Loss of control of a chemical reaction in a pharmaceutical plant

19 September 2017

Aramon (Gard)

France

Chemicals
Organomagnesium
Exothermic reaction
Rupture disc
Qualification

THE INSTALLATIONS CONCERNED

The site:

The company, located in the municipality of Aramon (Gard), is specialised in the manufacture of active ingredients for the pharmaceutical industry. In operation since 1973, the plant has 23 reactors with a total capacity of 100 m^3, which are used to conduct various chemical reactions (bromination, hydrogenation, crystallisation, etc.). The facility has 130 employees.

The site is located along the Rhone River, and no homes are located nearby. It is classified low-threshold SEVESO.

The unit involved:

The event took place in a workshop consisting of the following equipment:

- a 4,000-litre dual-wall stainless steel reactor, in which organomagnesium is manufactured,
- a 300-litre gauge,
- a condenser and post-condenser,
- containers to recover distillates,
- vacuum lines (discharge and pump),
- a vent line connected to a discharge tank, then to the VOC processing unit, all equipped with check valves.

All the equipment is protected by a rupture disc calibrated at 0.4 bar.

The reactor involved was the one used to synthesise organomagnesium. This synthesis takes place in an inert atmosphere, creating a reaction of an organo-bromine with magnesium, in a tetrahydrofuran (THF) solution, based on the following equation:

$$R\text{-}Br + Mg \rightarrow R\text{-}Mg\text{-}X$$

Synthesis begins with a primer from the previous batch. A fraction of para-bromo-N,N dimethylaniline (PBDMA) is added to the solution which starts the magnesium synthesis reaction. This synthesis is highly exothermic but is slow to start.

The signs of a start are:

- appearance of foam or a slight boil,

- temperature rise from 25°C to 34°C,
- slight reflux.

As soon as the reaction occurs, the PBDMA is gradually poured from the measuring vessel at a temperature between 21°C and 24°C for a period of 5 hours. An operator must be present in order to monitor the pressure and temperature variations and to control the introduction of reagent.

THE ACCIDENT, ITS CHRONOLOGY, EFFECTS AND CONSEQUENCES

The accident:

The incident began around noon on a Saturday when a new production batch of organomagnesium was being started. At the end of his shift, a technician loaded a priming quantity of 3.8 kg instead of 21 kg into the magnesium and THF solution, having confused the technical quantity of 100% with the quantity in solution at 18% indicated in the procedure.

In the afternoon, the technician on the following shift continued the synthesis of the organomagnesium without knowing that the quantity of primer was insufficient. He loaded the quantity of PBDMA (a bromo-organohalogen compound) stipulated in the procedure but in excess in relation to the quantity of primer present. As magnesium synthesis did not start (absence of exothermicity) after the first pouring (set at 36 l), the technician added another 36 l of PBDMA solution as provided for in the procedure, but without informing his supervisor. He noticed slight bubbling and waited 45 minutes for the temperature to change. While the medium continued to boil, he continued to gradually add the reagent, by volumes of 10 l, up to 500 l, always waiting for a temperature rise between additions, as is expected when the reaction starts.

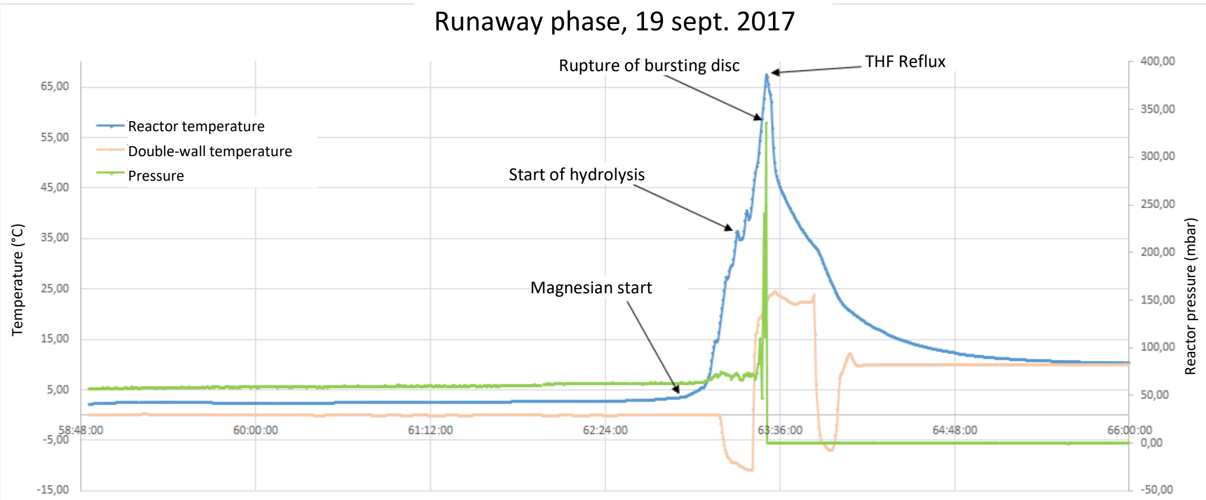
In the absence of exothermy, the technician finally notified the supervisor on-call late in the afternoon. The supervisor stopped the introduction of reagent and lowered the temperature of the reaction medium to 0 °C, with slow agitation. The permanent cooling of the reactor via the dual-wall allowed the energy to be dissipated and to avoid a runaway reaction. The reaction was stopped at 0 °C. The mixture was to be reprocessed at a later date. Nothing happened for 72 hours, during which the operator sought a solution to recover the mixture.

