Juul Labs Science

EVIDENCE FOR ARTEFACTUAL FORMATION OF GLYCIDOL DURING THE ANALYSIS OF ELIQUIDS.

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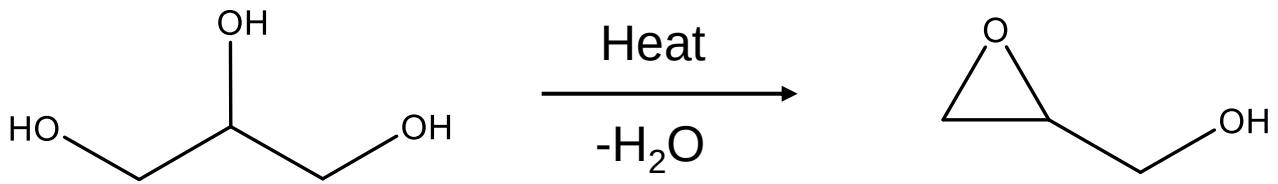
Background

Glycidol

- Probable carcinogen found in e-cigarette vapor.
- Detected in e-cigarette aerosol in 2016 by Sleiman et al#
- Aerosol was generated using an Ego CE4 Tank and Kangertech Aerotank
  - Samples were analyzed using Thermal Desorption with GC-MS detection
  - Collected aerosol was found to contain 32 μg/g* of Glycidol at 3.8V with the Aerotank Tank and 208 μg/g* of Glycidol at 3.8V with the CE4 Tank
  - Experiments conducted with 100% glycerin and 100% propylene glycol demonstrated that glycidol was a thermal degradation product of glycerin



Sleiman et al, Environ. Sci. Technol. 2016, 50, 17, 9644–9651

* = based on device mass loss during aerosol generation

Pyrolysis of Glycerin

- Pyrolysis of Glycerin can lead to the production of a range of thermal degradation products including formaldehyde, acetaldehyde, acrolein and glycidol.
- Moldvoveanu et al presented on the pyrolysis of glycerin (containing about 10% water) at five different temperatures in the range 350 °C to 750 °C, at three different heating rates 20 °C /ms, 5 °C/ms and 1 °C/ms.
- Formation of Glycidol began between 450 °C to 550 °C

