Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-10

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **133794** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-10 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-10 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn

The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice

If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

Signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-9

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **159490** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-9 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-9 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn

The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice

If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-8

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **200289** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-8 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-8 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn
The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice
If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

signed electronically

s22 [redacted]
Acting Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-6

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **235674** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-6 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-6 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn

The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice

If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-5

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **257012** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-5 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-5 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn

The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice

If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

Signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-7

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **209934** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-7 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-7 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn
The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice
If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-4

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **257013** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-4 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-4 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn
The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice
If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

Signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-3

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **285420** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-3 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-3 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn

The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice

If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

Signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-2

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **295664** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-1 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-1 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

PART D: Information about this Infringement Notice

This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

How this notice can be withdrawn

The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

You may make a written representation to the Secretary seeking the withdrawal of this notice. Your representation should explain why this notice should be withdrawn and include supporting documents.

Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice

If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

Signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Managing Director
Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

By Express Post and By Email:
s22 [redacted] @philips.com

Infringement Notice Number:
TGAIN-DPMRR-2022-1

Date given: 31/05/2022

Penalty total: $13,320

Payment due: 28/06/2022

Enquiries:
Devices Post Market Reform and Review Section
Telephone: 1800 020 653

Email: postmarketdevices@health.gov.au

INFRINGEMENT NOTICE GIVEN TO
Philips Electronics Australia Ltd

PART A: Infringement Notice given by

s22 [redacted]
Delegate of the Secretary of the Australian Government Department of Health

PART B: Details of alleged contravention

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (**the Act**). I have decided to give this Infringement Notice (**the notice**) to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that it has contravened subsection 41MPA(1) of the Act.

The details of the alleged contravention are that:

Philips Australia is the person in relation to whom a kind of device is included in the Australian Register of Therapeutic Goods (**ARTG**), namely the kind of device with ARTG number **327227** (**the Device**).

On or before 28 April 2021, Philips Australia became aware that the polyester-based polyurethane foam **(PE-PUR foam)** in the Device was known to degrade and present a significant biological risk to patients.

As of 31 May 2021, being 33 days after Philips Australia becomes aware, Philips Australia had not informed the Secretary that Philips Australia therefore contravened subsection 41MPA(1) of the Act.

The maximum penalty a court could impose on a company for a single contravention of subsection 41MPA(1) is 30,000 penalty units.[1] For the above-alleged contravention, this amounts to $6,660,000.

The amount payable under this notice is **$13,320**. The due date for payment of the penalty amount is specified in the red box at the top of this notice.

Please carefully read ***Part D: Information about this Infringement Notice***.

PART C: Payment details

Please ensure that you allow time for your payment to be received by the due date.

CHEQUE

Return **this notice** to **Department of Health, Accounts Receivable, GPO Box 9848, Canberra ACT 2601** with your cheque made payable to the Department of Health. Please allow 5 business days for payment to be received

CREDIT CARD

Use your credit card to pay your notice by calling the Collector of Relevant Monies directly on **(02) 6289 1095**. Please include the infringement notice number TGAIN-DPMRR-2022-1 as reference to identify your payment

ELECTRONIC FUNDS TRANSFER

Account name: Department of Health
BSB: 092 009
Account: 114 071
Bank: Reserve Bank of Australia, London Circuit, Canberra ACT 2601
Swift: RSBKAU2S (if overseas deposits are relevant). Please include the infringement notice number TGAIN-DPMRR-2022-1 in the description of your transfer and allow two business days for payment to be received.

Note: The Department of Health accepts payment on behalf of the Commonwealth and will issue a tax invoice on receipt of payment

[1] A penalty unit is currently $222 (section 4AA of the *Crimes Act 1914*).

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This information is designed to help you (the person to whom this notice has been given) understand the following:

- the compliance period (the period within which the penalty amount is payable)
- how to apply for an extension of time to pay the penalty amount
- how to make a written representation seeking withdrawal of this notice
- the effect of complying with this notice
- the effect of failing to comply with this notice.

This information is for **general guidance only**. You should obtain independent legal advice if you have specific concerns.

Compliance period

The compliance period for this notice is 28 days beginning on the day after the day that this notice is given to you. The Therapeutic Goods Administration (**TGA**) is not legally able to accept payment of the notice after it has lapsed.

How to request an extension of time to pay the penalty amount

You may apply to the Secretary of the Australian Government Department of Health (the **Secretary**) for an extension of the compliance period for this notice, provided your application is made before the end of that period. The Secretary may extend that period in writing before or after the end of that period. Requests can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of complying with this notice

If you pay the full penalty amount payable under this notice within the compliance period, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act will not be brought against you in relation to the alleged contravention described in this notice (unless this notice is withdrawn).

Your payment of the penalty amount payable under this notice is not an admission of guilt or liability.

The Australian Government Department of Health will, from time to time, make public reference to infringement notices that have been given to companies or individuals, including in media statements and publications by the TGA containing information about the alleged conduct of a company or an individual and the fact that compliance with the infringement notice does not amount to an admission or finding that the Act has been contravened.

Effect of failing to comply with this notice

An infringement notice is an opportunity for you to pay an amount as an alternative to having court proceedings brought against you in relation to the alleged contravention described in this notice. You may therefore choose not to pay the penalty amount payable under this notice. If you choose not to pay the penalty amount, proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act may be brought against you in relation to the alleged contravention described in this notice.

Effect of the lapsing of the compliance period for the notice

If the compliance period has passed and no payment has been received by the TGA, the notice is considered to have lapsed. No extension of time can be granted if the application is made after the compliance period has passed and no further payment can be accepted against a lapsed notice. If you pay

the penalty amount payable under this notice after the compliance period has lapsed, you will be refunded the amount paid.

Please be aware that once the infringement notice has lapsed, the Secretary may commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this notice.

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The Secretary may withdraw this notice even if you have already paid the penalty amount payable under this notice. In such a case, you will be refunded the amount paid.

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Please ensure that your written representation is addressed to and received by the person who has given you this notice within the compliance period. You can make written representations seeking withdrawal of this infringement notice at any time before the payment due date. However, to allow the Secretary to make a decision in relation to such a request before the payment due date, you should make it no less than seven business days before the payment due date.

Written representations can be made by sending them directly to:

- postmarketdevices@health.gov.au or
- PO Box 100; WODEN ACT 2609

Effect of withdrawal of this notice
If this notice is withdrawn, the TGA may nevertheless commence proceedings seeking a pecuniary penalty order under subsection 42Y(2) of the Act against you in relation to the alleged contravention described in this infringement notice.

signed electronically

s22 [redacted]
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration
E-mail: postmarketdevices@health.gov.au
PO Box 100 WODEN ACT 2609

Date: 31/05/2022

Australian Government
Department of Health
Therapeutic Goods Administration

s22
Managing Director Philips Electronics Australia Ltd
ABN: 24 008 445 743
65 Epping Road
North Ryde, NSW 2113
Australia

And by e-mail: s22 @philips.com

Our Reference: E21-327521

Dear s22

Infringement Notices given to Philips Electronics Australia Ltd

TGAIN-DPMRR-2022-01 toTGAIN-DPMRR-2022-10

I am a delegate of the Secretary of the Australian Government Department of Health under section 42YK of the *Therapeutic Goods Act 1989* (the Act). On 31 May 2022 I have decided to give these infringement notices to Philips Electronics Australia Ltd (**Philips Australia**) under Part 5A-2 of the Act on the basis that I reasonably believe that Philips Australia has contravened subsection 41MPA(1) of the Act.

I have decided to give Philips Australia infringement notices for 10 contraventions against subsection 41MPA(1) of the Act for failing to provide information relating to a deterioration in the characteristics or performance of the kind of device that might lead to the death of a patient or to a serious deterioration in his or her state of health. This amounts to a single contravention of subsection 41MPA(1) in relation to each of the following kinds of medical devices (**the Devices**):

ARTG ID	ARTG name
209934	Portable ventilator, electric
285420	Portable ventilator, electric
235674	Portable ventilator, electric
327227	Portable ventilator, electric
295664	Home CPAP unit
257012	Home BPAP unit
257013	Home CPAP unit
159490	Portable ventilator, electric
200289	Positive airway pressure unit, bi-level
133794	Positive airway pressure unit, bi-level

The total payable for these infringement notices is $133,200.

As subsection 41MPA(1) required Philips to provide information within a particular period of time, subsection 42YCA(2) of the Act applies. As such, every day that Philips Australia failed to provide the necessary information to the Therapeutic Goods Administration (TGA) was a separate contravention of subsection 41MPA(2). This means it would be open to me to give infringement notices in relation to each of the Devices for each day that Philips Australia was required to provide the information until such time as the TGA was finally notified by Philips Australia. However, in these circumstances I have chosen not to do so in light of Philips Australia's cooperation with the TGA since the notification.

The TGA considers it to be of the upmost importance that patients who are using devices that have been identified as requiring corrective action receive this advice and appropriate corrective action as quickly as possible. Despite Philips Australia working with the TGA to rectify the problems after Philips Australia notified the TGA of the problems, the fact remains that Philips Australia was in breach of its obligations to notify the TGA promptly with respect of such a serious issue. Now that the recall is well underway, and the TGA's primary concern of ensuring that patient safety is being addressed, I have decided to issue these infringement notices as an important form of deterrence to encourage future compliance with the Act.

The documents provided to the TGA show that Philips Respironics Inc (**Philips USA**) was first made aware that the polyester-based polyurethane foam (**PE-PUR foam**) had degraded in several units of the Devices in May 2019. An investigation was carried out by Philips USA into the causes and potential impacts of the degraded PE-PUR foam. A report dated 10 December 2020 summarised this investigation and found that "the degraded PE-PUR foam is not considered biocompatible and presents a significant biological risk to those patient populations who are exposed to degraded PE-PUR foam". This report shows that the Devices do not comply with Essential Principles (EPs) 1, 4, 7.1, and 9.2 in a way that has the potential to cause a serious deterioration in the health of the patient.

