SOLSTICE® AIR FOR INHALED APPLICATIONS

May 2022

Honeywell

AGENDA

1. Honeywell's Commitment to Carbon Neutrality
2. AIM Legislation
3. Solstice Air – HFO-1234ze properties overview
4. Solstice Air – Toxicology Evaluation
5. Base Formulations
6. GMP Production
7. Conclusion

HONEYWELL COMMITTED TO CARBON NEUTRALITY

Honeywell Commits To Carbon Neutrality In Its Operations And Facilities By 2035, driving Carbon Neutrality internally and supporting customers with their goals.

SOLSTICE® LOW-GWP PRODUCTS

Clear Skies Ahead

Greenhouse gas emissions are being reduced every day as more companies utilize Honeywell Solstice® materials. Scroll down to learn about the dramatic difference being made, and use the calculator at the bottom to see the potential impact your company can make, too.

TO DATE

263,174,000

Metric tons CO_2e have been removed from the Atmosphere by using Solstice Products

Examples of Supporting Customers to reduce Carbon emissions

130,000 metric tons of CO_2e reduction

> 99% reduction in CO_2e vs current propellants

14,000 tones of CO_2eq. Reduction for a typical fleet of 2,000 buses.

Energy use has dropped by 33 percent

25 million metric tons CO_2e per year reduction

Enabling CO_2e reductions through innovation

U.S. AMERICAN INNOVATION AND MANUFACTURING ACT

- The bipartisan American Innovation and Manufacturing (AIM) Act was included in the Omnibus spending bill/COVID relief package recently signed into law in December of 2020.
- The AIM Act mandates a 15-year phase-down of HFCs at a national level, administered by the US Environmental Protection Agency (EPA), and aligned with the Kigali schedule.
- It requires the EPA to implement a phase-down to reduce US HFC production and sales by 85% of a 2011 – 2013 baseline* by 2036.
- It also authorizes EPA to adopt sector-specific use restrictions.

The US EPA will implement the HFC phase-down, and will release a series of rules to outline details of implementation, including specifics on allocation methodology, enforcement, compliance, and future considerations.

Newly enacted US federal legislation to phase-down HFCs

*Majority of the baseline is average annual national HFC production and sales from 2011 - 2013

SECTOR-SPECIFIC BANS

The AIM Act authorizes the EPA to adopt sector-specific limitations

1. **Authority:** Congress gives EPA the authority to grant or deny industry petitions requesting sector-specific prohibitions.
2. **Timing:** EPA has 180 days after receipt of petition to grant/deny, and can then take up to 2 years to implement the petitioned bans (if approved).
3. **Petitions:** Numerous petitions were submitted to EPA in 2H21, requesting implementation of SNAP 20/21, and additional prohibitions, e.g. like CARB rule on a/c and commercial refrigeration.
4. **Future:** EPA approved 10 petitions outlining sector-specific HFC prohibitions in October 2021. Expected to finalize prohibitions by October 2023 latest.

Figure 1: Example Petitioned Prohibitions submitted April 13, 2021

End-Use	Substances Banned	Effective Date
Polystyrene Extruded Boardstock and Billet	134a, 245fa, 365mfc, and blends thereof, Formacel TI, Formacel B, Formacel Z-6	January 1, 2023
Standalone Food Refrigeration Equipment (retrofit)	404A, 507A	January 1, 2023
New Light Duty System for Mobile Air Conditioning	134a, 406A, 414A, 414B…	January 1, 2023*

The above examples were included in the NRDC/CDPHE/IGSD petition submitted to the EPA on April 13, 2021. This petition largely requested the re-implementation of SNAP 20/21 rulings at a federal level.

HFCs in MDI have 5-years of special treatment under the AIM Act. EPA is expected to review the MDI special treatment again approaching 2026.

AIM Act authorizes EPA to implement national sector-specific transitions

*Except for exports to countries with limited servicing infrastructure until Model Year 2025

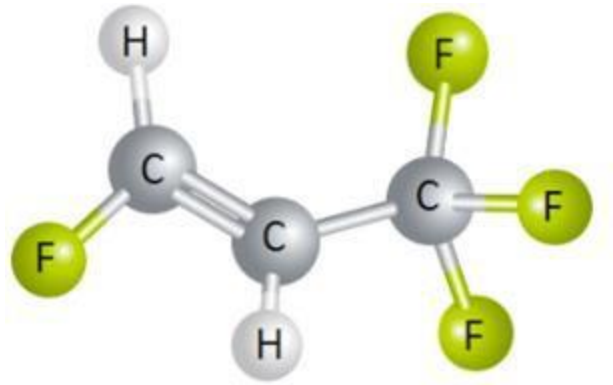
HONEYWELL AND ASTRAZENECA ANNOUNCE PARTNERSHIP

1. AstraZeneca and Honeywell will partner to develop next-generation respiratory inhalers using the propellant HFO-1234ze.

