaemia was established in rats and mice exposed by inhalation at 15 ppm (54 mg/m³) derived from combined chronic toxicity and carcinogenicity studies (similar to OECD TG 453) in both species. The degree of anaemia was not progressive with long-life repeated inhalation exposure. This development was primarily driven by this compensatory erythropoiesis.

In combined chronic toxicity and carcinogenicity studies (similar to OECD TG 453/EU B.33, whole body exposure, 6h/d, 5d/wk.), repeated exposure by inhalation to butanone oxime of rats and mice caused effects on the olfactory epithelium of the nasal turbinates at all tested exposure concentrations (≥ 15 ppm; equivalent to ≥ 54 mg/m³). After long-life repeated exposure to butanone oxime by inhalation, effects on the olfactory epithelium of the nasal turbinates were noted in rats and mice at all concentration tested (≥ 15 ppm, equivalent to 0.054 mg/L/6h/d).

Overall, the effects on blood and the nasal olfactory epithelium observed in rats and mice up to the highest concentration tested of 374 ppm (1.346 mg/L/6h/d) were not severe enough to justify a STOT RE classification.

3.4.5 Genetic toxicity

In vitro

Butanone oxime did not induce reverse mutations in Salmonella typhimurium strains or Escherichia coli. The tests were conducted up to the limit dose recommended by guideline, and cytotoxicity was noted at the highest tested dose level. A single reverse mutation bacterial assay conducted by the pre-incubation method reported a mutagenic response in only tester strain TA 1535 and only in the presence of high (not standard) levels of hamster liver activating enzymes. In mammalian *in vitro* systems, butanone oxime did not induce chromosomal aberrations in rat hepatocytes, gene mutation in mouse lymphoma cells, sister chromatid exchange or chromosome aberrations in cultured CHO cells.

In vivo

Butanone oxime did not induce mutations in the post-meiotic germ cells of male Drosophila melanogaster and micronuclei in peripheral blood erythrocytes in male and female B6C3F1 mice treated via drinking water and showed no significant increase in chromosomal aberrations in the

bone marrow of rats. In liver DNA from butanone oxime exposed rats by inhalation for 6 hours, DNA adducts could not be observed.

Overall, it was concluded that there is no concern for direct genotoxic properties of butanone oxime based on the available data from *in vitro* and *in vivo* tests.

3.4.6 Carcinogenicity

The carcinogenic potential of butanone oxime has been studied in two combined chronic toxicity and carcinogenicity studies and in two species. Butanone oxime was administered by whole-body inhalation as a vapour for 6h/day, 5 days/week for 26 months to F344 rats and 18 months to CD-1 mice, and both sexes each.

In these studies, butanone oxime induced tumour development in the liver in rats and mice at all tested exposure concentrations (≥ 15 ppm; actual concentration of 54 mg/m³). However, statistically significant increases in incidence were observed only at the mid and high concentration of 270 and 1346 mg/m³ for liver adenomas in male rats and at 1346 mg/m³ for liver carcinomas in male rats and mice. An increased incidence of liver adenomas compared to the concurrent controls occurred also in female rats and mice at 270 and 1346 mg/m³ but was not statistically significant. A dose-response relationship for tumour induction in the liver of rats and mice was observed in both sexes. A LOAEC of 15 ppm (54 mg/m³), lowest concentration tested in the study) for carcinogenicity (liver tumour development) was derived for rats and mice.

A statistically significantly increased incidence of mammary gland fibroadenomas was also observed in male rats at the high concentration of 1346 mg/m³.

Thus, butanone oxime induced malignant and benign tumours in the liver of rats and mice in well performed experimental studies and a classification as Carc. 1B H350 was concluded.

3.4.7 Toxicity to reproduction/ developmental toxicity

Butanone oxime was tested for effects on sexual function and fertility in a two-generation toxicity study in rats (similar to OECD TG 416). Toxicity in adult animals was noted in both generations and both sexes. Treatment-related parental deaths occurred at 200 mg/kg bw/d. At 100 and 200 mg/kg bw/d signs of haemolytic anaemia and compensatory erythropoiesis was present and contributed to the increased spleen weights and extramedullary haematopoiesis (hematopoietic cell proliferation) and hemosiderosis (pigment deposition from haemoglobin breakdown products) in spleens and livers. At 10 mg/kg bw/d the consistent parental findings were extramedullary haematopoiesis and hemosiderosis in spleens and livers unaccompanied with further lesions. A NOAEL for systemic effects of adult toxicity could not be established in this study. There were no treatment-related effects on parental reproductive parameters, on parental reproductive behaviour or on parental reproductive organ histology in rats dosed by gavage up to 200 mg/kg bw/d butanone oxime. There were no treatment-related effects on any offspring parameters, including pre- and postnatal survival and growth, for either generation. For butanone oxime a NOAEL of 200 mg/kg bw/d for reproductive toxicity in rats was established.

