Carbon monoxide can be formed when volatile anaesthetic agents such as desflurane and sevoflurane are used with anaesthetic breathing systems containing carbon dioxide absorbents. Initial anecdotal reports suggested that soda lime and Baralyme* absorbent (Table 1) could produce CO from inhaled anaesthetics. The first cases involved enflurane [1] and isoflurane [2]. Thirty-one cases of intra-operative CO poisoning were described, with some CO concentrations exceeding 1000 parts per million and carboxyhaemoglobin (COHb) concentrations reaching 30% or more. With desflurane, COHb concentrations of 32% were reported [3, 4].

In vitro experiments showed that with dried absorbents, CO production was in the following order: desflurane > enflurane > isoflurane and was trivial with halothane and sevoflurane [5]. Degradation appears to be inversely related to the water content of the absorbent and occurs more with Baralyme than with soda lime. It was shown in vitro that the rehydration of desiccated Baralyme prevents CO formation from desflurane [6]. A difluoromethoxy group is a structural requirement for halo ether degradation to CO [7]. The typical case of CO poisoning is the first patient on a Monday morning (Monday morning disease), when after the weekend an anaesthetic machine is used through which high gas flows had been maintained, resulting in drying of the absorbent.

**CO production**

Early studies found that sevoflurane was less stable than might be desired and that it breaks down at a rate determined by temperature: 13% over 1 h at 40 °C and 56% at 60 °C [8]. Baralyme produced a four-fold greater degradation of sevoflurane than did soda lime (0.66 ml.min⁻¹ vapour vs. 0.17 ml.min⁻¹), inducing a slight delay at the start of anaesthesia [9]. Degradation to compound A was inhibited by chilling the soda lime canister to 26 °C [10]. Baralyme dehydration increased and soda lime dehydration decreased the concentration of compound A in an in vitro model [11]. Until 2000 it was thought that the breakdown of sevoflurane was more or less associated with the production of compound A and that among the inhalation anaesthetics, CO production was mainly associated with desflurane. Indeed, in pigs anaesthetised with desflurane, high COHb concentrations were found when the CO₂ absorbent was partially dried [12]. With dehydrated Baralyme, peak CO concentrations of 37 000 ± 3500 parts per million and COHb concentrations of > 80% were found. It came as a surprise when Holak *et al.* reported that, with sevoflurane in
Specific experimental circumstances in vitro, the generation of 11 000 parts per million CO occurred, followed by an explosion and fire when the canister temperature exceeded 200 °C [13]. It is therefore of interest to review all the known in vitro and in vivo assessments concerning the production of CO, particularly with sevoflurane, and to describe the scarce clinical data on this problem.

**Laboratory studies with small amounts of soda lime and strict temperature control**

In an early effort to analyse the production of CO, barrels of simple 30-ml syringes were used with the open ends sealed with rubber corks, pierced with a needle through which gases were passed [5]. Dried and partially dried (1.4–9.7% water) absorbents (soda lime and Baralyme) were examined. Desflurane, enfurane and isoflurane were analysed at 25–45 °C, and halothane and sevoflurane at 45–60 °C. The magnitude of CO production was in the order: desflurane > enfurane > isoflurane > halothane = sevoflurane. Completely dry soda lime produced more CO than partially dry soda lime. Baralyme produced more CO than soda lime. An increased, controlled absorbent temperature increased CO production. At 60 °C the peak CO concentrations were only 79 parts per million with 3.6% sevoflurane (Table 2). In another study, sealed 20.7-ml vials were used which contained desiccated absorbent and a filter paper onto which anaesthetics were injected for volatilisation [7]. CO formation from desflurane, enfurane and isoflurane was greater with Baralyme (containing 4.6% potassium hydroxide) than with soda lime (containing only 2.5% potassium hydroxide), probably through greater base-catalysed difluoromethoxy proton removal with potassium than sodium hydroxide (Fig. 1).