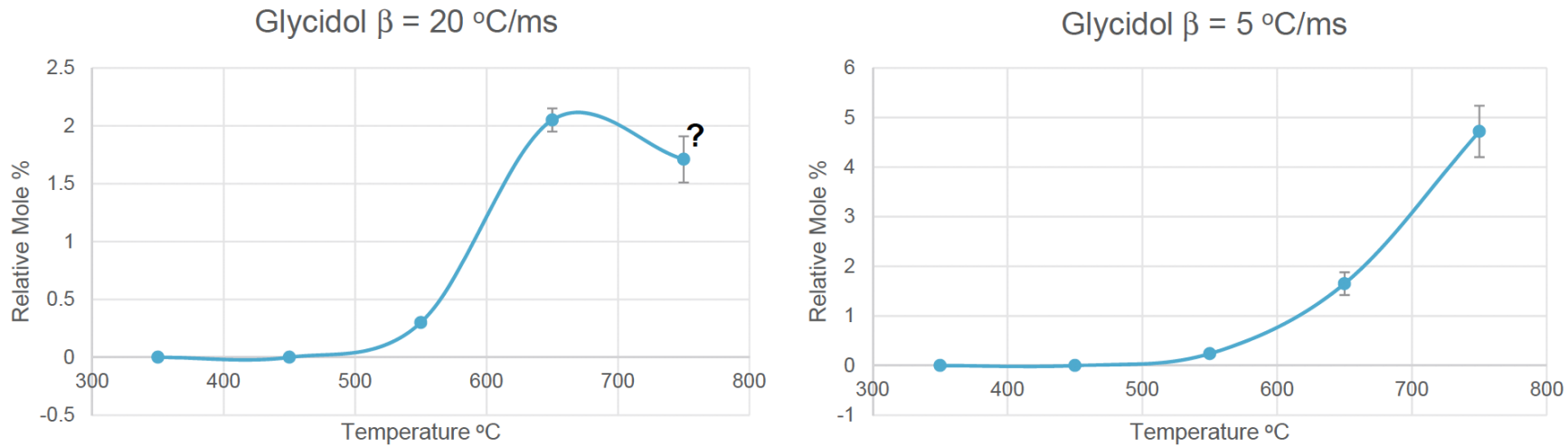
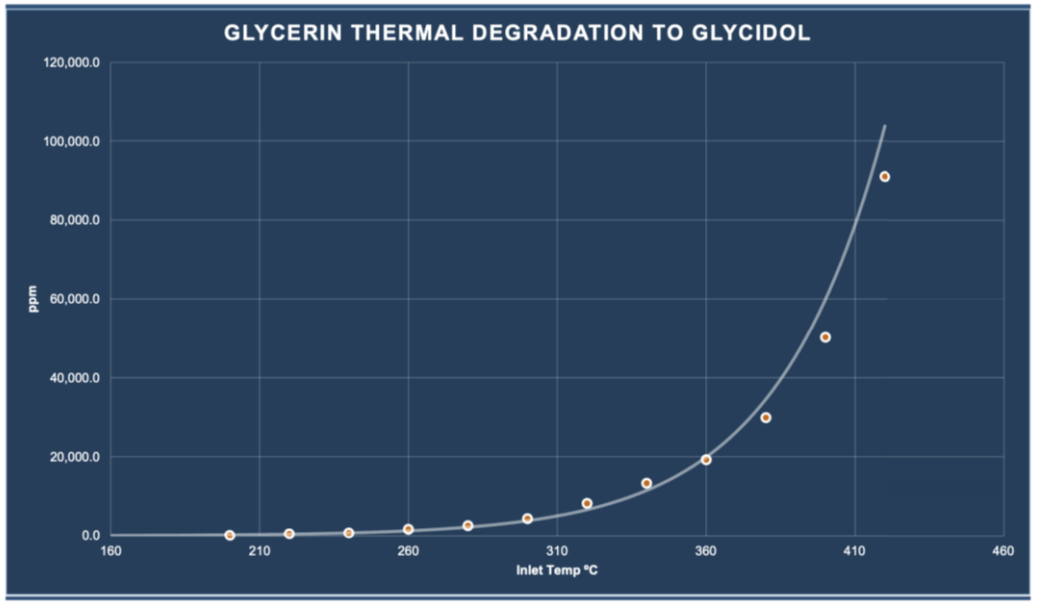


Image from: Pyrolysis of glycerin at different temperatures and heating rates, Moldvoveanu et al TSRC 2018

Formation of Glycidol during GC-MS analysis

- Fraley presented that glycerin could convert to glycidol in a GC inlet at temperatures above 220°C.
- 50 ppm (mg/g) of glycidol was produced at 400°C, with a one-minute residence time in the GC inlet .
- Reported that glycidol can form a glycidol dimer, starting at 100°C, and at elevated temperatures can convert into glycerin.



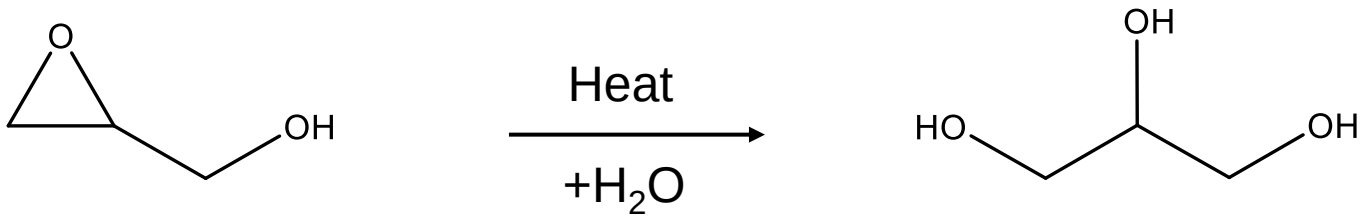
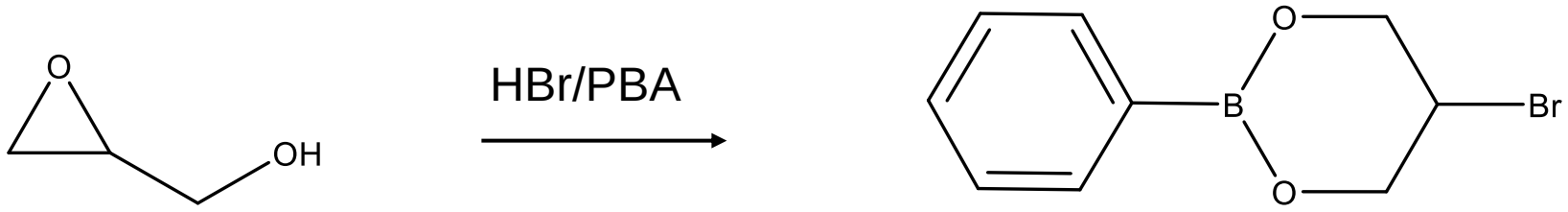