Effects of butanone oxime on development were investigated in rats and rabbits. In Sprague-Dawley rats and New Zealand White rabbits results of a preliminary dose range-finding study and of the main study are available. Based on the results of these studies, butanone oxime is not considered to be developmentally toxic at maternally toxic dose levels of up to 600 mg/kg bw/d in the rat. NOAEL values of 400 and 600 mg/kg bw/d for developmental toxicity, based on absence of treatment-related gestational effects, malformations or developmental variations at the highest dose.

Thus, the results available from examination of the effects on sexual function and fertility in rats and on developmental toxicity in rats and rabbits did not provide information concerning butanone oxime as a reproductive or developmental toxicant.

3.5 2-pentanone oxime (CAS 623-40-5)

All data described below is data found in the REACH-registration of the substance (data retrieved January 2019) : https://echa.europa.eu/da/registration-dossier/-/registered-dossier/14551.

It should be noted that further check of data has not been possible as the data are not published in literature and thus, the evaluation of the data is based on the presentation of the data by the REACH-registrant.

3.5.1 Acute toxicity

From an OECD Guideline 425 (Acute Oral Toxicity: Up-and-Down Procedure) study the oral LD50 value for rats was estimated to 1133 mg/kg. A classification with Acute tox. 4 was concluded from this study.

From an OECD Guideline 403 (Acute Inhalation Toxicity) study in rats' macroscopic examination of the lungs revealed grey discolouration and red spots in the lung after 4 hour exposure to 1224 mg/m3. No animal died at this dose-level but showed respiratory depression with dyspnoea during exposure. Thus, the LC50 > 1224 mg/m³ was established

No acute dermal toxicity data was reported.

3.5.2 Irritation/corrosion

In an OECD Guideline 404 (Acute Dermal Irritation / Corrosion) study the maximal score was 1 for each of the three rabbits included in the study i.e. clearly below the classification limit for skin irritation.

In an OECD Guideline 405 (Acute Eye Irritation / Corrosion) study the scoring of irritation response was sufficient for a classification as a.

3.5.3 Skin sensitisation

2-pentanone oxime was tested negative in a Buehler skin sensitisation test (OECD Guideline 406) and in an *in vivo* (LLNA) assay OECD Guideline (429).

3.5.4 Repeated dose toxicity

Oral exposure

In an OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test) rats were orally exposed to 15, 50 150 mg/kg bw/day for up to 6 weeks.

Treatment with 2-pentanone oxime at 50 and 150 mg/kg/day was associated with major adverse effects on the red blood cells. Males and females receiving 50 and 150 mg/kg/day showed low haematocrit and haemoglobin levels, low red blood cell counts, high reticulocytes and low mean cell haemoglobin concentrations, and for males only at those dose levels, high mean cell volumes. A dose relationship was also apparent.

Haemosiderosis was observed in the spleens of males and females treated at 15, 50 and 150 mg/kg/day. Congestion was also seen in males and females treated at 50 and 150 mg/kg/day. An increase in the incidence of extramedullary haemopoiesis was also observed in males and females treated at 150 mg/kg/day. These changes revealed dose-relationship. Extramedullary haemopoiesis was observed in liver in males and females treated at 50 and 150 mg/kg/day.

A NOAEL of 15 mg/kg bw/day was concluded from the study. Based on the findings on blood and spleen, a classification as STOT RE2 was concluded as well.

Inhalation

In an OECD Guideline 412 (Subacute Inhalation Toxicity: 28-Day Study) study rats were nose-only exposed to 2-pentanone oxime at concentration levels of 52.9, 149.3 and 298.9 ppm (corresponding to 220, 620 and 1240 mg/m³) 6h/day, 5/d/week during 4 weeks. The upper concentration was indicated to be just below the saturated vapour concentration. No effects were noted in the study i.e. a NOAEC of 1240 mg/m3 was concluded from the study.

In an OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study) study rats were nose-only exposed to 2-pentanone oxime at concentration levels of 49.7, 149 and 301 ppm (corresponding to 206, 618 and 1249 mg/m³) 6h/day, 5/d/week during 13 weeks. The upper concentration was indicated to be just below the saturated vapour concentration. Only slight effects on blood and relative organ weights (spleen, kidney and lever) were noted at the highest dose level but these findings were not considered as adverse and no microscopic findings were found. A NOAEC of 1249 mg/m³ was concluded from the study.

3.5.5 Genetic toxicity

In vitro

An OECD Guideline 471 (Bacterial Reverse Mutation Assay) study and an OECD Guideline 487 (*In Vitro* Mammalian Cell Micronucleus Test - human lymphocytes) study were conducted, both with negative response.

However, in an OECD Guideline 473 (*In Vitro* Mammalian Chromosome Aberration Test) study with human lymphocytes a positive response with increased number of chromosomal aberrations at 1012 µg/mL (a non-toxic guideline limit concentration), was found when compared to the vehicle control.

In vivo

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) study was conducted in male rats orally dosed 125, 250 and 500 mg/kg bw/day for two days. No increase in the induction of micronucleated polychromatic erythrocytes or bone marrow was found in this study.