**In vitro studies using clinical absorber systems**

In more clinically relevant studies, larger amounts of CO2 absorbents were studied in standard canisters with no control of absorbent temperature. Halothane, enfurane and isoflurane were assessed in a Dräger ISO system filled with completely dried CO2 absorbent [14]. Peak CO of 3500 parts per million was recorded with enfurane and isoflurane. Although maximal CO concentrations of only 450 parts per million were found with halothane, the temperature increased to 50 °C and more. Interestingly, it took about 75 min to attain a measurable halothane concentration. These findings suggest that halothane is absorbed in dried soda lime, with an exothermic chemical reaction between the absorbent and the anaesthetic.

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**Table 1** Brand and composition of CO2 absorbents mentioned in this review.

<table>
<thead>
<tr>
<th>Brand</th>
<th>Company</th>
<th>NaOH (%)</th>
<th>KOH (%)</th>
<th>Ca(OH)2 (%)</th>
<th>CaCl2 (%)</th>
<th>Ba(OH)2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baralyme</td>
<td>Chemetron, St. Louis, MO</td>
<td>–</td>
<td>5.3</td>
<td>74</td>
<td>–</td>
<td>11</td>
</tr>
<tr>
<td>Soda lime</td>
<td>Several</td>
<td>2–4</td>
<td>1–3</td>
<td>94</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Drägersorb 800</td>
<td>Dräger, Lübeck, Germany</td>
<td>2</td>
<td>3</td>
<td>79</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DrägerSorb Free</td>
<td>Dräger, Lübeck, Germany</td>
<td>3–5</td>
<td>–</td>
<td>74–82</td>
<td>3–5</td>
<td>–</td>
</tr>
<tr>
<td>Sofnolime</td>
<td>Molecular product, Thaxed, UK</td>
<td>3</td>
<td>–</td>
<td>&lt; 75</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Amsorb</td>
<td>Armstrong, Coleraine, Northern Ireland</td>
<td>–</td>
<td>–</td>
<td>83</td>
<td>0.7</td>
<td>–</td>
</tr>
<tr>
<td>AmsorbPlus</td>
<td>Armstrong, Coleraine, Northern Ireland</td>
<td>–</td>
<td>–</td>
<td>83.2</td>
<td>0.7</td>
<td>–</td>
</tr>
</tbody>
</table>

---

**Table 2** Peak CO concentrations in laboratory experiments.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Inhalation agent</th>
<th>Peak CO concentration (parts/10⁶)</th>
<th>Temperature</th>
<th>CO₂ absorbent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang (1995) [5]</td>
<td>3.6% sevoflurane</td>
<td>79</td>
<td>60 °C</td>
<td>Soda lime</td>
</tr>
<tr>
<td>Strauss (1996) [14]</td>
<td>Enflurane/isoflurane</td>
<td>3500</td>
<td>52.1 °C</td>
<td>Soda lime</td>
</tr>
<tr>
<td>Stabernack (2000) [23]</td>
<td>Desflurane</td>
<td>36 000</td>
<td>Dried Baralyme</td>
<td></td>
</tr>
<tr>
<td>Wissing (2001) [25]</td>
<td>5% sevoflurane</td>
<td>1600</td>
<td>130 °C</td>
<td>Drägersorb 800</td>
</tr>
<tr>
<td>Holak (2003) [13]</td>
<td>2.1% sevoflurane</td>
<td>11 000</td>
<td>&gt; 110 °C</td>
<td>Dried Baralyme</td>
</tr>
</tbody>
</table>
breathing tubing. With dried CO\textsubscript{2} absorbent and sevo-
flurane, no sevoflurane could be detected for about
20 min, followed by a short-lasting overshoot (about
twice the vapour dial). An irritating smell was also
noticed. In a Dräger circle system, sevoflurane 8% in O\textsubscript{2}
6 l min\textsuperscript{−1} was washed into the canister in which there was
previously dried Drägersorb 800 (containing potassium
hydroxide (KOH)) or Sofnolime (KOH free) CO\textsubscript{2}
absorbent [16]. With dry soda lime, sevoflurane could
not be measured before 3 min but compound A and
methanol were detectable after only 1 min, with an
absorbent peak temperature of 110 °C. Formaldehyde
was detected only with dry soda lime. Significant
interaction with inhalation anaesthetics was not observed
if the water content of the CO\textsubscript{2} absorbent was >5%.
Sevoflurane degradation was aggravated by high KOH
content of the lime. It was suggested that clinical airway
irritation might be caused by formic acid, which is
generated with methanol by the Cannizzaro reaction
(Fig. 2), in which certain aldehydes may undergo in
concentrated alkali: one molecule of the aldehyde is
reduced to the corresponding alcohol and another
molecule is simultaneously oxidised to the salt of a
carboxylic acid.