The Philips USA Health Hazard Evaluations show that the foam degradation could lead to serious injury that is life-threatening, a permanent impairment or necessitates medical intervention to preclude permanent impairment. This means Philips Australia was required to report it to the TGA within 30 days of receiving the information about this issue.

Whilst it is unclear when Philips Australia became aware that the foam degradation meant that the Devices did not comply with the EPs, Philips Australia announced the issue in an update on its website on 26 April 2021 and sent a letter to customers dated 28 April 2021 which means Philips Australia was aware of the issue by this date. This means the information should have been reported to the TGA by 28 May 2021 at the latest. Whilst Philips spoke to the TGA prior to 28 May 2021, those conversations did not include details of the non-compliance with the EPs nor of the kinds of devices effected and therefore cannot be considered a notification for the purposes of subsection 41MPA(1).

I note that the inclusion of the Device in the ARTG is also subject to the condition under paragraph 41FN(3)(d) of the Act that Philips Australia will give to the Secretary information of a kind mentioned in subsection 41MP(2) or 41MPA(2) of the Act within the period specified in the Therapeutic Goods (Medical Device) Regulations 2002. Failing to do so is a breach of the condition of inclusion, and is an offence under s41MN and contravention of a civil penalty provision under s41MNA of the Act.

I encourage you to familiarise yourself with the kinds of information Philips Australia is required to give to the Secretary under subsection 41MP(2) or 41MPA(2).

The infringement notices are attached to this letter, and include information on how to pay the infringement notice penalty amount, how to request an extension of the compliance period for payment of the infringement notice or how to request that the infringement notice be withdrawn. It is important that you carefully read the infringement notices and the information contained therein.

Yours sincerely,

signed electronically

s22
A/g Assistant Secretary
Medical Devices Surveillance Branch
Therapeutic Goods Administration

31 May 2022

HEALTH HAZARD EVALUATION FORM

ER 2242138 – DreamStation 1 Volatile Organic Compounds (VOC), Version 01

Step I – Identification of the Issue/Problem

CAPA Number:	858229	HHE Date Open:	19 May 2021	HHE Date Closed:	25 May 2021
- Product Data -					
Product Code:	BZD (noncontinuous ventilator (Intermittent positive pressure breathing - IPPB)) MNT (continuous ventilator, minimal ventilatory support, facility use) MNS (continuous ventilator, non-life supporting)				
Model:	All finished good part numbers under the devices listed below fall within the scope of this HHE. For a comprehensive list of all finished good numbers, refer to CAPA 858229.				
Device Name:	DreamStation 1 CPAP, Auto CPAP, BiPAP DreamStation 1 ASV DreamStation 1 ST, AVAPS Philips Respironics E30 ventilator (considered a part of the DreamStation 1 platform due to similar engineering/design)				
Lot/Serial Numbers:	All DreamStation 1 devices in the field and released in inventory currently using the polyester-based polyurethane foam (PE-PUR) could be subject to this potential failure mode.				
Marketing Status (Include 510(k) or PMA Number, Specify if Class I Exempt from 510(k)):	- DreamStation 1 - K131982 - DreamStation 1 ASV - K090539 - DreamStation 1 ST, AVAPS - K102465 - E30 Ventilator – cleared under Emergency Use Authorization (EUA)				
Manufacturing/Recall Firm Address:	Respironics Inc. 1010 Murry Ridge Ln Murrysville, PA 15668				
Product Description (Include Intended Use from Labeling):	***K131982*** **DreamStation Product Identification and Intended use:** **Regulation** : 21 CFR 868.5905 Identification : A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to				

	assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The Philips Respironics DreamStation systems deliver positive airway pressure therapy for the treatment of Obstructive Sleep Apnea in spontaneously breathing patients weighing over 30 kg (66 lbs.). It is for use in the home or hospital/institutional environment. **Device Description:** The DreamStation is designed to provide CPAP, CPAP-Check, Auto CPAP, Bi-Level and Auto Bi-Level therapy. The optional heated humidifier offers Heated Tube (via optional 15mm heated tube, HT15), Adaptive or Fixed humidification. In addition to the ramp function, depending on the therapy selected, one or more of the following pressure relief features is available to increase patient comfort: C-Flex, A-Flex, P-Flex, Bi-Flex and Rise Time. DreamStation is intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of disposable or reusable smooth lumen tubing, (22mm, 15mm, Heated Tube15, or 12mm tubing). A typical patient interface device provides a method of venting exhaled gases. Bluetooth wireless technology gives a patient access to their compliance data in markets where the DreamMapper mobile application is available. Optional modem accessories, Cellular Modem or Wi-Fi Accessory, automatically upload patient compliance data to their provider. If included, a Secure Digital (SD) card will also store compliance data allowing a provider to collect a patient's data periodically. ***K090539*** **DreamStation ASV Product Identification and Intended use**: **Regulation**: 21 CFR 868.5905 Identification: A noncontinuous ventilator (Intermittent positive pressure breathing - IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The BiPAP autoSV device is intended to provide non-invasive ventilatory support to treat adult patients (>30 kg/66 lbs.) with Obstructive Sleep Apnea and Respiratory Insufficiency caused by central and/or mixed apneas and periodic breathing. This device may be used in the hospital or home. **Device Description:** The BiPAP autoSV device is intended to augment breathing by supplying pressurized air through a circuit. It senses breathing effort by monitoring airflow in the circuit and adjusts its output to assist with inhalation. This therapy is known as Bi-level ventilation. Bi-level ventilation provides a higher pressure, known as IPAP (Inspiratory Positive Airway Pressure), during inhalation and a lower pressure, known as EPAP (Expiratory Positive Airway Pressure), during

	exhalation. The higher pressure makes it easier to inhale, and the lower pressure makes it easier to exhale. A user interface displays clinical data and enables the operator to set and adjust certain clinical parameters. The devices are intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of a six-foot disposable or reusable tubing and a patient interface device. ***K102465*** **DreamStation S/T and AVAPS Product Identification and Intended use**: **Regulation**: 21 CFR 868.5905 Identification: A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The BiPAP S/T device is intended to provide non-invasive ventilatory support to treat adult and pediatric (> 7 years of age and > 40 lbs) patients with obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. The device may be used in the hospital or home. The BiPAP AVAPS device is intended to provide non-invasive ventilatory support to treat adult and pediatric (> 7 years of age and > 40 lbs) patients with obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. The device may be used in the hospital or home. **Device Description:** The DreamStation BiPAP S/T and DreamStation BIPAP AVAPS devices are a microprocessor controlled blower based positive pressure system with optional integrated heated humidifier. The BiPAP S/T and BiPAP AVAPS devices are intended to provide non-invasive ventilatory support to Obstructive Sleep Apnea (OSA) and Respiratory Insufficiency patients weighing over 18 kg. This device may be used in the hospital or home. A user interface displays clinical data and enables the operator to set and adjust certain clinical parameters. The DreamStation BiPAP AVAPS and BiPAP S/T is fitted with alarms to alert the user to changes that will affect the treatment. Some of the alarms are pre-set (fixed), others are user adjustable. The devices are intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of a six-foot disposable or reusable tubing and a patient interface device. **Philips Respironics E30 Ventilator Product Identification and Intended use**: **Regulation**: The Cardigan ventilator will be an Emergency Use Authorization ventilator approved by the FDA.

	Classification and Identification: It will be a Class II, Ventilator, Continuous, Minimal Ventilator Support, Facility Use (Product Code MNT). **Intended Use**: The Philips Respironics E30 ventilator is intended to provide invasive and non-invasive ventilatory support for individuals with Respiratory Insufficiency. It is specifically for the care of adult and pediatric patients >7 years of age and >18kgs. It is intended to be used in the hospital or other institutional healthcare environments, as well as spaces converted for the care of large numbers of COVID-19 patients (e.g. convention centers, university dormitories, motels). The Philips Respironics E30 ventilator is intended for use by qualified, trained personnel under the direction of a physician. **Device Description:** The Philips Respironics E30 Ventilator is intended to reduce the burden and need for mechanical ventilation in acute settings during high census periods of respiratory distress related to the COVID health crisis. The Philips Respironics E30 Ventilator t is a simplified invasive and non-invasive device for clinicians to provide CPAP, non-invasive and invasive pressure ventilation with up to 40 lpm supplemental oxygen therapy in all modalities and modes 40 lpm of supplemental O2 can be integrated into the air path or bled into a patient's passive circuit. This Philips Respironics E30 Ventilator is meant to treat patients in the hospital or other institutional healthcare facilities where there are not enough mechanical ventilators to provide adequate care/therapy/ventilation, The Philips Respironics E30 Ventilator is for patients with respiratory insufficiency that may also experience shortness of breath.
Brief description of the issue/problem and how it was identified:	Testing conducted by Philips (in conjunction with Third-party laboratories) indicates that DreamStation 1 (DS1) devices with PE-PUR sound abatement foam were found to exceed acceptable levels of Volatile Organic Compound (VOC) emissions that could potentially cause patient harm per ISO 18562 (a standard released in 2017 and recognized by FDA in 2018). A recent PSN Test report (700025-RP-01(Rev E), dated May 25, 2021) indicated that dimethyl diazene and alkylphenol are Chemicals Of Concern (COC). When calculated with the ICH M7 guideline of 1.5 µg/day for long-term (exceeding 30 days) exposure to a potential mutagenic or carcinogenic analyte, the margin of safety is below 1, indicating a potential hazard for both 30 and 70 kg patient populations. This confirms dimethyl diazine (and its oxidized derivative azoxymethane) and alkylphenol as COCs. The other devices in this HHE are included as they share the same engineering platform but lack VOC testing data.