Image from: Glycidol Behavior in GC Systems, Norman Fraley, TSRC 2019

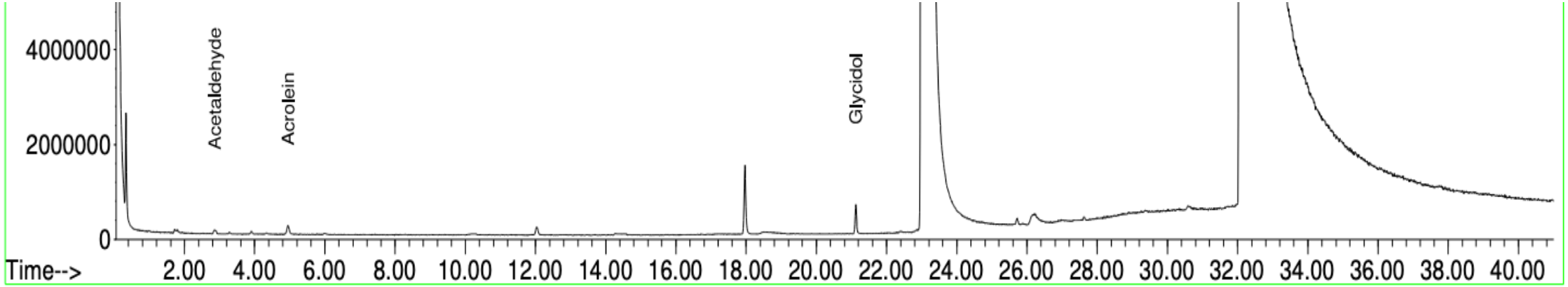
Experimental Design

- Pyrolysis of a liquid containing 60% Glycerin and 40% Propylene Glycol
  - Studies were conducted between 350°C and 575°C in 25°C increments
  - 1 minute hold time prior to GC-MS analysis
- Analysis of the flavored e-liquid formulations containing Glycerin, Propylene Glycol and Nicotine.
  - Direct injection, method based on Health Canada method T-115 with GC-MS detection, injector temperature ~250 C
    - Potential from artefactual formation of glycidol during analysis
    - Susceptible to low molecular mass interferences
  - Derivatization of glycidol prior to injection using HBr and Phenyl Boronic Acid (PBA)
    - Unlikely to form artefactual glycidol during analysis
    - Improved method selectivity and sensitivity