2. Recent results from the first in-human Phase I trial of the near-zero GWP propellant HFO-1234ze in a pMDI containing budesonide, glycopyrronium, formoterol fumarate in healthy adults were positive, demonstrating similar safety…

Products Scheduled to launch starting in 2025

SOLSTICE® AIR IN MDI

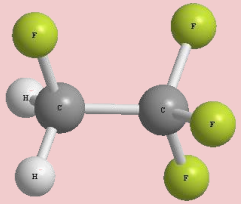
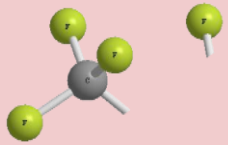
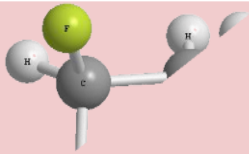
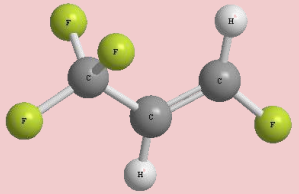


$CF_3CH=CHF$
HFO-1234ze(E)
Trade name : Solstice® Air
INCI : Tetrafluoropropene
Function : Propellant

- Lowest GWP vs. 134a, 227ea, 152a to meet brand carbon emission/sustainability goals
- Latest generation hydrofluoroolefin (HFO) chemistry replaces HFCs and complies with or exceeds current and future regulations
- Non-flammable propellant and safe toxicity profile
- A near drop-in for multiple 134a applications
- Current Toxicity data has been reviewed by FDA and phase III studies are being planned.
- GMP grade available for testing and commercial quantities available Q4 2022.

*Ultra-low global warming potential, VOC exempt – US EPA

PROPELLANT EVOLUTION

Properties	CFC 12	HFC 134a	HFC 227ea	HFC 152a	HFO 1234ze(E)
Propellant					
Molecular Weight	120.9	102.0	170.0	66.1	114.0
Boiling Point	-29.8°C	-26.1°C	-16.3°C	-24.0°C	-19°C
Liquid Density at 20°C	1.33 gm/mL	1.23 gm/mL	1.41 gm/mL	0.91 gm/mL	1.18 gm/mL
Vapor Pressure at 20°C	82.2 psi	82.9 psi	56.4 psi	74.4 psi	62.0 psi
Water Solubility in propellant, ppm	130	2200	610	1700	225
Flame Limits at 20°C	none	none	none	3.7 – 16.9 vol%	none
Ozone Depletion Potential	1.0	0	0	0	0
Atmospheric Lifetime*, yrs	102	14	36	1.6	0.052
Global Warming Potential*	11200	1530	3600	164	1.37

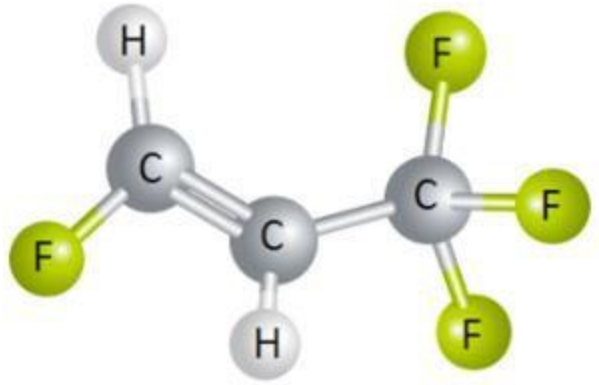
1234ze is well positioned to be the LGWP propellant of the future.