Affected Patient/User Population:	All patient groups that fall within the intended use of the devices referenced in the Product Description are within the affected patient population. The intended patient population broadly includes the following: adult and pediatric patients weighing over 18 kg with Respiratory Insufficiency. Higher risk populations within the intended patient population include infants, elderly, pregnant women, critically ill patients, and patients with comorbidities such as heart failure, COPD, and obesity.
HHE Author (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management
HHE Contributors (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management s22 [redacted] – Head of Global Clinical and Scientific Affairs s22 [redacted] – Medical Leader, SRC s22 [redacted] – Medical Director, Connected Care s22 [redacted] – Head of Design Quality Engineering s22 [redacted] – Medical Safety Manager

Step II – Analyze Post Release Health Risk Associated with Affected Units

Note: Assess the risk as if no corrective action will be taken and all affected devices will remain in the marketplace.

A. Identification of the Individual Hazard(s)

Hazard Category:	**Hazard Category:** Biological and Chemical **Hazard**: Biocompatibility / Toxicity of chemical constituents
Hazard Cause:	Emission of VOC's for devices with PE-PUR sound abatement foam. Investigation into the root cause of the VOC's emission is ongoing.
Hazardous Situation:	While receiving therapy patients may be exposed to hazardous levels of VOCs that are unacceptable per ISO standards.

B. Estimation of Severity

Description of reported and/or potential harm:	Dimethyl diazene is also known as azomethane with no specific pre-clinical toxicological data available in scientific literature, nor a known daily permissible daily exposure limit. A Quantitative Structure Activity Relationship (QSAR) analysis reveals a genotoxic alert based on the azo chemistry. The data also suggest that it has high skin permeability. Finally, the literature suggest that azo compounds have mutagenic potential.[1,2,3] The oxide derivative of this surrogate azomethane compound, azoxymethane (CAS Number 25843-45-2) is a potent carcinogen. Phenol, 2,6-bis(1,1-dimethylethyl)-4-(1-methylpropyl)- (CAS Number 17540-75-9) has no specific pre-clinical toxicological data available in scientific literature, nor a known daily permissible daily exposure limit. QSAR analysis with the Derek Nexus predictive software revealed an open structural alert for chromosome damage (in vitro chromosome aberration test) due to it being an alkylphenol, a potential mutagen.

[1] Sweeney EA, Chipman JK, Forsythe SJ. Evidence for direct-acting oxidative genotoxicity by reduction products of azo dyes. Environ Health Perspect. 1994 Oct;102 Suppl 6(Suppl 6):119-22. doi: 10.1289/ehp.94102s6119. PMID: 7889833; PMCID: PMC1566849.

[2] Mori H, Mori Y, Sugie S, Yoshimi N, Takahashi M, Ni-i H, Yamazaki H, Toyoshi K, Williams GM. Genotoxicity of a variety of azobenzene and aminoazobenzene compounds in the hepatocyte/DNA repair test and the Salmonella/mutagenicity test. Cancer Res. 1986 Apr;46(4 Pt 1):1654-8. PMID: 3081253.

[3] Shuji Tsuda, Naonori Matsusaka, Hiroo Madarame, Shunji Ueno, Nobuyuki Susa, Kumiko Ishida, Noriko Kawamura, Kaoru Sekihashi, Yu F Sasaki, The comet assay in eight mouse organs: results with 24 azo compounds, Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 465, Issues 1–2, 2000, Pages 11-26, ISSN 1383-5718, https://doi.org/10.1016/S1383-5718(99)00199-0.

<table>
<tr><td></td><td>It is not known what duration of exposure is required for certain harms to develop.

Potential harms that can be exhibited as a result of exposure to VOCs as a class:
• Headache/dizziness
• Irritation (eyes, nose respiratory tract, skin)
• Hypersensitivity
• Nausea/emesis
• Toxicity: genotoxic, mutagenic, carcinogenic effects
• Hepatotoxicity, nephrotoxicity, neurotoxicity[4]</td></tr>
<tr><td>Estimation of Severity of Harm</td><td>3 (Crucial)

Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment

This is considering the reasonable worst-case scenario.</td></tr>
<tr><td>Comments:

(Severity of Harm Rationale)</td><td>Severity of harm was estimated based on the findings in various test reports, literature searches, and the experience of credentialed medical professionals.

Based on a foreseeable worst-case patient population being exposed to the harms identified above, it was determined that the Crucial severity of harm (level 3) recognizes the seriousness of any potential harm that may significantly impact the clinical status of patients and require additional medical intervention.</td></tr>
<tr><td>Reference Information:</td><td>
<table>
<tr><th>Check (X) Applicable Level*</th><th>Examples</th></tr>
<tr><td>___ 4 (Catastrophic)</td><td>Directly results in death</td></tr>
<tr><td>x 3 (Crucial)</td><td>Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment</td></tr>
<tr><td>___ 2 (Marginal)</td><td>Results in moderate injury: temporary impairment, or self-limiting illness</td></tr>
<tr><td>___ 1 (Negligible)</td><td>Results in less than moderate or no injury</td></tr>
</table>
* Severity Levels 4 and 3 are “serious adverse health consequences”
</td></tr>
</table>

[4] United States Environmental Protection Agency (EPA). Volatile Organic Compounds’ Impact on Indoor Air Quality. Retrieved online on 4/29/21 from Volatile Organic Compounds' Impact on Indoor Air Quality | Indoor Air Quality (IAQ) | US EPA.

	per FDA's CDRH Health Hazard Evaluation Form Version 3-1 01/12/2007. Severity Levels 2 and 1 are not serious adverse health consequences per FDA's HHE Form.

C. Estimation of Probability of Harm Resulting from Affected Units

Estimated quantity of affected devices (# in field, # in factory, # in distribution centers, etc.):	A total of 7,166,491 DreamStation 1 platform devices were shipped between 2015 and April 2021. This includes : • 6909399 shipments of DS1 CPAP devices • 137042 shipments of DS1 AVAPS/ST NIV devices • 98860 shipments of DS1 ASV NIV devices • 21,190 shipments of E30 ventilator
Number and type of injuries/number of deaths attributed to the problem with the device (if any):*	It should be noted that harm may not be immediately recognizable and may not be something that the customer would/could report. Serious adverse events = 0 Deaths = 0
Describe the factor(s) that need to occur to create the hazardous situation (reasonably foreseeable sequence or combination of events):	A hazardous situation is created when a patient uses a DreamStation 1 therapy device with PE-PUR foam. COCs at unacceptable levels per ISO standard are released from the device, expelled through the airpath and patient circuit and delivered to the patient.
Factors that might mitigate risk (e.g., safety mechanisms present in the design, instructions for use, current label warnings, etc.):	There are no safety mechanisms present that would aid in mitigating the risks associated with harmful chemicals being emitted from device materials for devices in the field.
Would a user detect the hazardous situation prior to occurrence of harm? If so, describe how:	It is unlikely that a user would detect VOC exposure while using the device.

Probability Estimate

Estimation of Probability that the Harm will occur:	**2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend)

Comments:	Probability of Hazardous Situation Occurring (P1)
(Probability of Harm Rationale)	Hazardous situation: While receiving therapy, patients may be exposed to hazardous levels of VOCs that are unacceptable per ISO standards. **Probability that Hazardous Situation will Lead to Harm (P2)** There are no data to accurately estimate the probability of the hazardous situation leading to harm. **Probability of Occurrence of Harm (P)** Taking into consideration P1 and P2, it is challenging to accurately estimate the probability of harm quantitatively. A probability of 2 (Occasional) was chosen as the reasonable worst-case scenario for a Severity 3 harm.

Considering the factors above, assess the probability that use of, or exposure to, the affected devices will cause future harm during the product's lifetime. Consider segments of the population most at risk (e.g. infants, elderly, pregnant women, critically ill patients, etc.).

Check (X) applicable level*	***Example of probability of harm***
___ **4** **(Always)**	Occurs 'every time'*
___ **3** **(Likely)**	'Reasonable probability' that use will cause harm*; good chance/ considerable certainty to cause harm
X **2** **(Occasional)**	'Remote probability' that use will cause harm*; expected to cause harm rarely/ from time to time (e.g., with no clear trend)
___ **1** **(Unlikely)**	'Not likely' that use will cause harm*; possible but improbable
___ **0** **(Inconceivable)**	Inconceivable; not possible

*** Corresponds with probability levels set forth in FDA's CDRH HHE Form Version 3-1 01/12/2007.**

***Note: If harm has already occurred as a result of the issue under review, then:**

- Probability level zero (0) and one (1) can only be used if the investigation shows the harm was the result of an isolated incident and no other units are likely to be affected; a detailed rationale for why harm is not likely to occur again must be provided.
- Probability level 0 rarely applies to post-market risk evaluation in cases where harm has occurred.

Step III – Health Hazard Evaluation Conclusion

Probability	Severity			
	1	2	3	4
4	Unacceptable	Unacceptable	Unacceptable	Unacceptable
3	Acceptable	Unacceptable	Unacceptable	Unacceptable
2	Acceptable	Further Analysis Required[1)]	**Unacceptable**	Unacceptable
1	Acceptable	Acceptable	Further Analysis Required[1)]	Unacceptable
0	Acceptable	Acceptable	Acceptable	Acceptable

[1)] If the results of a risk evaluation fall into one of these two cells (3x1 or 2x2), then a risk/benefit analysis and/or appropriate justification must be documented in section C below.

Note:

- The original premarket risk/benefit analysis may be reused if still applicable as the evaluation to justify an acceptable risk.
- The above Risk Table helps assess whether the risk is acceptable or not; however, reviewer/approvers of this document make the final determination.
- Even if a risk is deemed "acceptable", action to address the issue may still be warranted.

A. Document the results of the Health Hazard Evaluation for each hazardous situation under review:

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

B. If the risk of the individual hazardous situation is acceptable, review the Risk Management File and consider combined impact of all the individual risks to evaluate whether overall residual risk of the device is still acceptable. Is the summary of all the risks acceptable or not acceptable?

UNACCEPTABLE (acceptable / unacceptable)

C. Any additional information (if applicable):	The risk management files associated with these products will be evaluated and updated per the information above. The Philips Respironics team is continuing to conduct additional investigational activities to better understand the root cause of the PE-PUR sound abatement foam to emit VOCs that exceed the acceptable limits provided in ISO 18562. Testing is currently underway to understand the nature of VOC emission in degraded foam.