**Animal studies**

Baralyme was 'conditioned' by passing a 5 l min\textsuperscript{−1} O\textsubscript{2}
flow through the canister for 40 h [17]. Pigs were
anaesthetised with a rebreathing circuit containing the
dehydrated Baralyme and using sevoflurane, aiming at
an end-tidal concentration of 3.0–3.2%. Compound A
peaked at a concentration of 357 parts per million and the
Baralyme temperature at 310 °C. However, in one
experiment the temperature rose very rapidly, reaching
401 °C after 80 min, the absorbent began to melt,
smoulder and smoke appeared in the circuit. CO

![Figure 1](image1.png)

**Figure 1** Simplified mechanism of carbon monoxide (CO) formation from desflurane (Baxter); the source of CO is the –CF\textsubscript{2} moiety.

![Figure 2](image2.png)

**Figure 2** Cannizzaro reaction showing the production of methanol (from Morio et al. [21], with permission).
concentrations were not analysed. In the study by Frink et al. [12] Baralyme or soda lime dried for 24 or 48 h was used while anaesthetising pigs with desflurane in a conventional circle system. Extremely high COHb concentrations of > 80% were found with Baralyme dried for 48 h. For CO2 absorbents dried for 24 h, peak CO concentrations of 8800–13 600 parts per million were reached. Peak COHb concentrations of 73% for Baralyme and 53% for soda lime were recorded with absorbent temperatures of 50 °C. Sevoflurane was not assessed in this study.

Clinical information
In a large clinical trial of patients having low-flow anaesthesia, no evidence of accidental CO intoxication was found when the CO2 absorbent was properly maintained [18]. Severe CO poisoning during desflurane anaesthesia has been reported [19]: in a 24-year-old woman during 5% desflurane anaesthesia in the presence of dehydrated Baralyme, the S\textsubscript{a}O\textsubscript{2} decreased to 93% and HbO\textsubscript{2} to 63%, and 36% COHb was found. She recovered completely after immediate replacement of the Baralyme. Five cases were reported in which sevoflurane reacted with accidentally dried soda lime [20]. In a 14-year-old girl, despite a vapour concentration of 8% sevoflurane on the dial, an effective circuit concentration of less than 1% was found; the insufflation pressure was high at 45 cm H\textsubscript{2}O and the O\textsubscript{2} saturation decreased to 81%, followed by coughing, tachycardia and cyanotic skin colouration. Arterial blood gas analysis revealed a COHb concentration of 4.4% (Table 3). The soda lime turned dark blue and subsequent analysis showed a water concentration of only 1.3%. The girl had to be ventilated for 1 day, and had coughing and mild dyspnoea for some days, but she had recovered completely by the 9th day. In a 2-year-old boy, induction with 4% sevoflurane by mask produced intense coughing and, despite an increase to 7% sevoflurane, induction was not successful in the next 15 min, with coughing and extreme salivation. It was noticed that the CO2 absorbent had turned blue and that the canister was extremely hot, while a pungent smell escaped. An arterial sample revealed a COHb concentration of 8.4%, which decreased to 3.4% after 3 h ventilation. Subsequent analysis of the soda lime showed that it was completely dry, as it had not been changed for 3 weeks. In another 2-year-old boy, induction with 7% sevoflurane by mask produced intense coughing and salivation. The breathing gases had an irritating smell, the breathing tubes were hot and water vapour was generated. The CO2 absorber felt overheated and the CO2 absorbent turned blue; subsequent analysis showed a water content of 0.5%. In two inductions with sevoflurane 2.5% in boys weighing 18 and 22 kg, less than the expected concentrations were found: in the first, changing to isoflurane resolved the problem, while in the second, a blue colouration of the CO2 absorbent was noticed; the O\textsubscript{2} saturation was unchanged. After changing the CO2 absorber, anaesthesia progressed without problems. It was found that the CO2 absorbent in the induction room had not been changed for 3 weeks. All the above-mentioned cases fortunately recovered, thanks to early diagnosis and appropriate measures. They clearly show that in routine clinical practice, sevoflurane reacts with accidentally desiccated CO2 absorbents by absorption and/or destruction of the anaesthetic and with intense heat generation. In another published case, a 46-year-old woman could not be induced with 5% sevoflurane, but the temperature of the absorbent canister increased sharply and the Drägersorb 800 absorbent turned blue, with condensing water visible in the tubing. Subsequent analysis showed a water content of < 1% [21].