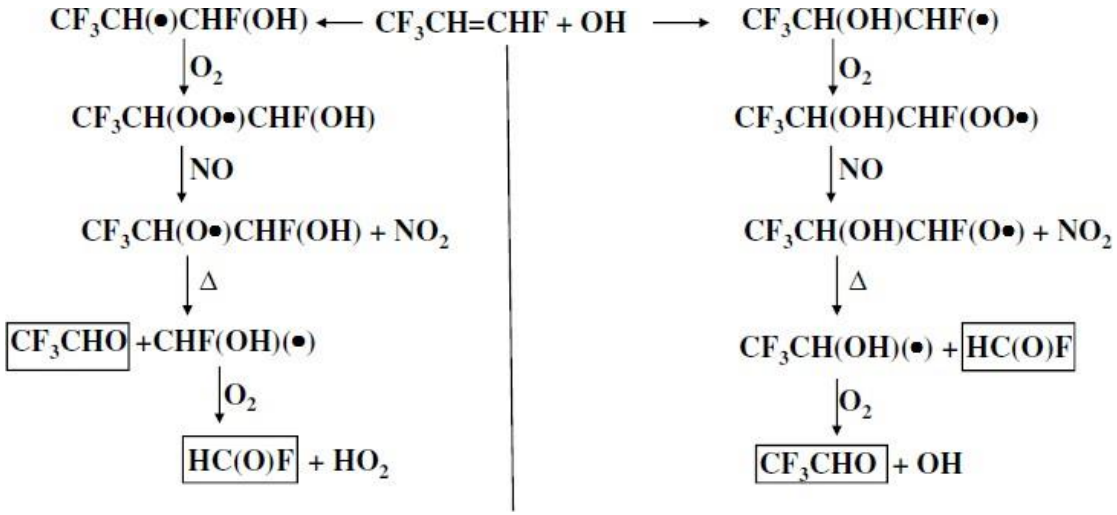
* IPCC AR6
**These are some of a mosaic of properties that must be assessed in identifying a suitable propellant

ATMOSPHERIC CHEMISTRY OF HFO-1234ze(E)

- Atmospheric lifetime is **19 days**
- **GWP_{100yrs} = 1.37**
- **Non-ozone depleting**
- POCP = 6.4

* Lifetime and GWP taken from IPCC AR6 and Hodnebrog et al., 2020
* POCP relative to ethene ($POCP_{ethene}$ = 100, Wallington et al. 2015)





Adopted from Javadi et al., 2008

Javadi et al. (2008) studied the atmospheric degradation of 1234ze(E):

- The most significant loss process of 1234ze(E) in the atmosphere is **OH-initiated oxidation**
- The decomposition intermediates of OH-initiated oxidation are **trifluoroacetaldehyde, CF_3CHO and formyl fluoride, HC(O)F**
- HC(O)F decomposes (aqueous phase chemistry) to formic and hydrofluoric acid
- Trifluoroacetaldehyde, CF_3CHO, decomposes primarily to CO_2 and HF
- Javadi et al. (2008) and the Wallington et al. review (2015) concludes that the **final degradation products have a negligible environmental impact**

Short lifetime and degradation mechanism leads to an insignificant impact

ATMOSPHERIC CHEMISTRY OF HFO-1234ze(E)

- Atmospheric lifetime is **19**
- **GWP_{100yrs} = 1.37**
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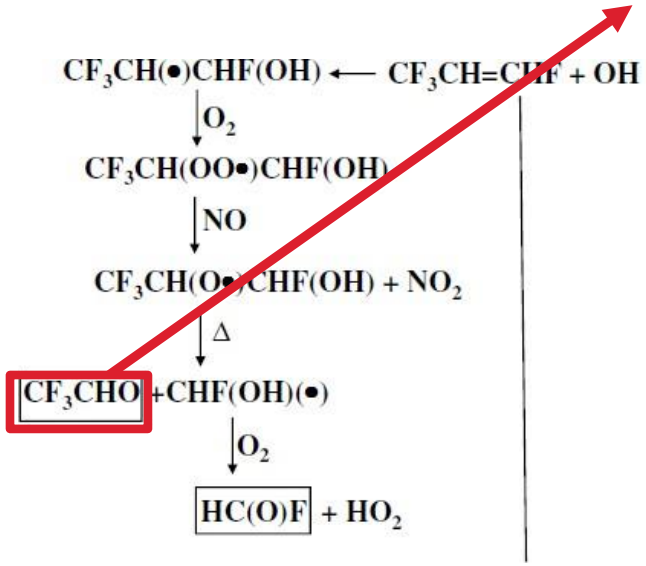
- POCP = 6.4

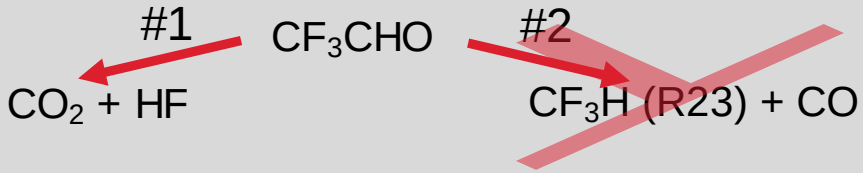
* Lifetime and GWP taken from IPCC AR6
* POCP relative to ethene ($POCP_{ethene}$ = 1



Adopted from Javadi et al., 2008

Recent discussion on decomposition of CF_3CHO to potentially form R23 (fluoroform).