	To ensure that we maintain our perspective and focus on our users, we have made conservative assumptions in identifying the severity and probability of the harms associated with this issue. This HHE will be updated (as required) when additional testing on degraded foam is completed.
Health Hazard Evaluation Conclusion:	**Medical Assessment** The Health Hazard Evaluation conducted by the Philips Respironics Team concluded that the Hazards described herein represent an unacceptable risk to users. **Severity 3; Probability 2** The severity of harm (level 3) recognizes the seriousness of any potential harm and the need for medical intervention to preclude permanent impairment. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (i.e., with no clear trend).

Step IV – Outcome approved by the following individuals:

Prepared By:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Design Quality Engineer / Safety Risk Management

Approved By Director of BIU QARA:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Head of Design Quality Engineering

Approved By VP of Corporate QA – HHS Q&R (or delegate):

Signature Date

See attached signature sheet

Print Name and Title

s22 – Head of Quality SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Leader SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Director Connected Care

Approved By Clinical Affairs Representative:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Head of Clinical Affairs

Note: This form may be emailed or faxed to the person(s) above. Signature (electronic or fax) is required for all HHEs.

HEALTH HAZARD EVALUATION FORM

ER 2241623 – Foam Degradation in Trilogy Devices, Version 00

Step I – Identification of the Issue/Problem

CAPA Number:	**7211**	**HHE Date Open:**	11/16/2020	**HHE Date Closed:**	04/26/2021
- Product Data -					
Product Code:	CBK (Ventilator, Continuous, Facility Use)				
Model:	All finished good part numbers under the devices listed below fall within the scope of this HHE. For a comprehensive list of all finished good numbers, refer to CAPA 7211.				
Device Name:	Trilogy Ventilator				
Lot/Serial Numbers:	All devices in the field and released in inventory currently using the polyester-based polyurethane foam (PE-PUR) could be subject to this potential failure mode.				
Marketing Status (Include 510(k) or PMA Number, Specify if Class I Exempt from 510(k)):	Trilogy 100: K083526 Trilogy 200: K093416				
Manufacturing/Recall Firm Address:	Respironics Inc. 1010 Murry Ridge Ln Murrysville, PA 15668				
Product Description (Include Intended Use from Labeling):	**Trilogy Product Identification and Intended use**: **Regulation**: 21 CFR 868.5895 Identification: A continuous ventilator (respirator) is a device intended to mechanically control or assist patient breathing by delivering a predetermined percentage of oxygen in the breathing gas. Adult, pediatric, and neonatal ventilators are included in this generic type of device. Classification: Class II (performance standards) **Intended Use for Trilogy 100** - The Philips Respironics Trilogy100 system provides continuous or intermittent ventilatory support for the care of individuals who require mechanical ventilation. Trilogy100 is intended for pediatric through adult patients weighing at least 5 kg (11 lbs.). The device is intended to be used in home, institution/hospital, and portable applications such as wheelchairs and gurneys, and may be used for both invasive and non-invasive ventilation. It is not intended to be used as a transport ventilator. The system is recommended to be used only with various combinations of Philips Respironics-approved patient circuit accessories, such as patient interface devices, humidifiers, water				

	traps, and circuit tubing. **Intended Use for Trilogy 200** - The Philips Respironics Trilogy200 system provides continuous or intermittent ventilatory support for the care of individuals who require mechanical ventilation. Trilogy200 is intended for pediatric through adult patients weighing at least 5 kg (11 lbs.). The device is intended to be used in home, institution/hospital, and portable applications such as wheelchairs and gurneys, and may be used for both invasive and non-invasive ventilation. It is not intended to be used as a transport ventilator. The system is recommended to be used only with various combinations of Philips Respironics-approved patient circuit accessories, such as patient interface devices, humidifiers, water traps, and circuit tubing. **Device Description (100 and 200):** The Trilogy ventilator provides invasive and non-invasive, positive pressure ventilation to pediatric through adult patients with a minimum weight of 2.5 kg. It is an electronically-controlled, pneumatic ventilation system that is compatible with a range of accessories to provide a variety of therapy modes. The subject devices provide different modes of ventilator support. Mode of ventilation refers to the method of inspiratory support provided by the ventilator. It is the specific combination of breathing pattern and control variables to deliver inspiration. Selection of the modes to be used will depend on the patient's condition and Clinician's decision.
Brief description of the issue/problem and how it was identified:	Philips Respironics received complaints in 2019 regarding SystemOne CPAP devices from Thailand (Complaint numbers RA 307829970 and 307806329) alleging the presence of black debris/particles within the airpath circuit (extending from the device outlet, humidifier, tubing, and mask). In one of these complaints, the patient's family member expressed concerns that the black particulate was delivered to the patient's airway and could affect the user's health. The SystemOne devices for both complaints were returned and visual inspection showed signs of foam degradation. Chemical analysis of the foam confirmed degradation, triggering the initiation of CAPA 7211 and additional investigational activities. The sound abatement foam is an open-cell polyester-based polyurethane (PE-PUR) foam that is widely used for sound dampening purposes in many industries. The PE-PUR foam is also used in Philips Respironics Trilogy devices, the subject of this Health Hazard Evaluation (HHE). A complaint analysis performed as part of CAPA 7211 indicated that complaints for PE-PUR foam degradation were also identified for the Trilogy devices. Specifically, 66 complaints were identified suggesting the presence of degraded foam with Trilogy devices. In addition, the complaint analysis showed an overall increase in complaints related to alleged PE-PUR foam degradation across the PRI PAP devices, NIV, and ventilators. The majority of complaints were reported by Philips service personnel and were found subsequent to investigating the patients'

	primary complaints. As of the date of this HHE, 268,140 Trilogy devices have been shipped. Accordingly, Philips Respironics initiated this HHE to evaluate potential foam degradation in the context of Trilogy devices based on available data generated to date. Prior to the 2019 complaints, Philips Respironics received two complaints (RA # 307114335 and 307270215) alleging that a Trilogy device displayed a "vent INOP" error (a "Ventilator Inoperable" alarm). The investigation (INV0988) into the complaint identified that the alarm was triggered due to foam debris that had built up in the motor blower. Following these complaints, an HHE was conducted for the Trilogy platform (see ER 2227646, v06). Based on the data available at that time, the HHE concluded acceptable risk. Based on the results of the 2018 HHE, Philips added foam replacement as part of an existing preventive maintenance (PM) program. This Health Hazard Evaluation only assesses the risks associated with physical exposure to foam particulates. Emission of chemical compounds as a result of foam breakdown is recognized as a potential source of harm, however testing is ongoing to further investigate the potential harms associated with this. As additional information becomes available, this HHE will be updated to reflect any changes to the overall risk profile.
Affected Patient/User Population:	All patient groups that fall within the intended use of the devices referenced in the Product Description are within the affected patient population. The intended patient population across the Trilogy platforms broadly includes the following: adult and pediatric patients weighing over 11 lbs. (5 kg) who require mechanical ventilation. Higher risk populations within the intended patient population include pediatrics; the elderly; pregnant women; and patients with comorbidities such as heart failure, COPD, and obesity.
HHE Author (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management
HHE Contributors (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management s22 [redacted] – Design Quality, Sr. Manager s22 [redacted] –Quality Engineering, Manager s22 [redacted] – Head of Design Quality Engineering s22 [redacted] – Sustaining Engineering Manager s22 [redacted] – Sr. Quality Engineer s22 [redacted] – Sr. Bio Safety and Verification Engineer s22 [redacted] – Head of Global Clinical and Scientific Affairs s22 [redacted] – Medical Director, Connected Care s22 [redacted] – Director of Regulatory Affairs s22 [redacted] – Medical Leader, SRC s22 [redacted] – Medical Safety Manager, SRC

Step II – Analyze Post Release Health Risk Associated with Affected Units

Note: Assess the risk as if no corrective action will be taken and all affected devices will remain in the marketplace.

A. Identification of the Individual Hazard(s)

Hazard Category:	**Hazard Category:** Biological and Chemical **Hazard**: Biocompatibility / Toxicity of chemical constituents
Hazard Cause:	Polyester-based polyurethane foam (PE-PUR) is used as a sound abatement foam in the Trilogy device airpath. Based on all available data generated to date, Philips Respironics determined that the PE-PUR foam's reaction with moisture (hydrolysis) was a source of the foam degradation potentially caused and/or exacerbated by the following factors: • Device operation in higher heat and humidity environmental conditions; and/or • Use of unapproved cleaning and disinfection methods with the Trilogy device (e.g. ozone). *Environmental Conditions* The labeled environmental conditions for operating temperature are 5° to 40° C (41° to 104° F) with storage temperatures ranging from -20° to 60° C (-4° to 140° F). Preliminary test results conducted by Philips Respironics show that high temperature (90° C) contributes to significant degradation of the foam. Testing is ongoing to further refine the impact of various ambient temperatures and humidity on foam degradation including: (1) models that may better simulate real world device operation conditions; and (2) lower temperatures within the labeled range. Refer to Section III,C for additional information on planned testing. *Unapproved Cleaning and Disinfection Methods* The Trilogy user manual cleaning instructions do not include ozone disinfection; rather, the instructions recommend water and a mild liquid dishwashing detergent for cleaning and Hydrogen Peroxide, Isopropyl Alcohol or a Chlorine Bleach solution for disinfection. The manual states that any deviation from these instructions or agents not listed in this guide may impact the performance of the product. Ozone disinfection devices appear to have become more readily available around the same time as Philips Respironics received complaints of foam degradation, however further investigation is ongoing. Foam degradation has also been reported even when ozone disinfection was not reported.
Hazardous Situation:	**Exposure to particulate by-products of foam degradation during use.** If PE-PUR foam degrades, small particulates (estimated size range of 2.69 µm-724 µm) may be expelled from the device blower box, through the motor and patient circuit and could enter the patient respiratory tract and/or Gastrointestinal (GI) tract. Based on our analysis of the degraded foam, the particles may include compounds such as diethylene glycol (DEG), toluene diamine isomers (TDA), and toluene diisocyanate isomers (TDI). Due to an inability to obtain a sufficient quantity of representative field

	samples for biocompatibility lab testing, we created lab degraded foam used for such testing, including: cytotoxicity, genotoxicity, irritation, and sensitization tests.