An OECD Guideline 475 (Mammalian Bone Marrow Chromosome Aberration Test) study was conducted in male rats exposed by nose-only inhalation to 52.9, 149.3 and 298.9 ppm of 2-pentanone oxime (corresponding to 220, 620 and 1240 mg/m³) 6 hours/day, 5 days/week for 10 days. The exposure did not induce chromosome aberrations in the bone marrow of male rats at any dose level.

A study very similar to an OECD guideline 489 (*In Vivo* Mammalian Alkaline Comet Assay) study was conducted with male rats exposed by nose-only inhalation to 52.9, 149.3 and 298.9 ppm of 2-pentanone oxime (corresponding to 220, 620 and 1240 mg/m³) 6 hours/day, 5 days/week for 10 days. The exposure did not induce primary DNA damage to hepatocytes of male rats at any dose level.

3.5.6 Toxicity to reproduction/ developmental toxicity

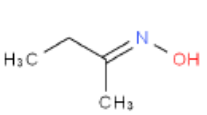
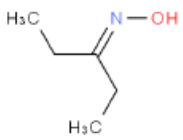
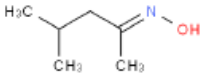
In an OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test) rats were orally exposed to 15, 50 150 mg/kg bw/day. 2-pentanone oxime was administered for two weeks before pairing up to necropsy (at least five weeks) for males and two weeks before pairing then throughout pairing and gestation until Day 6 of lactation for females. Recovery animals were treated for approximately six weeks and completed a further 14 days without treatment. No effects on fertility or development were found in this study. A NOAEL of 150 mg/kg bw/day for effects on fertility and development was concluded, while a NOAEL of 15 mg/kg bw/day was concluded for maternal toxicity (see repeated dose section).

3.6 QSAR predictions

As a first-choice tool for QSAR predictions of the substances, the Danish QSAR database is selected. First-of-all, the tool is recommended by ECHA and further the tool makes predictions for each human health endpoint with up to three different recognised QSAR models, which enables predictions with a high reliability. Short descriptions of the QSAR models used is given in appendix A. Further the specific QSAR predictions for the three leaving group is attached to this report.

The relevant data from the predictions are given in Table 1 below. i.e. only data from hazard endpoints where predictions could be made by model are included, whereas hazard endpoints that could not be predicted for any of the chemical structures are not indicated in the table. The first column contains the predictions for 2-butanone oxime as this is the substance with most experimental animal data to compare with (experimental data indicated with EXP in the table). In the columns for 2-pentanone oxime and 4-methylpentan-2-one oxime, QSAR prediction results that differ from the prediction of butanone oxime are given in **bold** for high-lighting differences in predictions between the three substances.

Table 1. Danish QSAR predictions for the three leaving group substances

	butanone oxime	*2-pentanone oxime*	*4-methylpentan-2-one oxime*
CAS No	96-29-7	623-40-5	105-44-2
Chemical formula	C_4H_9NO	$C_5H_{11}NO$	$C_6H_{13}NO$
Chemical structure			
Molecular weight	87.12	101.15	115.18
Log Kow	1.69	2.18	2.6
Water solubility based on Log Kow (mg/L)	36630	1582	626
Hydrolyses	T1/2 < 0.3 minutes pH4	half-life time of > 1 year at 25°C) at pH 4, pH 7 and pH 9.	No data

	butanone oxime	*2-pentanone oxime*	*4-methylpentan-2-one oxime*
	14% hydrolyses at pH 7 after 4 days at 20°C 0% hydrolysis at pH 9 after 7 days (REACH-reg)	(REACH-reg)	
Boiling point	157 °C	178 °C **EXP:** 172 °C (REACH-reg)	187 °C
Vapour pressure	156 Pa **EXP:** 1070 Pa (20 °C) (REACH-reg)	65 Pa **EXP:** 214 Pa (20 °C) (REACH-reg)	22 Pa -
pKa acid	12.5	12.5	12.5
Toxicity			
Mouse oral LD50 (mg/kg)	1200 **EXP:** 930 -1620 (rats REACH-reg)	1200 **EXP:** 1133 (rats REACH-reg)	1200
Allergic Contact Dermatitis in Guinea Pig and Human	Positive (CASE Ultra) Negative (Leadscope) Negative (SciQSAR) **EXP: positive**	**NA** (CASE Ultra) Negative (Leadscope) Negative (SciQSAR) **EXP: negative**	**NA** (CASE Ultra) Negative (Leadscope) **NA** (SciQSAR)
Endocrine effects			
Estrogen Receptor α Binding, Full training set (Human *in vitro*)	Negative (CASE Ultra) NA (Leadscope) Negative (SciQSAR)	Negative (CASE Ultra) NA (Leadscope) Negative (SciQSAR)	Negative (CASE Ultra) NA (Leadscope) Negative (SciQSAR)
Androgen Receptor Antagonism (Human *in vitro*)	Negative (CASE Ultra) NA (Leadscope) Negative (SciQSAR)	Negative (CASE Ultra) NA (Leadscope) Negative (SciQSAR)	Negative (CASE Ultra) NA (Leadscope) Negative (SciQSAR)
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)	NA (CASE Ultra) Negative (Leadscope) NA (SciQSAR)	NA (CASE Ultra) Negative (Leadscope) NA (SciQSAR)	NA (CASE Ultra) Negative (Leadscope) NA (SciQSAR)
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)	NA (CASE Ultra) Negative (Leadscope) NA (SciQSAR)	NA (CASE Ultra) Negative (Leadscope) NA (SciQSAR)	NA (CASE Ultra) Negative (Leadscope) NA (SciQSAR)
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	NA (CASE Ultra) NA (Leadscope) Negative (SciQSAR)	NA (CASE Ultra) NA (Leadscope) Negative (SciQSAR)	NA (CASE Ultra) NA (Leadscope) Negative (SciQSAR)