Pyrolysis of mixed Glycerin and Propylene Glycol

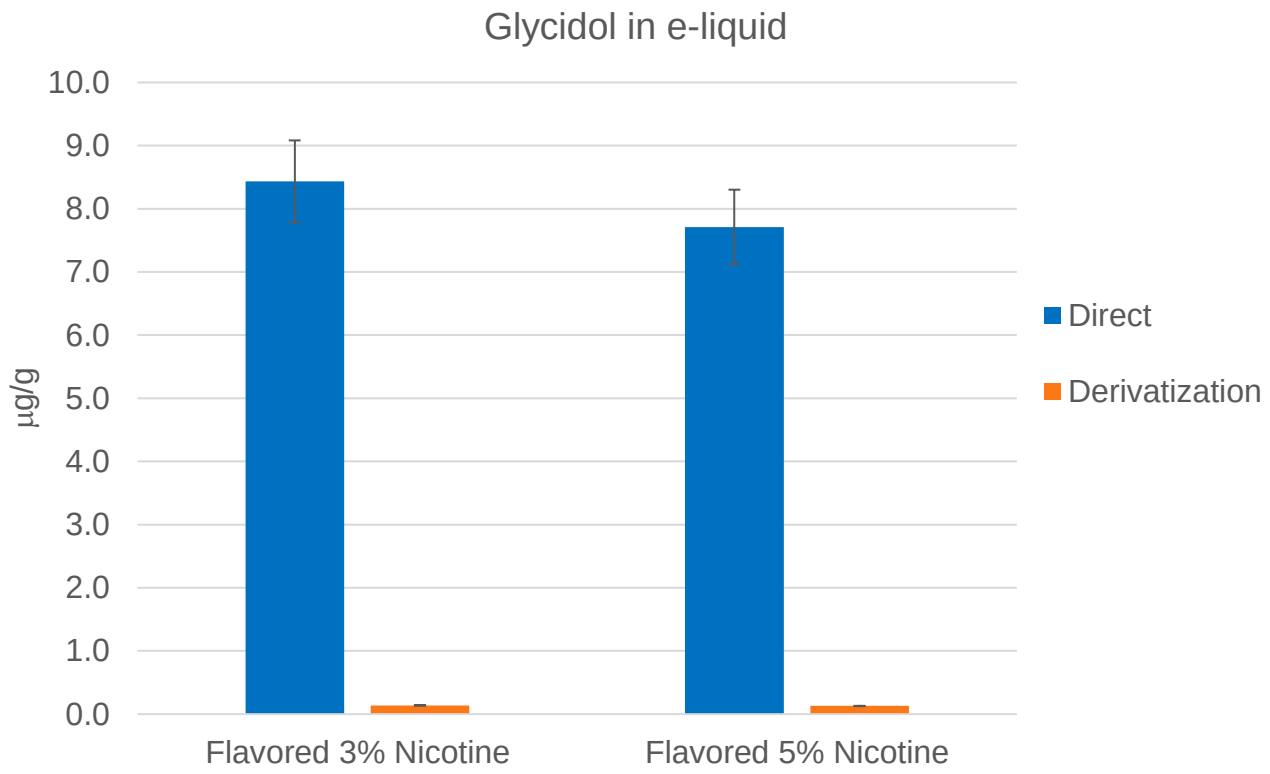
- Samples consisted of 60% Glycerin and 40% Propylene Glycol
  - Studies were conducted between 350°C and 575°C in 25°C increments
  - Frontier EGA/PY-3030D Pyrolyzer with Eco-Cup LF
  - Analysis by GC-MS using an Agilent VF-WaxMS column
  - Glycidol was first formed at 475°C and increased in concentration to 575°C



Pyrolysis of Glycerin at 475°C

Method Comparison

- ~ 8 μg/g of glycidol was measured using the the direct injection GC-MS method
- ~ 0.13 μg/g of glycidol was measured using the PBA derivatization GC-MS method
- Measured levels of glycidol increased by ~60 fold in the Direct injection GC-MS method compared to the Derivatization GC-MS method
- Measured values from the PBA derivatization method were confirmed using a second derivatization method. Values for both methods overlapped within mean and standard deviation of the measured values



Summary

- Our results indicate the direct injection GC-MS analysis can lead to the *in situ* thermal degradation of glycerin to produce quantifiable levels of glycidol.
  - Sleiman et al reported non-detectable levels of glycidol in three e-liquids included in their study.
- Data from two independent derivatization methods demonstrated that ~98% of the measured glycidol from direct injection GC-MS was a by product for the analytical method.
  - The direct injection GC-MS method measured ~8 μg/g of glycidol in two flavored e-liquids.
  - The PBA derivatization GC-MS method measured ~0.13 μg/g of glycidol in the same flavored e-liquids.

Conclusion

- A standardized analytical method for the analysis of glycidol, in e-liquids, does not currently exist.
  - Published or presented work uses a variety of methods including direct injection, cool on column, derivatization and thermal desorption with GC-MS detection.
- Our work indicates that direct injection GC-MS analysis of glycerin containing samples can result in the generation of artefactual formation of glycidol.
  - Our measured values, using the direct injection GC-MS method represent, 3.8% to 25% of the values reported by Sleiman et al, at 3.8V.*
  - Values reported using the direct injection GC-MS method may be biased high due to the artefactual formation of glycidol.

* Sleiman used a Thermal Desorption GC-MS method that is unlikely to produce artefactual glycidol

Conclusion

- Method accuracy should be determined during validation per ICH guidelines. We have demonstrated that comparison of multiple analytical techniques can provide an assessment of method accuracy.
- Our results demonstrate that pyrolysis experiments did not predict the thermal degradation of glycerin that occurred in the GC inlet at 250^{o}C.

Thank you and questions