B. Estimation of Severity

Description of reported and/or potential harm:	**Harm resulting from Short-Term and Intermediate-Term Exposure:** exacerbation or worsening of the underlying patient condition Potential Harms: • Irritation (skin, eye, and respiratory tract) • Inflammatory response • Headache • Asthma • Effects to reproductive system • Neoplasia While no harm was reported for Trilogy devices, 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or the use of PAP therapy in general. **Harm resulting from Long-Term Exposure:** cytotoxic, genotoxic, and potential carcinogenic effects Zero cases of harm have been directly or indirectly linked to this failure mode.
Estimation of Severity of Harm	**3 (Crucial) – Short/Intermediate Term Exposure** Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment This is considering the reasonable worst-case scenario, per the rationale in the comments section below. **3 (Crucial) – Long Term Exposure** Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment Philips Respironics identified no significant difference in the estimated severity of harm when considering the general and higher risk patient populations.
Comments: (Severity of Harm Rationale)	A Bio Endpoint Analysis and toxicological risk assessment was performed on the specific chemical constituents and their potential impact to patients. This analysis is included as part of CAPA 7211; the testing is summarized below. Due to the difficulty in obtaining a sufficient quantity of representative field

samples for biocompatibility lab testing, laboratory accelerated aged foam was used to conduct the cytotoxicity, genotoxicity, irritation, and sensitization tests. The following results were noted:

- Cytotoxicity was noted for all extraction concentrations.
- Two genotoxicity assays confirmed a positive mutagenic response.
- Irritation results for the non-polar extract returned a passing result.
- Sensitization results from both polar and non-polar extracts returned a passing result.

Daily chemical dosages and concentrations are unknown at this time. Philips is in the process of constructing a model that calculates the start and rate of foam degradation. Further investigations are ongoing and detailed in Step III, Section C. Additionally, the literature does describe tolerable intake (TI) references for some of the major degradative by-products of the polyester polyurethane foam: TDA, TDI and DEG. Specifically:

- **Toluene diamine isomers (TDA)**, such as toluene-2,4-diamine, are primarily used in the synthesis of polyurethane, various dyes, and heterocyclic compounds.[1,2]
    - A chronic reference dose (RfD) for 2, 6 toluene diamine has been listed by the IRIS EPA at 0.03 mg/kg per day.[3]
- **Toluene diisocyanate isomers (TDI)** such as 2,4-toluene diisocyanate are chemical intermediates utilized in the production of polyurethane products.[4]
    - A reference concentration of 0.00007 mg/m^3 (0.07 µg/m^3) has been recommended for toluene diisocyanates by the EPA IRIS risk assessment.[5]
    - The U.S. Office of Environmental Health Hazard Assessment (OEHHA) has listed the Safe Harbor Levels at 20 µg/day for the no significant risk level (NSRL) to toluene diisocyanates.
- **Diethylene glycol (DEG)** is a polyol building block utilized in the synthesis of polyurethane.
    - Literature suggests a proposed human oral ingestion reference dose of 0.3 mg/kg for DEG.[6]
    - A WEEL occupational level of 10 mg/m^3 has been proposed by TERA for inhalational limits of DEG[7]- but this is not adequate or protective for sensitive patient populations and only accounts for an occupational worker exposure.
    - Per prior informal feedback from the FDA, 1% of the WEEL occupational value (10 mg/m^3) would be an adjusted tolerable intake of 0.1 mg/m^3.

Philips Respironics is working to complete the additional investigatory activities described in Step III, Section C to assess whether the amount of

degraded PE-PUR form inhaled and/or ingested by the patient may potentially exceed the TI references provided above.

In order to evaluate the risks posed by the PE-PUR foam particulates, exposure time and patient airway physiology must be considered. Data generated to date suggests that the PE-PUR foam degrades into particulates of varying sizes. The location of collected particulates in the respiratory tract and the body's response to them is partially dictated by size.

- For this HHE, the PE-PUR foam particulates are assumed to reach the patient airway (the amount or concentration in µg/m^3 is unknown).

  The location of where aerosolized particulates collect in the respiratory tract and the body's response to them is partially dictated by size.[1] A multitude of tissues compose the respiratory tract which includes the conducting airways that consist of the nose and mouth, pharynx, larynx, leading into the trachea, main bronchi, lobar, segmental bronchi, and terminal bronchioles.[2] The terminal bronchioles then lead into the respiratory bronchioles, alveolar ducts, and lastly alveolar sacs.[2] There are defense mechanisms in the respiratory system which help prevent particulates from entering into the lung, these include cilia and mucous layers. Cilia are hair-like projections of the cells that line the airway and propel the liquid layer of mucous which can trap pathogens and particulates prior to reaching the lungs.[3]

- The nose and accompanying respiratory tract is capable of filtering foreign particles dependent on particle size and airflow rate with a filtration efficacy decreasing with particulate size.[4] Small particles (<1-3 µm) are capable of diffusing into deep lung tissue and deposit into the alveoli whereas larger particulates (> 8 µm) will be deposited throughout the nasal passages and larger bronchioles.[1]

- Macrophages: one of the three types of alveolar cells, also known as dust cells, can eliminate foreign particles and bacteria through the process of phagocytosis

Philips Respironics particle size analysis identified that the majority of particulate (> 8 µm) is of a size that is unable to penetrate into deep lung tissue and thus will remain in the patient upper airway. A smaller fraction of the particulate (<1-3 µm) may still penetrate into the lower respiratory tract.

Our conclusions are as follows:

- Based on the cytotoxicity and genotoxicity results and toxicological risk assessment, combined with our conclusion that particles are likely to reach the upper airway and potentially the lower respiratory track, a reasonable worst-case estimate for the **general** and **higher risk** (e.g., patient populations with preexisting conditions or comorbidities) patient populations is a severity level 3 (Crucial) for both short/intermediate and long term exposure.

Reference Information:

Check (X) Applicable Level*	Examples
___ 4 (Catastrophic)	Directly results in death
X 3 (Crucial)	Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment
___ 2 (Marginal)	Results in moderate injury: temporary impairment, or self-limiting illness
___ 1 (Negligible)	Results in less than moderate or no injury

*Severity Levels 4 and 3 are “serious adverse health consequences” per FDA’s CDRH Health Hazard Evaluation Form Version 3-1 01/12/2007. Severity Levels 2 and 1 are not serious adverse health consequences per FDA’s HHE Form.

References:

1. Thomas, R. J. Particle size and pathogenicity in the respiratory tract. Virulence 4, 847–858 (2013).

2. Patwa, A. & Shah, A. Anatomy and physiology of respiratory system relevant to anaesthesia. Indian J. Anaesth. 59, 533–541 (2015).

3. Defense Mechanisms of the Respiratory System - Lung and Airway Disorders. Merck Manuals Consumer Version Available at: https://www.merckmanuals.com/home/lung-andairway-disorders/biology-of-the-lungs-and-airways/defense-mechanisms-of- the-respiratorysystem. (Accessed: 23rd May 2018)

4. Imre Salma, Imre Balásházy, Renate Winkler-Heil, Werner Hofmann, Gyula Záray,. Effect of particle mass size distribution on the deposition of aerosols in the human respiratory system, Journal of Aerosol Science, Volume 33, Issue 1, 2002, Pages 119-132, ISSN 0021-8502, https://doi.org/10.1016/S0021-8502(01)00154-9. (https://www.sciencedirect.com/science/article/pii/S0021850201001549)

5. Knowles, M. R. & Boucher, R. C. Mucus clearance as a primary innate defense mechanism for mammalian airways. J. Clin. Invest. 109, 571–577 (2002)

C. Estimation of Probability of Harm Resulting from Affected Units

Estimated quantity of affected devices (# in field, # in factory, # in distribution centers, etc.):	Between 2008 through March 2021, a total of 268,140 shipments of Trilogy Devices.
Number and type of injuries/number of deaths attributed to the problem with the device (if any):*	No instances of harm have been reported in Trilogy devices where foam degradation was alleged. Injuries = 0 Deaths = 0 In the case of long-term exposure, it should be noted that harm may not be immediately recognizable and may not be something that the customer would/could report. A total of 66 complaints were filed for foam degradation with Trilogy devices. The reported complaint rate for this failure mode is 0.025%. While no harm was reported for Trilogy devices, 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or PAP therapy in general.
Describe the factor(s) that need to occur to create the hazardous situation (reasonably foreseeable sequence or combination of events):	A hazardous situation is created when a patient uses a Trilogy device where the PE-PUR foam exhibits degradation. As described in Step II, Section A under Hazard Cause, foam may degrade when exposed to specific conditions. Once the foam starts to degrade, airborne particulates from degraded foam material could potentially enter the Trilogy system air flow path. The particulate must travel through the path outlined below. Trilogy Air Flow Path: Air enters through the inlet filter and into the blower box that contains the PE-PUR foam. From the blower box, the air continues through the angled elbow of blower and through the blower impeller. Air then travels through the angled outlet port, continuing through the patient circuit. The patient circuit consists of a 6 ft tube, an angled connection interface, and mask, before reaching the patient airway.
Factors that might mitigate risk (e.g., safety mechanisms present in the design, instructions for use, current label warnings, etc.):	<u>Device inspection per device IFU</u>: Exposure to the hazard may be partially mitigated through device, tubing and mask inspection. Device User Manuals instruct patients to “Periodically inspect electrical cords, cables, tubing, and accessories for damage or signs of wear.” This same mitigation factor applies to care providers when used in a clinical setting, such as a hospital. However, patients or care providers may not detect the particles (e.g., because the particles are too small).