On Tuesday morning, at 9:20 a.m., a rapid increase in the temperature of the reaction medium was observed. At that time, the personnel present in the workshop began flooding the mixture in the reactor with water in an attempt to control the temperature. The medium, in the process of hydrolysis, produced a vigorous boil. The pressure in the reactor increased to the point that the rupture disc burst (calibrated at 0.4 bar), and was released through the stack on the workshop's roof.

As a precaution, the internal contingency plan was initiated at 9:30 a.m. and the workshop was evacuated. The operators continued to introduce water, and the boiling decreased rapidly until finally stopping. The medium stabilised at 10°C with slow agitation in the reactor.

The internal contingency plan was lifted at 9:35 p.m. No consequences were noted, and there was no release of the reaction medium into the atmosphere.

The operator established “real-time” communication with the production crews to provide information regarding the situation that led to the triggering of the internal contingency plan.

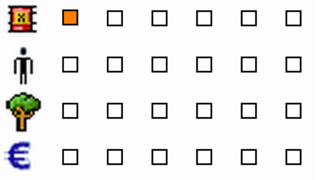


The consequences:

The operator suffered production losses as a result of the flooding of the batch in the reactor. Approximately 2,000 litres of THF, primer, PBDMA, and flooding water was drained from the reactor and filtered. The sludge was sent to an external entity for incineration, and the filtered effluents were processed at the site's wastewater treatment facility. There was no impact on the reactor itself. It was returned to service after cleaning, drying and replacement of the rupture disc.

European scale of industrial accidents:

By applying the rating rules applicable to the 18 parameters of the scale officially adopted in February 1994 by the Member States' Competent Authority Committee for implementing the "SEVESO" Directive for hazardous substances and in light of available information, this accident can be characterised by the following four indices:



The substance in question is classified SEVESO with a threshold of 50 T. No product was released, so the index for the hazardous materials released is therefore 1 (see parameter Q1).

No human, social or environmental consequences were observed. No data is currently available regarding the economic consequences.

The parameters associated with these indices and their rating scale are available at the web site: https://www.aria.developpement-durable.gouv.fr/en-cas-daccident/echelle-europeenne-des-accidents-industriels/

THE ORIGIN, CAUSES AND CIRCUMSTANCES SURROUNDING THIS ACCIDENT

1- An ambiguous procedure which led to an operating error:

The incident originated from the ongoing operation in the reactor, which did not comply with the manufacturing specifications. At his workstation, the technician had a production sheet that listed each action to be carried out. The sheet indicated the quantity to be loaded:

“3.8 kg to 100% at coefficient 1 and 3.8 kg (100%)/0.18 = 21 kg of solution”.

Despite his experience, the technician, at the end of his shift, had misinterpreted this instruction as the wording could have been confusing.

2- A lack of communication:

The technician on the following shift was unaware of the quantity of primer that was 5 times lower than expected: the production sheet for these operations was used by the first technician, correctly filled in and then forwarded to the operator. Communication between the 2 technicians proved to be insufficient.

3- Absence of a technician stopping point to correct the error:

The procedure provided for the possibility of adding reagent if the reaction did not begin. In this case, approval from the supervisor is required. Given the low availability of the hierarchy on that day (weekend), each time the reagent (PBDMA) was added, the 2nd technician waited for the temperature to change between each addition. With each addition, he noted slight boiling in the reactor, indicating that the reaction had started. He thus continued to add reagent, thinking that the reaction was going to start. In any case, it would not have been possible to correct the amount of primer after the reagent had been added.

On average, the production cycle lasts 5 to 6 hours. Seeing that the reaction had not started late in the afternoon, the technician who had added the excessive amount of reagents informed the on-call staff.

4- Appropriate decision-making that limited the consequences:

The reaction situation which the technicians encountered during the synthesis (low priming effect, large quantity of reagent) had not been taken into account by the operator in specific instructions.