Studies in the last 5 years with more modern CO2 absorbents
During the last 5 years, the particular importance of the chemical composition and brand of the CO2 absorbent has been recognised. The strong alkali hydroxides, KOH and sodium hydroxide (NaOH), were held responsible for the decomposition of inhalation anaesthetics and elimination of these substances have made the CO2 absorbent safer, as tested in a study published in 1999 [22]. That study, using barrels of 30-ml syringes, demonstrated

<table>
<thead>
<tr>
<th>Patient (age or body weight, sex)</th>
<th>Inspired sevoflurane</th>
<th>Clinical problems</th>
<th>Oxygenation</th>
<th>Absorbing characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 year, ♂</td>
<td>8%</td>
<td>Coughing, tachycardia</td>
<td>O\textsubscript{2} sat = 81%; COHb = 4.4%</td>
<td>Blue; H\textsubscript{2}O = 1.3%</td>
</tr>
<tr>
<td>2 year, ♂</td>
<td>7%</td>
<td>Coughing, salivation</td>
<td>COHb = 8.4%</td>
<td>Blue, hot; dry</td>
</tr>
<tr>
<td>2 year, ♂</td>
<td>7%</td>
<td>Coughing, salivation</td>
<td>O\textsubscript{2} saturation normal</td>
<td>Blue; H\textsubscript{2}O = 0.5%</td>
</tr>
<tr>
<td>18 kg, ♂</td>
<td>2.5%</td>
<td>Concentration not reached</td>
<td>O\textsubscript{2} saturation normal</td>
<td>Light blue; hot</td>
</tr>
<tr>
<td>22 kg, ♂</td>
<td>2.5%</td>
<td>Concentration not reached</td>
<td></td>
<td>Blue; hot; H\textsubscript{2}O &lt; 1%</td>
</tr>
</tbody>
</table>
that NaOH and KOH are the primary determinants of the degradation of desflurane to CO, and that they modestly augment the production of compound A from sevoflurane. Elimination of these bases in the desiccated lime decreased CO production 10-fold and decreased compound A by 41%. In a further study, it was shown that absorbents differ enormously in their capacity to produce compound A and CO [23]. Again, 30-mll barrels immersed in water at 45 °C (at 80 °C for lithium hydroxide (LiOH)) were used. The highest CO production with desflurane was found with Baralyme (36 100 parts per million) dried for 24 h; minimal or no CO occurred with dried Amsorb (containing no NaOH or KOH) and LiOH. In an in vitro experiment, it was found that when exposed to desflurane, enflurane or isoflurane, dehydrated Amsorb produced only minimal CO (1.2, 2.3 and 1.5 parts per million, respectively) [24]. Unfortunately, in these last three studies, the production of CO with sevoflurane was not assessed. When different inhalation agents were passed from bottom to top through a Dräger ISO canister filled with Drägersorb 800 (containing NaOH and KOH) dried for at least 72 h, intense CO formation was noticed with desflurane, enflurane and isoflurane [25]. A smaller but significant production of 1600 parts per million CO was found with 5% sevoflurane, at or after the canister temperature increased to 130 °C. This temperature increase was much higher than with the other anaesthetics. CO production ceases when heat reaches its maximum at the outlet of the canister. The temperature increase seems to precede the production of CO with sevoflurane. In another report, it was suggested that CO could be formed as a reaction product from hexafluoroisopropanol, postulated as an intermediate of sevoflurane degradation [26]. In pigs it has been shown that dried Amsorb (NaOH- and KOH-free absorbent), in contrast to classic soda limes, produced minimal if any CO with desflurane and isoflurane [27]. Sevoflurane was not examined in this context, but dried Amsorb caused negligible formation of compound A with sevoflurane. Consistent with the lack of compound A formation, dehydrated Amsorb did not increase COHb concentrations [27]. During an in vitro study with two new-generation absorbents, DrägerSorb Free and Amsorb Plus, it was found that with desflurane, no CO was formed with either dehydrated absorbent [28], but regrettably sevoflurane was not examined for CO production.