	Bacteria Filter: Labeling recommends that a main line outlet bacteria filter (Part Number 342077) be used whenever the device is used for invasive therapy or if the ventilator may be used on multiple patients. When a bacterial filter is used within the patient circuit, particulate is unable to reach the patient. According to the Ambu 20801 performance sheet, the filter tested 99.97% effective on an inert test particle of 0.3µm. Based on the particle size report (detailed in CAPA 7211), the bacteria filter will effectively filter out any foam particulate that could make its way up the patient circuit. Routine Maintenance: Periodic routine maintenance instructs service centers to replace blower foam every 10,000 blower hours or every 24 months (whichever may come first). After being implemented in June 2018, a total of 63,099 devices have undergone the routine maintenance. Zero complaints of foam degradation have been reported for these devices that received PM. However, complaints of foam degradation have been received for devices that did not receive the PM. Although there are factors that may mitigate the risk of exposure to foam particulates, e.g. using a filter and completion of prescribed PMs, we cannot ensure that these are followed by all end users / customers and thus we need to be cautious when estimating the actual protections afforded from these mitigations. References: • IFU > Replacing the Air Inlet Path Foam • IFU > Bacteria filter (Part Number 342077) • Service Manual 1002735 > Ch. 8 Maintenance • AARC Clinical Practice guideline 2007 revision & Update, Respiratory Care, August 2007 VOL 52 NO 1 – recommends "Humidification systems are essential for invasive mechanical ventilation"(sec 10.1.7.)
Would a user detect the hazardous situation prior to occurrence of harm? If so, describe how:	Detection of Foam Particulate: The particulate analysis (as detailed in CAPA 7211) demonstrates a variety of small and large particles that may or may not be detectable based on size and quantity. Small, black contaminants may become visible near the air outlet port or within the patient circuit. Particulate that is large enough to be seen with the naked eye, however, may have a greater chance of detection considering that many of these devices

	are used in a hospital setting and subject to mandatory cleaning and inspection by hospital staff. Because Trilogy devices follow a 2-year PM schedule, the chance of detecting foam degradation is greater.

Probability Estimate

Estimation of Probability that the Harm will occur:	Short/Intermediate-Term Hazard Exposure **2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend) This Hazard has zero reports of harm from 2008 through March 2021 for Trilogy devices. While no harm was reported for Trilogy devices, 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or PAP therapy in general. Long-Term Exposure **2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend) This Hazard has zero reports of harm from 2008 through March 2021
Comments: (Probability of Harm Rationale)	**Probability of Hazardous Situation Occurring (P1)** While Philips Respironics' testing and investigation to date indicates that the PE-PUR foam within the devices is degrading, and the degradation may be due to device exposure to certain conditions (e.g., environmental, disinfection using unauthorized cleaning agents) over a period of time, Philips Respironics is in the process of conducting additional studies to better understand: (1) the specific conditions that cause the foam to degrade; and (2) the rate of foam degradation when the device experiences such conditions. For example, if the device must experience certain environmental conditions for an extended period of time for the foam to degrade (e.g., high humidity, high temperature), not all users may subject their device to such conditions. Therefore, completion of these ongoing and planned studies will help Philips Respironics better estimate the reasonable worst-case probability of the foam degrading within the device population. See ongoing and planned investigational activities described in Step III, Section C. Although the observed complaint rate is 0.025%, as noted above, the complaint rate may not accurately reflect the probability of the failure because patients may not detect the particles and/or report

	the event to Philips Respironics. Time is a critical variable that must also be taken into account. Periodic routine maintenance may help to minimize the impact of this variable as much as possible by replacing blower foam every 10,000 blower hours or every 24 months (whichever may come first). Although complaint data may not accurately reflect the occurrence of the failure, there have been zero complaints of foam degradation for devices that have undergone the recommended routine maintenance. Additional factors to consider when assessing whether or not a patient could be exposed to foam particulate is the use of a bacteria filter in-line with the patient circuit. If used, the bacteria filter prevents particulate of 0.3µm or larger from reaching the patient. This would effectively filter out all particulate, based on the sizes observed in the foam particulate analysis performed as part of CAPA 7211. Nonetheless, based on the available information and test data collected to date, Philips Respironics estimates that the reasonable worst-case probability of the foam degrading in the device to be *occasional* over the device's useful life. **Probability that Hazardous Situation will Lead to Harm (P2)** The probability that the hazardous situation will lead to harm is dependent upon the amount of degraded foam a patient may inhale and/or ingest and may be exacerbated by the patient's underlying comorbidities. As noted in Step II, Section B, further investigations are ongoing and detailed in Step III, Section C. Short and long-term exposure to the hazard may cause generalized inflammation in patients that could facilitate clinical deterioration in certain patient populations as dictated by the underlying disease or associated comorbidities. As an inhalational therapy, it is possible that patients with low cardio-pulmonary reserve (e.g. COPD, CHF) may experience a meaningful deterioration in their function that requires medical intervention. Clinical events of this nature may not be easily linked to the hazardous situation or device use in general. Based on lab testing, exposure to the degraded foam and its components may lead to cellular DNA mutations. Such mutations may lead to uncontrolled cellular replication given a sufficient dose and duration of exposure that have not been determined. Patient related factors including bodily defenses, target tissue deposition, and immune function will also likely impact the development of the reasonable worst-case scenario harm. Additionally, a presumed lag time from exposure to harm development may make it difficult for patients to attribute their individual harm to the device usage. No severity 3 (Crucial) harm has been reported to date. It should be noted that harm in this case may not be immediately recognizable and may not be something that the patient would/could report. **Probability of Occurrence of Harm (P)** Taking into consideration P1 and P2, it is challenging to accurately estimate the probability of harm quantitatively. A probability of 2 (Occasional) was chosen as the reasonable worst-case scenario, despite taking into consideration existing risk mitigations and the

	information known at this time.

Considering the factors above, assess the probability that use of, or exposure to, the affected devices will cause future harm during the product's lifetime. Consider segments of the population most at risk (e.g. infants, elderly, pregnant women, critically ill patients, etc.).

Check (X) applicable level*	***Example of probability of harm***
___ **4** **(Always)**	Occurs 'every time'*
___ **3** **(Likely)**	'Reasonable probability' that use will cause harm*; good chance/ considerable certainty to cause harm
X **2** **(Occasional)**	'Remote probability' that use will cause harm*; expected to cause harm rarely/ from time to time (e.g., with no clear trend)
___ **1** **(Unlikely)**	'Not likely' that use will cause harm*; possible but improbable
___ **0** **(Inconceivable)**	Inconceivable; not possible

*** Corresponds with probability levels set forth in FDA's CDRH HHE Form Version 3-1 01/12/2007.**

***Note: If harm has already occurred as a result of the issue under review, then:**

- Probability level zero (0) and one (1) can only be used if the investigation shows the harm was the result of an isolated incident and no other units are likely to be affected; a detailed rationale for why harm is not likely to occur again must be provided.
- Probability level 0 rarely applies to post-market risk evaluation in cases where harm has occurred.

Step III – Health Hazard Evaluation Conclusion

Probability	Severity			
	1	2	3	4
4	Unacceptable	Unacceptable	Unacceptable	Unacceptable
3	Acceptable	Unacceptable	Unacceptable	Unacceptable
2	Acceptable	Further Analysis Required[1)]	Unacceptable Short/Intermediate-Term Exposure Long-Term Exposure	Unacceptable
1	Acceptable	Acceptable	Further Analysis Required[1)]	Unacceptable
0	Acceptable	Acceptable	Acceptable	Acceptable

*These conclusions will be re-evaluated once the additional testing described in Section III.C is completed.

[1)] If the results of a risk evaluation fall into one of these two cells (3x1 or 2x2), then a risk/benefit analysis and/or appropriate justification must be documented in section C below.

Note:

- The original premarket risk/benefit analysis may be reused if still applicable as the evaluation to justify an acceptable risk.
- The above Risk Table helps assess whether the risk is acceptable or not; however, reviewer/approvers of this document make the final determination.
- Even if a risk is deemed "acceptable", action to address the issue may still be warranted.

A. Document the results of the Health Hazard Evaluation for each hazardous situation under review:

Short/Intermediate-Term Exposure

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

Long-Term Exposure

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

B. If the risk of the individual hazardous situation is acceptable, review the Risk Management File and consider combined impact of all the individual risks to evaluate whether overall residual risk of the device is still acceptable. Is the summary of all the risks acceptable or not acceptable?

UNACCEPTABLE (acceptable / unacceptable)

C. Any additional information (if applicable):	As noted above, the Philips Respironics team is continuing to conduct additional investigational activities to better understand the myriad of variables and considerations related to the reported foam degradation. To ensure that we maintain our perspective and focus on our users, we have made conservative assumptions in identifying the severity and probability of the harms associated with this issue. As we complete the testing listed below, we will update this HHE (as required). The risk management files associated with these products will be evaluated and updated per the information above. ADDITIONAL TESTING CONSIDERATIONS: Accelerated PE-PUR Foam Life Testing • The goal of this testing is to develop a model to help us understand the foam degradation behavior at ambient conditions within the specified operating temperature and humidity ranges, in the presence or absence of ozone. • Preliminary results, at the experiments' mid-point, show visual separation between the ozone and non-ozone groups, within the operating temperature ranges, indicating that ozone does accelerate degradation at lower temperatures. These results are not yet final; therefore, this potential impact has not been considered in the overall residual risk rating. Ozone Cycling on PE-PUR Foam • The purpose of this benchtop testing is to understand how ozone impacts the visual and chemical breakdown of PE-PUR foam at ambient conditions. The outcome of this test could provide further confirmation on the hypothesis that ozone has a direct connection to the premature breakdown of device sound abatement foam. • Preliminary results indicate that PE-PUR foam exposed to various cycles of ozone at ambient temperatures show significant accelerated foam degradation, even after only one cycle. As these results are also not yet final, this potential impact has not been considered in the overall residual risk rating. Dosage Test • The goal of this test is to estimate the daily and total dosage of particulate being delivered to a patient over the device's expected use life. Foam Volatile Organic Compounds(VOC) Testing • As more details become known, additional information will be added to this section.
Health Hazard	

Evaluation Conclusion:	**Health Hazard Evaluation Medical Assessment** The Health Hazard Evaluation conducted by the Philips Respironics Team concluded that the Hazards described herein represent an unacceptable risk to patients. **Short/Intermediate-Term Exposure to Hazard: Severity 3; Probability 2** The severity of harm (level 3) recognizes the seriousness of any potential harm that may significantly impact the clinical status of patients and require additional medical intervention. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend). **Long Term Exposure to Hazard: Severity 3; probability 2** The severity of harm (level 3) recognizes the seriousness of any potential malignancy and the need for medical intervention to preclude permanent impairment. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend).