	butanone oxime	*2-pentanone oxime*	*4-methylpentan-2-one oxime*
Genotoxicity *in vitro*			
Ames test in S. typhimurium (*in vitro*)	Positive (CASE Ultra) Negative (Leadscope) NA (SciQSAR) **EXP: negative**	Positive (CASE Ultra) Negative (Leadscope) NA (SciQSAR) **EXP: negative**	Positive (CASE Ultra) Negative (Leadscope) **Negative** (SciQSAR)
Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells	NA (CASE Ultra) NA (Leadscope) Positive (SciQSAR) **EXP: negative**	NA (CASE Ultra) **Negative** (Leadscope) Positive (SciQSAR)	NA (CASE Ultra) **Negative** (Leadscope) **Negative** (SciQSAR)
Chromosome Aberrations in Chinese Hamster Lung (CHL) Cells	Negative (CASE Ultra) Negative (Leadscope) NA (SciQSAR)	Negative (CASE Ultra) Negative (Leadscope) NA (SciQSAR)	Negative (CASE Ultra) Negative (Leadscope) **Negative** (SciQSAR)
Mutations in Thymidine Kinase Locus in Mouse Lymphoma Cells	Positive (CASE Ultra) NA (Leadscope) NA (SciQSAR) **EXP: negative**	Positive (CASE Ultra) NA (Leadscope) NA (SciQSAR	Positive (CASE Ultra) NA (Leadscope) NA (SciQSAR)
Syrian Hamster Embryo (SHE) Cell Transformation	Positive (CASE Ultra) Negative (Leadscope) Positive (SciQSAR)	Positive (CASE Ultra) Negative (Leadscope) Positive (SciQSAR)	Positive (CASE Ultra) Negative (Leadscope) Positive (SciQSAR)
Genotoxicity *in vivo*			
Comet Assay (*in vivo*)	NA in all 3 models	NA in all 3 models **EXP: negative**	NA in all 3 models
Mammalian Erythrocyte Micronucleus Test (*in vivo*)	NA in all 3 models **EXP: negative**	NA in all 3 models **EXP: negative**	NA in all 3 models
Mammalian Bone Marrow Chromosome Aberration Test (*in vivo*)	NA in all 3 models **EXP: negative**	NA in all 3 models **EXP: negative**	NA in all 3 models
Additional endpoints			
Carcinogenicity	Negative (CASE ultra 7/7 submodels) Negative (Leadscope 1/7 submodels) NA (Leadscope 6/7 submodels)	Negative (CASE ultra 7/7 submodels) Negative (Leadscope 1/7 submodels) NA (Leadscope 6/7 submodels)	Negative (CASE ultra 6/7 submodels) **NA** (CASE ultra 1/7 submodels) Negative (Leadscope 1/7 submodels) NA (Leadscope 6/7)

	butanone oxime	*2-pentanone oxime*	*4-methylpentan-2-one oxime*
	EXP: positive		
Teratogenic Potential in Humans	NA (CASE Ultra) NA (Leadscope) NA (SciQSAR) **EXP: negative**	NA (CASE Ultra) NA (Leadscope) NA (SciQSAR) **(EXP: negative)***	NA (CASE Ultra) NA (Leadscope) **Positive** (SciQSAR)

EXP: experimental data NA: not applicable/ outside domain of the model
*only data from screening test which are not conclusive for the endpoint
Predictions in **bold**: different prediction than the prediction from 2-petanone oxime

3.7 Discussion of QSAR table

As can be seen by the chemical structures, the three substances can be considered as a homologue series of oximes starting with 2-butanonoxime and with one CH3-group attached for *2-petanone oxime* and a C2H5-group attached for *4-methylpentan-2-one oxime*.

As would be expected the boiling points increase with increasing molecular size and the vapour pressure decreases. A major difference is that 2-butanon oxime is very susceptible to hydrolysis (to methyl ethylketon and hydroxylamine) under acid conditions whereas 2-pentanone oxime is very stable to hydrolysis (data from REACH-registrations).

Based on the very similar structure of the substances indicating same type of chemical reactivity, a very common toxicological profile would be expected. However, butanone oxime may be considered more chemically reactive due to rapid hydrolysis and formation of hydroxylamine, which may also have impact on toxicity, as *hydroxylamine* in the REACH registration dossier is classified as:

> Acute Tox. 4 H302/H312; Skin Irrit. 2 H315; Eye Damage 1 H318; Skin Sens. 1 H317; Carc. 2 H351; STOT Single Exp.3 H335; STOT Rep.2 H373 (blood, spleen).

