SCENARIO SHEET

Sterling

Designing a safe and scalable diazomethane process

THE SITUATION

Diazomethane is a powerful methylating agent[1] that has many potential use cases in API development and manufacturing, but its highly reactive nature also makes it highly explosive. Diazomethane's toxicity and ability to detonate even in the absence of air, makes it exceedingly difficult to work with at large scales.

In some cases, diazomethane is the most efficient and effective means of achieving a desired chemical product, but many manufacturers refuse to work with such a volatile compound. Handling diazomethane in a safe and scalable way requires significant research and testing, specialised equipment and a thorough approach to hazard evaluation and prevention.

THE CHALLENGES

Safety considerations

While most compounds require oxygen to detonate, diazomethane can explode without exposure to air. Beyond its explosive properties, diazomethane is also a highly toxic respiratory irritant with a number of potential health hazards and a permissible exposure limit of only 0.2 ppm TWA.[1] This makes it a particularly challenging compound to work with, requiring stringent containment and safety measures. Thorough testing must occur to understand at which point the material explodes, evaluate the starting material's explosive potential and proactively mitigate the risk of safety incidents.

Limited resources

Because of diazomethane's high sensitivity and significant potential for detonation, it is not commercially available and must instead be synthesised for use in reactions. Its lack of availability, coupled with its toxic and explosive properties, prevent most organisations from handling this material at a large scale. In addition, since the substance is so dangerous to handle and hazard naturally increases with volume, most published research on diazomethane comes from academic studies that have been carried out at a small scale. Therefore, significant additional research and testing is required to work with diazomethane in a safe and scalable way.

Specialised equipment and containment

Because diazomethane is not widely used in API development, researching, manufacturing and utilising it requires specialised equipment to ensure it is properly handled and contained at all times. In particular, highly pressurised equipment is critical for testing diazomethane's explosive potential in a lab setting, with remote operation and monitoring to keep human operators at a distance. After thorough testing, diazomethane may be handled at the plant scale, but only with continuous monitoring by team members who have significant knowledge of safety protocols.

The Sterling solution

At Sterling, we have more than 50 years of expertise in complex and hazardous chemistry to mitigate risk and develop purpose-built processes for our customers' hazardous projects, including those that involve diazomethane.

Thorough testing for hazard mitigation

Because limited literature exists around handling diazomethane at a large scale, Sterling's approach is built upon significant research to help overcome key challenges associated with the substance in order to design a safe and scalable process. Sterling has performed extensive lab work to assess the material's explosiveness. The team's results aligned closely with the limited published material available on diazomethane reactions. In some cases, the starting material used in a process may also pose a risk of explosion, requiring its own set of research to demonstrate safety for use.

Safely handling diazomethane first requires a thorough assessment of which conditions result in explosion and the identification of a lower explosion limit. To mitigate the risks associated with this testing process, Sterling utilises custom-made equipment, with a pressure of 1,400 PSI to ensure safe containment in the event of an explosion. This equipment works in combination with infrared online detection equipment to carefully monitor and maintain reaction conditions. With a primary focus on operator safety, the Sterling engineering team developed remote operation and monitoring capabilities to enable full operator control during testing without proximity-associated risks.

Safe and scalable process design

Based on our evaluation of the explosive potential of diazomethane and numerous smaller scale trial runs, the Sterling team defined an upper limit for how much material can be used in a reaction vessel at a given time. This level was set with an especially high safety margin to mitigate risk and ensure operator and plant safety.

With an appropriate limit defined and all necessary safety and containment measures in place, the Sterling team has successfully run diazomethane projects at the plant scale with zero safety incidents. Drawing upon our rigourous research and careful methodology for containment, we can now safely and efficiently perform diazomethane reactions up to the 100-kilogram scale.

Ongoing research for continuous improvement

While Sterling has developed and proven a safe process for diazomethane reactions at the plant scale using batch reactors, the team continues to perform process improvement work to support diazomethane reactions using continuous manufacturing. As only small volumes of material at a time are processed in flow reactors relative to traditional batch reactors, a continuous manufacturing method for diazomethane can deliver significant safety and efficiency advantages. To support this approach, the team at Sterling's Centre of Excellence in Flow Chemistry is currently testing continuous processing for diazomethane using several different starting materials to determine their viability for manufacture.

> "Diazomethane is a unique substance, and it was absolutely critical that we performed thorough research and small-scale studies before handling it at a large scale. The team put a great amount of time and effort into testing and developing a safe and scalable process, and I look forward to the potential to handle this compound with continuous manufacturing."
>
> **- Paul Fenwick,**
> *Hazard Evaluation Manager, Sterling Pharma Solutions*

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1. Diazomethane. National Library of Medicine. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/Diazomethane

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