Step IV – Outcome approved by the following individuals:

Prepared By:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Design Quality Engineer / Safety Risk Management

Approved By Director of BIU QARA:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Head of Design Quality Engineering

Approved By VP of Corporate QA – HHS Q&R (or delegate):

Signature Date

See attached signature sheet

Print Name and Title

s22 – Head of Quality SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Leader SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Director Connected Care

Approved By Clinical Affairs Representative:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Head of Clinical Affairs

Note: This form may be emailed or faxed to the person(s) above. Signature (electronic or fax) is required for all HHEs.

HEALTH HAZARD EVALUATION FORM

ER 2241621 – Foam Degradation in PAP Devices, Version 00

Step I – Identification of the Issue/Problem

CAPA Number:	**7211**	**HHE Date Open:**	11/16/2020	**HHE Date Closed:**	04/26/2021
- Product Data -					
Product Code:	BZD (noncontinuous ventilator (Intermittent positive pressure breathing - IPPB))				
Model:	All finished good part numbers under the devices listed below fall within the scope of this HHE. For a comprehensive list of all finished good numbers, refer to CAPA 7211.				
Device Name:	SystemOne (Q-Series) DreamStation CPAP, Auto CPAP, BiPAP DreamStation Go CPAP, Auto CPAP Dorma				
Lot/Serial Numbers:	All devices in the field and released in inventory currently using the polyester-based polyurethane foam (PE-PUR) could be subject to this potential failure mode.				
Marketing Status (Include 510(k) or PMA Number, Specify if Class I Exempt from 510(k)):	K130077 • Dorma K131982 • SystemOne • DreamStation • DreamStation Go				
Manufacturing/Recall Firm Address:	Respironics Inc. 1010 Murry Ridge Ln Murrysville, PA 15668				
Product Description (Include Intended Use from Labeling):	***K130077*** **Dorma Product Identification and Intended use**: **Regulation**: 21 CFR 868.5905 Identification : A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing.				

	Classification: Class II (performance standards) **Intended Use**: These devices are intended to deliver positive airway pressure therapy for the treatment of Obstructive Sleep Apnea in spontaneously breathing patients weighing over 30kg (66 lbs.). They are for use in the home or hospital/institutional environment. **Device Description:** This device delivers CPAP/Auto CPAP and incorporates a ramp function that allows the patient to start therapy at a lower pressure (e.g., 4 cm H2O) when trying to fall asleep and gradually increases the delivered pressure up to the prescription pressure over the time interval selected. For example, air pressure can be gradually increased in 0.5 cm H2O increments if ramp time is set to > 0 and therapy pressure is > 4 cm H2O, until the prescription pressure is reached. Depending on the therapy mode, therapy pressure setting could be any of the following: CPAP pressure, CPAP-Check pressure, or Auto minimum pressure. Also, a Flex comfort feature provides pressure relief during exhalation. ***K131982*** **SystemOne (Q-Series) Product Identification and Intended use:** **Regulation** : 21 CFR 868.5905 Identification : A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: SystemOne devices deliver positive airway pressure therapy for the treatment of Obstructive Sleep Apnea in spontaneously breathing patients weighing over 30 kg. For use in the home or hospital/institutional environment. **Device Description:** This device delivers CPAP/Auto CPAP and incorporates a ramp function that allows the patient to start therapy at a lower pressure (e.g., 4 cm H2O) when trying to fall asleep and gradually increases the delivered pressure up to the prescription pressure over the time interval selected. For example, air pressure can be gradually increased in 0.5 cm H2O increments if ramp time is set to > 0 and therapy pressure is > 4 cm H2O, until the prescription pressure is reached. Depending on the therapy mode, therapy pressure setting could be any of the following: CPAP pressure, CPAP-Check pressure, or Auto minimum pressure. Also, a Flex comfort feature provides pressure relief during exhalation. In addition to these features, these devices incorporate additional features including BiPAP (one level of output pressure during the expiratory breath phase and a second higher level during the inspiratory breath phase), auto-BiPAP, and auto Bi-Level Split Night. A ramp function is also available, and depending on the therapy selected, one or more of the following pressure relief features is available to increase patient comfort: C-Flex, A-Flex, C-Flex+, P-Flex, and mask

	resistance compensation. **DreamStation Product Identification and Intended use:** **Regulation** : 21 CFR 868.5905 Identification : A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The Philips Respironics DreamStation systems deliver positive airway pressure therapy for the treatment of Obstructive Sleep Apnea in spontaneously breathing patients weighing over 30 kg (66 lbs.). It is for use in the home or hospital/institutional environment. **Device Description:** The DreamStation is designed to provide CPAP, CPAP-Check, Auto CPAP, Bi-Level and Auto Bi-Level therapy. The optional heated humidifier offers Heated Tube (via optional 15mm heated tube, HT15), Adaptive or Fixed humidification. In addition to the ramp function, depending on the therapy selected, one or more of the following pressure relief features is available to increase patient comfort: C-Flex, A-Flex, P-Flex, Bi-Flex and Rise Time. DreamStation is intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of disposable or reusable smooth lumen tubing, (22mm, 15mm, Heated Tube15, or 12mm tubing). A typical patient interface device provides a method of venting exhaled gases. Bluetooth wireless technology gives a patient access to their compliance data in markets where the DreamMapper mobile application is available. Optional modem accessories, Cellular Modem or Wi-Fi Accessory, automatically upload patient compliance data to their provider. If included, a Secure Digital (SD) card will also store compliance data allowing a provider to collect a patient's data periodically. **DreamStation Go Product Identification and Intended use:** **Regulation**: 21 CFR 868.5905 Identification : A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The Philips Respironics DreamStation Go systems deliver positive airway pressure therapy for the treatment of Obstructive Sleep Apnea in spontaneously breathing patients weighing over 30 kg (66 lbs.). It is for use in the home or hospital/institutional environment. **Device Description:** The DreamStation Go device targets a market segment of compliant

	PAP patients looking for smaller therapy solutions. DreamStation Go is designed to provide CPAP, CPAP-Check and Auto CPAP therapy by a smaller, lightweight portable device offering patients an alternative to packing and re-assembling their home CPAP system. The DreamStation Go system offers three configurations: CPAP only, CPAP and battery pack or CPAP and heated humidifier and comes standard with 12mm micro tubing. In addition to the ramp function, depending on the therapy selected, one or more of the following pressure relieve features is available to increase patient comfort: C-Flex, A-Flex, and P-Flex. DreamStation Go is intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of disposable or reusable smooth lumen tubing, (22mm, 15mm, or 12mm tubing). A typical patient interface device provides a method of venting exhaled gases.
Brief description of the issue/problem and how it was identified:	Philips Respironics received complaints in 2019 regarding SystemOne CPAP devices from Thailand (Complaint numbers RA 307829970 and 307806329) alleging the presence of black debris/particles within the airpath circuit (extending from the device outlet, humidifier, tubing, and mask). The patient's nephew expressed concerns that the black particulate was delivered to the patient's airway and could affect her health. The SystemOne devices were returned and visual inspection showed signs of foam degradation. Chemical analysis of the foam confirmed degradation, triggering the initiation of CAPA 7211 and additional investigational activities. The sound abatement foam is an open-cell polyester-based polyurethane (PE-PUR) foam that is widely used for sound dampening purposes in many industries. A complaint analysis performed as part of CAPA 7211 indicated that complaints for PE-PUR foam degradation were identified across various PAP device platforms. Specifically, 1,105 complaints were identified suggesting the presence of degraded foam with PAP devices. In addition, the complaint analysis showed an overall increase in complaints related to alleged PE-PUR foam degradation across the PRI PAP devices, noninvasive ventilators (NIV), and ventilators. The majority of complaints were reported by Philips service personnel and were found subsequent to investigating the patients' primary complaints. As of the date of this HHE, 14,792,965 PAP devices have been shipped. Accordingly, Philips Respironics initiated this HHE to evaluate potential foam degradation in the context of PAP devices based on available data generated to date. This Health Hazard Evaluation (HHE) only assesses the risks associated with physical exposure to foam particulates. Emission of chemical compounds as a result of foam breakdown is recognized as a potential source of harm, however testing is ongoing to further investigate the potential harms associated with this. As additional information becomes available, this HHE will be updated to reflect any changes to the overall risk profile.

Affected Patient/User Population:	All patient groups that fall within the intended use of the devices referenced in the Product Description are within the affected patient population. The intended patient population across multiple PAP platforms broadly includes the following: adult and pediatric patients weighing over 66 lbs. with Obstructive Sleep Apnea. Higher risk populations within the intended patient population include pediatrics; the elderly; pregnant women; and patients with comorbidities such as heart failure, COPD, and obesity.
HHE Author (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management
HHE Contributors (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management s22 [redacted] – Design Quality, Sr. Manager s22 [redacted] –Quality Engineering, Manager s22 [redacted] – Head of Design Quality Engineering s22 [redacted] – Sustaining Engineering Manager s22 [redacted] – Sr. Quality Engineer s22 [redacted] – Sr. Bio Safety and Verification Engineer s22 [redacted] – Head of Global Clinical and Scientific Affairs s22 [redacted] – Medical Director, Connected Care s22 [redacted] – Director of Regulatory Affairs s22 [redacted] – Medical Leader, SRC s22 [redacted] – Medical Safety Manager, SRC

Step II – Analyze Post Release Health Risk Associated with Affected Units

Note: Assess the risk as if no corrective action will be taken and all affected devices will remain in the marketplace.