Acute toxicity

For oral LD50 values the same value of 1200 mg/kg is predicted for all three substances. This value is very comparable to the experimental data on rats.

Skin sensitisation

For skin sensitisation, the QSAR models generally predict negative results for the three substances; however, one model predicted a positive response for butanone oxime, which in fact was confirmed by experimental data showing the substance as a weak sensitiser (placed in category 1B). Two models predicted negative result for pentanone oxime, which was supported by two experimental studies. Based on the negative prediction for *4-methylpentan-2-one oxime* this does not indicate concern for a skin sensitising potential of this substance.

Endocrine effects

In the models, endocrine receptor-binding properties and endocrine activity, identical predictions are obtained for all of the three substances indicating the absence of receptor binding and endocrine activity.

Genotoxicity

Also, the models for prediction of genotoxicity *in vitro* and *in vivo* predict the substances in a very identical manner with overall negative substances. This has further been proven by the experimental data on butanone oxime and 2-pentanone oxime indicating no concern for a genotoxic potential. It may, however, be noted that one model consistently predicts the substances as positive in relation to Ames test in bacteria; however, test data showed negative results.

Carcinogenicity

The models indicate the three substances to be of no concern for carcinogenicity. However, for the only substance - butanone oxime - that has been tested for carcinogenic effects, the studies showed a clear positive response in rats and mice, so the models may not be considered reliable in their predictions of these substances.

Reproductive/ developmental toxicity

The models can make only one prediction, and this prediction is positive for developmental toxicity for 4-methylpentan-2-one oxime. However, it is generally recognised that valid QSAR models for predictions for reproductive toxicity are lacking, and thus the concern expressed should be evaluated with great caution. It should be noted that butanone oxime has been thoroughly tested for reproductive toxicity with negative outcome and that a reproduction toxicity screening test for 2-pentanone oxime also came out with a negative result. So based on this the concern expressed by the QSAR model is not considered relevant.

No further predictions with the QSAR tools TOXtree and QSAR VEGA seem warranted, as these tools primarily focus on genotoxicity and sensitisation for which experimental data already exist.

4 Overall toxicological evaluation of the three leaving groups

In the table below an overview of the experimental data for butanone oxime and 2-pentanone oxime as described in sections 3.4 and 3.5 is given. No toxicological data besides the QSAR predictions were found for 4-methylpentan-2-one oxime.

Table 2. Overview of experimental toxicological data on butanone oxime and 2-petanone oxime

	butanone oxime	*2-pentanone oxime*
Acute toxicity, oral	LD50 rats: 930-1620 mg/kg LD50 rabbits: < 160 mg/kg Rabbits more susceptible Acute tox 3 classification	LD50 rats: 1133 mg/kg (not tested in rabbits) Acute tox 4 classification
Acute toxicity, inhalation	LC50 rats > 10.5 mg/L (8h) No classification	LC50 rats > 1.224 mg/L
Acute toxicity, dermal	LD50 rabbits: 1848 mg/kg Acute tox 4 classification	No data
Effects single exposure	Narcotic effects after oral exposure and inhalation STOT RE3 classification	No data

	butanone oxime	*2-pentanone oxime*
Skin Irritation/ corrosion	No/ mild irritation in rabbits. No classification	No/ mild irritation in rabbits. No classification
Eye irritation/ damage	Conjunctival necrosis in rabbits Eye dam. 1 classification	Irritation in rabbits Eye Irrit 2 classification
Skin Sensitisation	Positive in GPMT and Buehler test Skin sens. 1B classification	Negative in LLNA and Buehler test No classification
Repeated dose toxicity, oral	Subacute 28-day: LOAEL 20 mg/kg bw/day anaemia effects on spleen. NOAEL: 4 mg/kg bw/day Subchronic 90-day: LOAEL: 10 mg/kg bw/day (anaemia and neurobehavioral effects) No STOT RE classification	Subacute 4-6 weeks: LOAEL: 50 mg/kg bw/day anaemia and effects on spleen NOAEL: 15 mg/kg bw/day STOT RE2 classification
Repeated dose toxicity, inhalation	Subacute 28-day: LOAEC 360 mg/m^3 anaemia NOAEC: 90 mg/m^3 Chronic carc. study: LOAEC: 54 mg/m^3 (anaemia and effects on nasal epithelium). No STOT RE classification	Subacute (28-day): NOAEC 1240 mg/m^3 Subchronic (90-day): NOAEC 1249 mg/m^3 Slight effects on blood and relative organ weight observed at highest tested concentration. Considered as non-adverse by the registrant. No STOT RE classification
Genotoxicity *in vitro*	Negative in bacteria. Negative in mammalian cells for both mutagenicity, micronuclei and chromosome aberrations	Negative in bacteria. Negative in mammalian cells for micronuclei formation. Positive in mammalian cells for chromosome aberrations
Genotoxicity *in vivo*	Negative in Drosophila melanogaster. Negative micronuclei in mice, oral. Negative for chromosome aberration in rats, oral. No DNA adduct formation in rats, inhalation. No classification	Negative for micronuclei in rats, oral. Negative for chromosome aberration in rats, inhalation. Negative in Comet assay in rats, inhalation No classification
Carcinogenicity	Malignant and benign tumours in both rats and mice by inhalation. Carc. 1B classification	No data