Potential Breakdowns routes



Different investigators have evaluated this breakdown mechanism at atmospherically relevant conditions and have concluded Route #1 is the preferred mechanism.

1. Chiappero et al. (2006) concludes: *"…formation of HFCs from the tropospheric photolysis of fluoroaldehydes is of no significance."* Route #2 is not preferred.
2. Anderson, M; Nielsen, O. (2022) concludes: *"Our results show no detectable (< 0.3 %) CF3H produced during the tropospheric photolysis of CF3CHO."* Route #2 is not preferred.
3. Campbell et al. (2021) states: *"There are also several ground state pathways shown in black in Fig. 1 which have **yet to be observed**. These include the analogous pathways to those observed in acetaldehyde photodissociation. The decarbonylation pathway produces CO and CHF3 molecules and is exothermic…"* (emphasis added)

   The preprint of this article had stated *"In this paper, we demonstrate that CF3CHO photolyses to form HFC-23. Although the quantum yield is small, this pathway could account for the fate of 11.0 ± 5.5 % of atmospheric CF3CHO."* These comments were removed from the peer reviewed and published paper.

Short lifetime and degradation mechanism leads to an insignificant impact

FLAMMABILITY: NOT BLACK OR WHITE

Even when a product is classified as nonflammable – it's important to know that under certain conditions, flame limits can be observed

- Both temperature and relative humidity can affect results of LFL / UFL

HFO-1234ze is classified as nonflammable by GHS, DOT, IATA and IMDG (measured by ASTM E-681, ISO 10156 and EU A11), but under certain conditions, a very narrow flammable range can be observed:

- When temperature is ≥ 86°F/30°C, **AND**
- Relative humidity ≥50%, **AND**
- High energy ignition source or open flame is present

Many Criteria Are Used to Evaluate Flammability

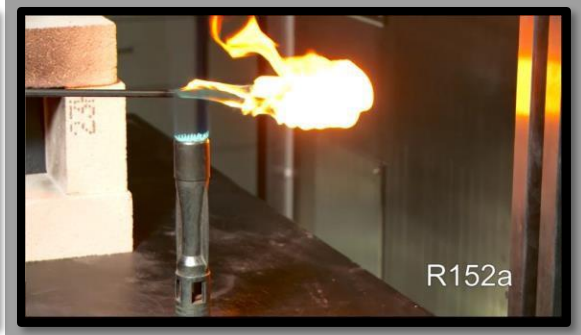
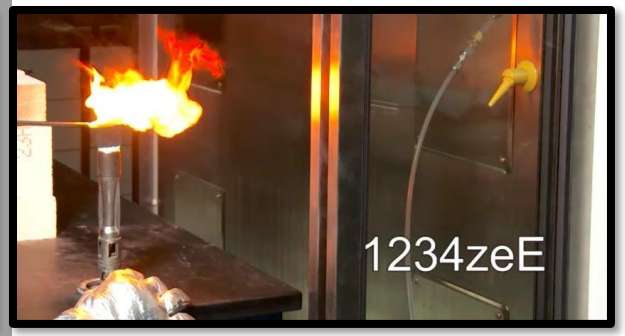
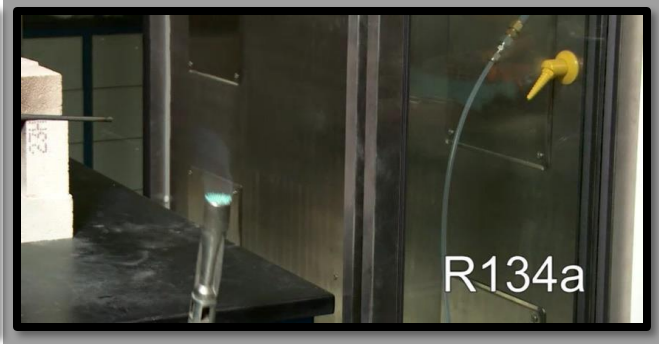
FLAMMABILITY STANDARDS VARY BY REGION AND APPLICATION

Regulations by Region				
Region	**Shipping / storage**	**Refrigeration**	**Blowing Agent**	**Propellant**
US	49 CFR 173.115	ASHRAE 34	Same as Shipping	UN GHS - Aerosol
EU	Method A11 / ISO 10156	ISO 817	Same as Shipping	UN GHS - Aerosol
China	UN GHS - Shipping	ISO 817	Same as Shipping	UN GHS - Aerosol
Japan	HPGL	HPGL / ISO 817	HPGL	HPGL