The Holak in vitro study is the most convincing report of the possible dangers of CO generation with sevoflurane and dry CO2 absorbents [13]. The study simulated respiration by the addition of CO2 to an artificially ventilated circuit. Baralyme that had been desiccated for at least 1 week was examined, together with sevoflurane at a 2.1% end-tidal concentration (1 MAC). No significant degree of anaesthetic breakdown or CO production was noticed with normally hydrated Baralyme. Desiccated absorbent produced measurable sevoflurane breakdown; 1 MAC could not be obtained with 2 l.min⁻¹ fresh gas flow, despite a vaporiser output of 8%. Under other conditions, CO concentrations of 239–542 parts per million were recorded. Most clinically relevant, CO concentrations did not occur until the absorbent temperature exceeded 80 °C. The absorbent in the upper canister turned blue. In one particular condition, the upper canister was heated to >110 °C and turned blue within 10 min. An exponential increase in CO concentration began, exceeding 11 000 parts per million after 50 min. Somewhat later, an explosion occurred, together with a flash of light in the breathing circuit. Just before the explosion, formaldehyde and methanol were detected but were not quantified. Interestingly, at no time did the infrared gas monitor detect an erroneous anaesthetic. Holak suggests that CO production depends on the temperature of the absorbent and that 80 °C may be the temperature threshold for important CO production [13]. It is likely that methanol, formaldehyde, CO and sevoflurane all contributed to the development of a flammable gas mixture. In a recent in vitro study [29], desiccated Baralyme was used in an artificially ventilated circuit. With desflurane and isoflurane (1.5 and 3.0 MAC, respectively) the canister temperature increased to a maximum of 100 °C. However, with sevoflurane (1.5 MAC) the temperature increased to over 200 °C and, in two of five runs, flames appeared in the anaesthetic circuit.

**The general problem of CO generation with inhalation agents**

It is now evident that in particular circumstances CO can be formed during sevoflurane administration. A dry CO2 absorbent seems to be essential for this occurrence, and from the published data, it appears that Baralyme is the most reactive absorbent. Although Baralyme is now an outdated CO2 absorbent and is not used in Europe, other absorbents are also reactive. Formal studies are still needed on all the newer NaOH- and KOH-free CO2 absorbents. Holak’s report [13] was so important that it provoked the sending of a ‘Dear doctor’ letter in the USA by the makers of sevoflurane, pointing to the clinical importance of the problem and stressing the need to avoid using dry CO2 absorbent. An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporiser setting may be associated with excessive heating of the CO2 absorbent canister. Lack of significant colour change should not be taken as an assurance of adequate hydration of the CO2 absorbent.
Measures to prevent accidental drying of the CO₂ absorbent in clinical use

Firm guidelines on the use of anaesthetic machines should prevent accidental drying of the CO₂ absorbent contained in the canister of the breathing circuit [20, 30]. After the anaesthetic, the gas flows should be turned off completely, particularly at the end of the day. The CO₂ absorbent should be changed routinely regardless of the state of the colour indicator and certainly if the machine has not been used for some time. Flushing of the breathing circuit with fresh gas before use will not prevent CO exposure [31]. If the gas flow has not been shut off during the night or weekend, the absorbent should be replaced in both canisters [32]. If excessive heat from the CO₂ absorbent canister is noted, the absorbent should be replaced and the patient monitored for CO exposure. There is also a case for using low-flow anaesthesia techniques to preserve the water contained in the CO₂ absorbent.

References