	butanone oxime	*2-pentanone oxime*
Reproductive toxicity (fertility and teratogenicity)	No effects on fertility or development in two-generation study and in developmental toxicity studies. No classification	No effects on fertility or development in OECD 422 screening test. No classification
Overall classification	*Currently*: Acute Tox. 4 H312 Skin Sens. 1 H317 Eye Dam. 1 H318 Carc. 2 H351 *Proposed in ECHA:* Acute Tox. 3 H301 Acute Tox. 4 H312 Skin Sens. 1B H317 Eye Dam. 1 H318 Carc. 1B H350 STOT SE 3 H336	Acute Tox. 4 H302; Eye Irrit. 2 H319; STOT RE2 H373 (blood and spleen) Aquatic Chronic 3 H412
DNEL (inhalation workers)	9 mg/m^3 (systemic effects) 3.3 mg/m^3 (local effects)	8.3 mg/m^3 (systemic effects)
DNEL (dermal workers)	1.3 mg/kg bw/day (systemic effects)	0.21 mg/kg bw/day (systemic effects)
OEL value	No OEL found	No OEL found

In relation to the following hazard endpoints, the two substances (butanone oxime and 2-pentanone oxime) seems very comparable:

Acute toxicity (about same oral LD50 values in rats)

Skin irritation (no / mild irritation)

Genotoxicity (no concern)

Reproductive toxicity (no concern)

With respect to *local eye effects,* butanone oxime has an eye damaging potential, whereas 2-pentanone oxime is only an eye irritant, indicating more severe effect of butanone oxime.

For *skin sensitisation,* butanone oxime was tested positive, while 2-pentanone oxime was tested negative. Here a rapid hydrolysis of butanone oxime into 2-butanone and hydroxylamine may contribute to this as hydroxylamine is skin sensitising. 2-petanone oxime has been shown to be stable towards hydrolysis.

For *repeated oral dose toxicity,* a very similar pattern of toxicological effects was observed as both substances produced anaemia and effects on the spleen at comparable dose levels. Oral LOAELs for butanone oxime and for 2-petanone oxime have been determined to be 10 mg/kg bw/day and 50 mg/kg bw/day, respectively.

For *repeated inhalation toxicity,* a very big difference exists between the two substances. Butanone oxime causes the same type of systemic effects as for oral exposure and in addition induces effects in the nasal epithelium of rats and mice. A LOAEC of 54 mg/m^3 was found for

these effects. For 2-pentanone oxime on the other hand a NOAEC of 1249 mg/m³ was achieved in a 90-day inhalation study in rats.

If 100% of the inhaled amount of 2-pentanone oxime was absorbed by the rats during the 6 hr inhalation/day, and a default bodyweight of a rat is 0.35 kg and the inhalation volume is 0.0157 m³/h (default values from ECHA (2012)) then the exposure would correspond to a daily exposure of:

- 6 h/day x is 0.0157 m³/h x 1249 mg/m³ / 0.35 kg bw = 336 mg/kg bw/day

If such a dose was used in an oral study this would have led to severe toxicity as a LOAEL of 50 mg/kg bw/day was found in an oral 28-day study.

There are no data that can explain why 2-pentanone oxime is far less toxic by inhalation compared to oral exposure or compared inhalation exposure to butanone oxime. It is unclear whether high stability towards hydrolysis and therefore no generation of hydroxylamine in the respiratory tract may play a rule.

Carcinogenicity studies are only available from butanone oxime, where inhalation exposure studies produced benign and malignant tumours primarily located in the liver in rats and mice.

As no toxic effects at all occurred in the 90-day inhalation study with 2-pentanone oxime at a dose level of 1249 mg/m³, it seems very unlikely that the substance would be carcinogenic by inhalation using an extended exposure period.

Butanone oxime may - although no long-term oral studies have been conducted - be considered as having a carcinogenic potential by the oral exposure route, as the effects on target organs, effects from oral and inhalation exposure, are very comparable. As the toxicological effects from oral exposure to butanone oxime is very comparable to the toxicological effects from oral exposure to 2-pentanone oxime, there may also be a concern for carcinogenic effects from 2-pentanon oxime in relation to oral exposure.
However, these data/ arguments are not considered sufficient to warrant a classification with *Carc. 2* of 2-pentanone oxime, as further evidence would be needed for fulfilling the CLP classification criteria for such a classification.

For the oral exposure route, hydrolysis of both butanone oxime and 2-pentanone oxime has been shown to be an important metabolic route in experimental animals indicating similarities of the substances after oral uptake as hydroxylamine is generated. Furthermore, the liberated hydroxylamine is known to induce anaemia and affect the spleen and to induce tumours by oral exposure. However, other metabolites than metabolites generated by hydrolysis have been detected from the two substances, and it cannot be assessed whether these other metabolites would contribute to differences in carcinogenic potential.