Regulations by Application			
Method	**Classification of HFO-1234ze(E)**	**Application**	**3rd Party Reports**
49 CFR 173.115	2.2 – **non-flammable compressed gas**	**US Shipping**	**UL**
ISO 10156	**Non-flammable**	**EU Shipping**	**DEKRA**
Method A11	**Non-flammable**	**EU Shipping**	**Chilworth**
UN GHS - Aerosol	**Non-flammable**	**Aerosol**	**Stresau**
UN GHS - Shipping	2.2 – **non-flammable compressed gas**	**Shipping**	
HPGL	**Specified Inert Gas**	**Use in Japan**	
ASHRAE 34	A2L – **mildly flammable**	**Refrigeration**	**UL**
ISO 817	A2L – **mildly flammable**	**Refrigeration**	**UL**

EXAMPLE OF DIFFERENT DEGREES OF FLAMMABILITY

1. Vapor Leak through a strong ignition source (burner).
2. Allow material to ignite then remove burner from flow path.

	Isobutane	HFC-152a	HFO-1234ze(E)	HFC-134a
1.				
2.				

Flammability is on a continuum and must be evaluated for a specific use.
1234ze(E) is a non-flammable propellant.

TOX DATA FOR SOLSTICE® AIR

Toxicology package component	Species (duration)	GLP status	Ongoing / Complete	Data support progression?
Genetic toxicology	In-vitro, in-vivo	GLP	Complete	✓
Acute toxicology	Rodent	GLP	Complete	✓
Chronic toxicology	Rodent (6M) & Non-rodent (9M)	GLP	Complete	✓
Safety pharmacology	Rodent & non-rodent	GLP	Complete	✓
Toxicokinetics	Rodent & non-rodent	GLP	Complete	✓
Reproductive toxicology	Rodent & non-rodent	GLP	Complete	✓
Carcinogenicity	2 x rodent (2Y)	GLP	Ongoing	Report 2024
Dermal	Rabbit	GLP	Complete	Not applicable

Current TOX data has been reviewed by the FDA and CHMP. Phase 3 trials are scheduled to proceed.

SOLSTICE® AIR COMPATIBILITY

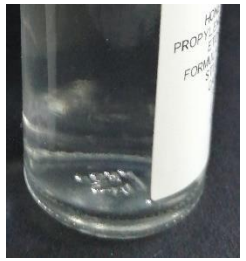
Good Solubility of common Excipients in HFO-1234ze(E)

Oleic Acid/Ethanol

- 0.25%/5% w/w

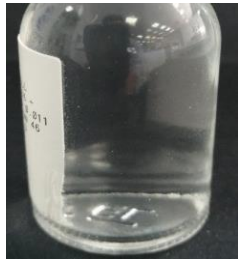
Ethanol

- 15% w/w



Propylene Glycol/Ethanol

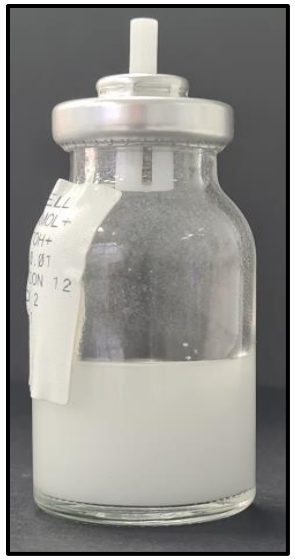
- 0.5%/5% w/w



Citric Acid/Water/Ethanol

- 0.011%/0.5%/5% w/w

APIs are easily formulated with HFO-1234ze(E)



Albuterol Sulfate

- 0.335% w/w

Fluticasone Proprionate

- 0.323% w/w

Ipratropium Bromide

- 0.034% w/w

HFO-1234ze(E) is compatible with commonly used excipients and APIs

cGMP PRODUCTION

2020				2021				2022			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

- Q2: cGMP Pilot Scale Production In Place
- Q3: First Solstice Air Sample Produced for Customer
- Q3: Construction of large-scale commercial facility in Baton Rouge started
- Q4: Pilot Scale Production. Produced material for clinical scale trials.
- Q4: Commercial quantity of cGMP Solstice Air Available

Solstice® Air is available today for evaluations, commercial quantity available in Q4, 2022

SUMMARY

- Solstice® Air is a low GWP propellant solution for MDI applications.
- Atmospheric degradation products have been fully studied and found acceptable for Solstice Air.
- Significant toxicology evaluations for Solstice Air has been completed. The 2 rodent / 2-year carcinogenicity test is in progress.
- When handled at typical conditions in MDI filling and use Solstice Air is non-flammable.
- cGMP production is online with large scale capacity ready by Q4 2022.

Solstice Air is low GWP, safe, and allows MDI producers to meet sustainability goals

THANK YOU!

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