The mixture was maintained at 0°C because the organomagnesium synthesis reaction was known as being impossible at that temperature. This decision, made by the workshop foreman, finally made it possible to stop the reaction but, given the quantities of reagents added, the batch could not be used.

The anomaly (lack of primer) was quickly identified based on the analysis of the worksheet and the weight of the primer drum.

5- A totally unexpected loss of control of the reaction:

According to the operator, the highly exothermic reaction had occurred 72 hours after having "frozen" the mixture, as the reagents (primer + PBDMA) were present in the mixture and eventually reacted together. The cooling effect generated by the glycol-water in the dual-wall of the reactor was intended to stop the reaction that eventually took place. The start of the reaction caused the temperature to rise rapidly.

At a temperature above 35°C, the flooding of the reactor with water caused a hydrolysis reaction. The organomagnesium decomposed into magnesium hydroxide and bromine hydroxide with a high accumulation of energy and heat, which caused the pressure to rise and the reactor disc to rupture.

The modelling of the disturbances and causes leading up to the incident is available in the appendix.

ACTIONS TAKEN

This event resulted in a site visit by the Classified Facilities Inspection authorities, which noticed the immediate actions undertaken by the operator. In order to avoid this type of accident, the operator has:

- modified the production worksheet to eliminate any risk of misinterpretation and clarified the quantities of reagents to be loaded;
- instituted audits to evaluate compliance with the manufacturing procedures;
- updated the qualification procedures for the production staff.

The Classified Facilities Inspection authorities have requested that the operator monitor these actions, in particular through the procedures of its safety management system. Although the site is classified only as low-level SEVESO, its prefectoral authorisation decree requires the implementation of a safety management system.

LESSONS LEARNT

Once the immediate actions had been undertaken, the operator began implementing long-term corrective actions.

1- Technician training and qualification:

The operator has reference manuals and procedures for the training and qualification of workshop personnel. An internal accreditation system had been created for staff performing the organomagnesium syntheses.

The operator stopped the accreditation system after the transition to the 5-day, 8-hour shift schedule in August 2016, due to the increase in the number of synthesis operations, the increased number of people performing these duties, and the absence of incidents. The process was seen as “routine,” in spite of the highly exothermic nature of the reactions.

Following the incident, however, the operator resumed the accreditation system. Organomagnesium synthesis is a complex reaction, which requires specific expertise, mainly to get the reaction started. The operator updated the procedures to improve the qualification level of employees and to ensure follow-up of “accredited” technicians. These reactions are now supervised by highly experienced people. A collection of good practices regarding organomagnesium synthesis has also been created.

2- Criticality study and planning:

Since this incident, the operator has analysed all the synthesis reactions conducted at the site. A reaction rating system was set up to strengthen training according to the rating and to define which operations could be conducted during the day, at night and on weekends depending on their criticality. It is now prohibited to initiate organomagnesium synthesis reactions in the evening and over the weekend. Such operations can only be initiated at the start of a shift so that the same crew can monitor the entire process.

3- Review of risk analysis and improvement of safety:

Following this incident, the operator initiated a detailed review process for organomagnesium syntheses in order to establish manufacturing and reaction standards to deal with any anomalies encountered, applicable to all the group's plants concerned.

A working group was set up in late 2017. This group conducted the HAZOP (Hazard Operability analysis) of the synthesis reaction, which made it possible to:

- rework the production sheet with stopping points for the operators during the preparation and start of the reaction. For example, a checklist is provided to validate or invalidate the start of the synthesis reaction;

- implement reflex action sheets explaining the steps to be taken if the reaction does not start;

- issue recommendations to improve the process. For example, limiting the volume of reagent introduced by installing a technical barrier on the measuring vessel, and searching for other barriers to monitor reactions on key parameters: temperature, pressure, visual appearance (bubbling, etc.). The human barrier remains essential given the specificity of magnesium synthesis reactions. This is why the operator has reinforced the sharing of experience and the development of technicians' skill level. Campaigns to raise operator awareness have been conducted to present and explain the new production sheets and the reflex action sheets.

The observations made by the working group following the accident have led to the conclusion that the synthesis reaction can start regardless of the temperature of the medium, as long as the reagents have been mixed, with very slow kinetics. The temperature ultimately has a regulating role in preventing a poison formation reaction.

The group also defined the usage rules and quality standards regarding magnesium: very stable magnesium will be used, in small containers to avoid venting during handling.

The working group also made it possible to share feedback between the group's sites and chemists in general.

The objective was thus to translate the results obtained by the working group into site-specific action plans in collaboration with the sites' process industrialisation managers.

Appendix, detailed sheet: modelling of disturbances and causes which led to rupture of the bursting disc