Currently, 2-pentanone oxime is not found to be in focus for further investigation or assessment of regulatory bodies. In EU, no initiatives are indicated by ECHA for the substance with regard to the CLP or REACH regulation. In the U.S. neither U.S. EPA nor the U.S. Department of Health and Human Services (leading the National Toxicology Program that prioritizes and conduct cancer testing of chemicals in the U.S.) indicate any initiatives or prioritizations of the substance.

5 Implications for the choice of antifouling agents

When comparing the antifouling agent, from which butanone oxime is a leaving group, with the antifouling agent, from which 2-petanone oxime is a leaving agent, the latter may be considered of less concern in relation to potential health risks in the working environment. This can be concluded for various reasons:

- *2-pentanone oxime is an eye irritant whereas butanone oxime may cause irreversible eye damage*
- *2-pentanone oxime is not a skin sensitiser whereas butanone oxime is a skin sensitiser*
- *2-pentanone has a lower vapour pressure than butanone oxime, and thus lower occupational levels would be expected*
- *Further, 2-pentanone oxime is considered of significantly less toxicological concern by inhalation compared to inhalation of vapours from butanone oxime*
- *As a non-genotoxic substance, the lack of toxicity by inhalation at high exposure level of 2-petanone oxime also indicates a lack of any carcinogenic potential by inhalation.*

As indicated above, a carcinogenic potential for 2-pentanone oxime cannot be ruled out in relation to oral exposure. As neither butanone oxime nor 2-petanone oxime have any genotoxic potential a carcinogenic mode of action is considered as having a threshold level. For such non-genotoxic carcinogens, the induction of tumours is typically driven by sustained toxicity towards the target organs and the development of tumours are a follow of this. Thus, if toxicity in the organs is avoided the carcinogenic potential is avoided as well. So, if exposure is kept below the threshold for any sign of toxicity then no concern for carcinogenic effects applies.

For *4-methylpentan-2-one oxime* as a leaving group no conclusion can be made based on specific experimental data on the substance or the data from the QSAR predictions. The toxicity often decreases with increasing molecular size within a homologue group of chemicals as the data on butanone oxime and 2-pentanone oxime also indicate. Although it could be tempting to conclude that *4-methylpentan-2-one oxime* would be even less toxic than 2-pentanone oxime this would warrant further data to substantiate such a conclusion.

6 References

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APPENDIX A

Danish QSAR database and predictions on:
butanone oxime, CAS 96-29-7;
2-pentanone oxime, CAS 623-40-5;
4-methylpentan-2-one oxime, CAS 105-44-2

Description of the applied models from the Danish QSAR database:

Case Ultra QSAR model

CASE Ultra is a fragment-based statistical model system. The methodology involves breaking down the structures of the training set into all possible fragments from 2 to 10 heavy (non-hydrogen) atoms in length. The fragment generation procedure produces simple linear chains of varying lengths and branched fragments as well as complex substructures generated by combining the simple fragments. A structural fragment is considered as a positive alert if it has a statistical significant association with chemicals in the active category. It is considered a deactivating alert if it has a statistically significant relation with the inactive category. Once final lists of positive and deactivating alerts are identified, CASE Ultra attempts to build local (Q)SARs for each alert in order to explain the variation in activity within the training set chemicals covered by that alert. The program calculates multiple molecular descriptors from the chemical structure such as molecular orbital energies and two-dimensional distance descriptors. A stepwise regression method is used to build the local (Q)SARs based on these molecular descriptors. For each step a new descriptor (modulator) is added if the addition is statistically significant and increases the cross-validated R2 (the internal performance) of the model. The number of descriptors in each local model is never allowed to exceed one fifth of the number of training set chemicals covered by that alert. If the final regression model for the alert does not satisfy certain criteria ($R2 \geq 0.6$ and $Q2 \geq 0.5$) it is rejected. Therefore, not all alerts will necessarily have a local (Q)SAR. The collection of positive and deactivating alerts with or without a local (Q)SAR constitutes a global (Q)SAR model for a particular endpoint and can be used for predicting the activity of a test chemical.

Leadscope QSAR model

Leadscope Predictive Data Miner is a software program for systematic sub-structural analysis of a chemical using predefined structural features stored in a template library, training set-dependent generated structural features (scaffolds) and calculated molecular descriptors. The feature library contains approximately 27,000 pre-defined structural features such as functional groups, heterocycles and pharmacophores. The training set-dependent structural features (scaffold generation) can be added to the pre-defined structural features from the library and be included in the descriptor selection process. The program also calculates a number of physico-chemical descriptors such as logP, molecular weight and the number of hydrogen bond acceptors and donors. Leadscope has a default automatic descriptor selection procedure. This procedure selects the top 30% of the descriptors (structural features and molecular descriptors) according to X2-test for a binary variable or the top and bottom 15% descriptors according to t-test for a continuous variable. After selection of descriptors the program performs partial least squares (PLS) regression for a continuous response variable, or partial logistic regression (PLR) for a binary response variable, to build a predictive model.

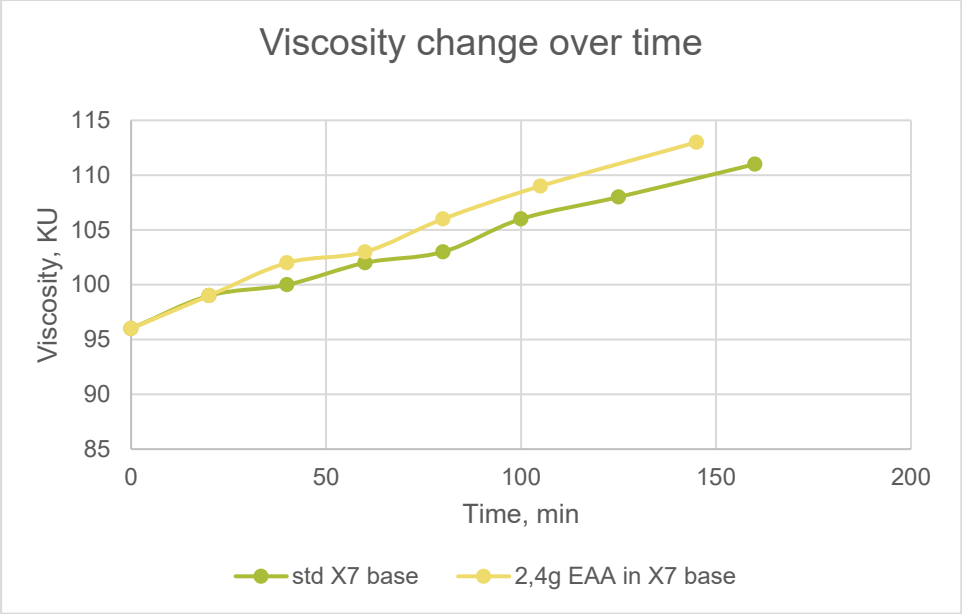
SciQSAR QSAR model

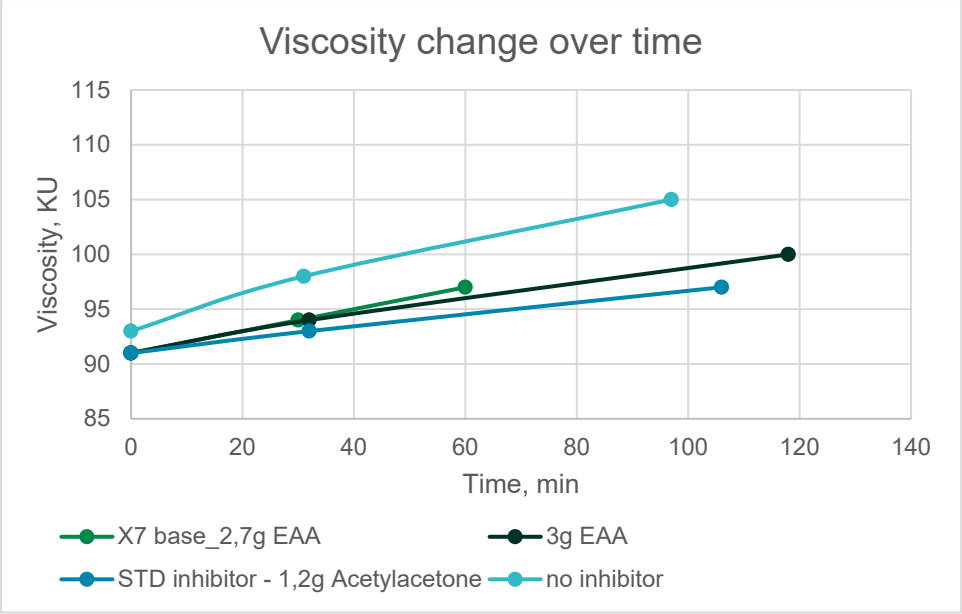
The SciQSAR software provides over 400 built-in molecular descriptors such as connectivity indices, electrotopological (atom E and HE-state) indices, and other descriptors. Furthermore, the program provides a variety of statistical tools that can be used to build predictive models for binary and continuous data. SciQSAR uses discriminant analysis for binary data and includes the capability to perform parametric and nonparametric discriminant analyses. For continuous data, regression analysis is used to build the predictive model, and a number of different regression methods are available such as regression on principal components (PCR) and partial least squares regression (PLS).

- The predictions on the three leaving groups are due to the size of the documents forwarded as separate files -

Appendix 3

Graphs showing how the viscosity changes over time for different inhibitors and their concentrations.





Substitution of tin catalyst in antifouling paint

This report describes methods, results and conclusions from a development project between Hempel A/S, DHI and Danish Technological Institute. The aim of the project was to develop new silicone antifouling paints without the use of tin-based catalysts. The project was supported by the Danish Environmental Protection Agency and carried out in the period 2017-2019.

It was not possible to make a simple 1:1 substitution of the catalyst in this project. It was found necessary to develop a whole new paint system in order to be able to use another type of catalyst or to completely eliminate the need for catalysts.

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