A. Identification of the Individual Hazard(s)

Hazard Category:	**Hazard Category:** Biological and Chemical **Hazard**: Biocompatibility / Toxicity of chemical constituents
Hazard Cause:	Polyester-based polyurethane foam (PE-PUR) is used as a sound abatement foam in the PAP device airpath. Based on all available data generated to date, Philips Respironics determined that the PE-PUR foam's reaction with water (hydrolysis) was a source of the foam degradation potentially caused and/or exacerbated by the following factors: • Device operation in higher heat and humidity environmental conditions; and/or • Use of unapproved cleaning and disinfection methods with the PAP device (e.g. ozone). *Environmental Conditions* The labeled environmental conditions for operating temperature are 5° to 35° C (41° to 95° F) with storage temperatures ranging from -20° to 60° C (-4° to 140° F). Preliminary test results conducted by Philips Respironics show that high temperature (90° C) contributes to significant degradation of the foam. Testing is ongoing to further investigate the impact of ambient temperature and humidity on foam degradation including: (1) models that may better simulate real world device operation conditions; and (2) lower temperatures within the labeled range. Refer to Section III,C for additional information on planned testing. *Unapproved Cleaning and Disinfection Methods* The PAP user and provider manual cleaning instructions do not include ozone disinfection; rather, the instructions recommend water and a mild liquid dishwashing detergent for cleaning and DisCide Ultra Towelettes or a Chlorine Bleach solution for disinfection. The manual states that any deviation from these instructions or agents not listed in this guide may impact the performance of the product. Ozone disinfection devices appear to have become more readily available around the same time as Philips Respironics received complaints of foam degradation, however further investigation is ongoing. Foam degradation has also been reported even when ozone disinfection was not reported.
Hazardous Situation:	**Exposure to particulate by-products of foam degradation during use.** If PE-PUR foam degrades, small particulates (estimated size range of 2.69 µm-724 µm) may be expelled from the device blower box, through the motor and patient circuit and could enter the patient respiratory tract and/or Gastrointestinal (GI) tract. Based on our analysis of the degraded foam, the particles may include compounds such as diethylene glycol (DEG), toluene diamine isomers (TDA), and toluene diisocyanate isomers (TDI). Due to an inability to obtain a sufficient quantity of representative field

	samples for biocompatibility lab testing, we created lab degraded foam used for such testing, including: cytotoxicity, genotoxicity, irritation, and sensitization tests.

B. Estimation of Severity

Description of reported and/or potential harm:	**Harm resulting from Short-Term and Intermediate-Term Exposure:** exacerbation or worsening of the underlying patient condition Potential Harms: • Irritation (skin, eye, and respiratory tract) • Inflammatory response • Headache • Asthma • Effects to reproductive system • Neoplasia A total of 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or the use of PAP therapy in general. **Harm resulting from Long-Term Exposure:** cytotoxic, genotoxic, and potential carcinogenic effects Zero cases of harm have been directly or indirectly linked to this failure mode.
Estimation of Severity of Harm	**3 (Crucial) – Short/Intermediate Term Exposure** Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment This is considering the reasonable worst-case scenario, per the rationale in the comments section below. **3 (Crucial) – Long Term Exposure** Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment Philips Respironics identified no significant difference in the estimated severity of harm when considering the general and higher risk patient populations.
Comments: (Severity of Harm Rationale)	A Bio Endpoint Analysis and toxicological risk assessment was performed on the specific chemical constituents and their potential impact to patients. This analysis is included as part of CAPA 7211; the testing is summarized below. Due to the difficulty in obtaining a sufficient quantity of representative field samples for biocompatibility lab testing, laboratory accelerated aged foam was used to conduct the cytotoxicity, genotoxicity, irritation, and sensitization tests. The following results were noted:

- Cytotoxicity was noted for all extraction concentrations.
- Two genotoxicity assays confirmed a positive mutagenic response.
- Irritation results for the non-polar extract returned a passing result.
- Sensitization results from both polar and non-polar extracts returned a passing result.

Daily chemical dosages and concentrations are unknown at this time. Philips is in the process of constructing a model that calculates the start and rate of foam degradation. Further investigations are ongoing and detailed in Step III, Section C. Additionally, the literature does describe tolerable intake (TI) references for some of the major degradative by-products of the polyester polyurethane foam: TDA, TDI and DEG. Specifically:

- **Toluene diamine isomers (TDA)**, such as toluene-2,4-diamine, are primarily used in the synthesis of polyurethane, various dyes, and heterocyclic compounds.[1,2]
    - A chronic reference dose (RfD) for 2, 6 toluene diamine has been listed by the IRIS EPA at 0.03 mg/kg per day.[3]
- **Toluene diisocyanate isomers (TDI)** such as 2,4-toluene diisocyanate are chemical intermediates utilized in the production of polyurethane products.[4]
    - A reference concentration of 0.00007 mg/m^3 (0.07 µg/m^3) has been recommended for toluene diisocyanates by the EPA IRIS risk assessment.[5]
    - The U.S. Office of Environmental Health Hazard Assessment (OEHHA) has listed the Safe Harbor Levels at 20 µg/day for the no significant risk level (NSRL) to toluene diisocyanates.
- **Diethylene glycol (DEG)** is a polyol building block utilized in the synthesis of polyurethane.
    - Literature suggests a proposed human oral ingestion reference dose of 0.3 mg/kg for DEG.[6]
    - A WEEL occupational level of 10 mg/m^3 has been proposed by TERA for inhalational limits of DEG[7]- but this is not adequate or protective for sensitive patient populations and only accounts for an occupational worker exposure.
    - Per prior informal feedback from the FDA, 1% of the WEEL occupational value (10 mg/m^3) would be an adjusted tolerable intake of 0.1 mg/m^3.

Philips Respironics is working to complete the additional investigatory activities described in Step III, Section C to assess whether the amount of degraded PE-PUR form inhaled and/or ingested by the patient may potentially exceed the TI references provided above.

In order to evaluate the risks posed by the PE-PUR foam particulates, exposure time and patient airway physiology must be considered. Data generated to date

	suggests that the PE-PUR foam degrades into particulates of varying sizes. The location of collected particulates in the respiratory tract and the body's response to them is partially dictated by size. • For this HHE, the PE-PUR foam particulates are assumed to reach the patient airway (the amount or concentration in µg/m^3 is unknown). The location of where aerosolized particulates collect in the respiratory tract and the body's response to them is partially dictated by size.[8] A multitude of tissues compose the respiratory tract which includes the conducting airways that consist of the nose and mouth, pharynx, larynx, leading into the trachea, main bronchi, lobar, segmental bronchi, and terminal bronchioles.[9] The terminal bronchioles then lead into the respiratory bronchioles, alveolar ducts, and lastly alveolar sacs.[9] There are defense mechanisms in the respiratory system which help prevent particulates from entering into the lung, these include cilia and mucous layers. Cilia are hair-like projections of the cells that line the airway and propel the liquid layer of mucous which can trap pathogens and particulates prior to reaching the lungs.[10] • The nose and accompanying respiratory tract is capable of filtering foreign particles dependent on particle size and airflow rate with a filtration efficacy decreasing with particulate size.[11] Small particles (<1-3 µm) are capable of diffusing into deep lung tissue and deposit into the alveoli whereas larger particulates (> 8 µm) will be deposited throughout the nasal passages and larger bronchioles.[8] • Macrophages: one of the three types of alveolar cells, also known as dust cells, can eliminate foreign particles and bacteria through the process of phagocytosis Philips Respironics particle size analysis identified that the majority of particulate (> 8 µm) is of a size that is unable to penetrate into deep lung tissue and thus will remain in the patient upper airway. A smaller fraction of the particulate (<1-3 µm) may still penetrate into the lower respiratory tract. Our conclusions are as follows: • Based on the cytotoxicity and genotoxicity results and toxicological risk assessment, combined with our conclusion that particles are likely to reach the upper airway and potentially the lower respiratory track, a reasonable worst-case estimate for the **general** and **higher risk** (e.g., patient populations with preexisting conditions or comorbidities) patient populations is a severity level 3 (Crucial) for both short/intermediate and long term exposure.

Reference Information:

Check (X) Applicable Level*	Examples
___ 4 (Catastrophic)	Directly results in death
_X_ 3 (Crucial)	Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment
___ 2 (Marginal)	Results in moderate injury: temporary impairment, or self-limiting illness
___ 1 (Negligible)	Results in less than moderate or no injury

*Severity Levels 4 and 3 are "serious adverse health consequences" per FDA's CDRH Health Hazard Evaluation Form Version 3-1 01/12/2007. Severity Levels 2 and 1 are not serious adverse health consequences per FDA's HHE Form.

References:

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C. Estimation of Probability of Harm Resulting from Affected Units

Estimated quantity of affected devices (# in field, # in factory, # in distribution centers, etc.):	Between 2008 through March 2021, a total of 14,792,965 shipments of PAP Devices (see list of devices above).
Number and type of injuries/number of deaths attributed to the problem with the device (if any):*	10 cases of harm have been reported in PAP devices where foam degradation was suspected. Injuries (Severity 2) = 10 Injuries (Severity 3) = 0 Deaths = 0 In the case of long-term exposure, it should be noted that harm may not be immediately recognizable and may not be something that the customer would/could report. A total of 1,105 complaints were filed for foam degradation with PAP devices. The reported complaint rate for this failure mode is 0.007%. A total of 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or PAP therapy in general.
Describe the factor(s) that need to occur to create the hazardous situation (reasonably foreseeable sequence or combination of events):	A hazardous situation is created when a patient uses a PAP device where the PE-PUR foam exhibits degradation. As described in Step II, Section A under Hazard Cause, foam may degrade when exposed to specific conditions. Once the foam starts to degrade, airborne particulates from degraded foam material could potentially enter the PAP system air flow path. The particulate must travel through the path outlined below. PAP Air Flow Path: Air enters through the inlet filter and into the blower box that contains the PE-PUR foam. From the blower box, the air continues through the angled elbow of blower and through the blower impeller. Air then travels through the angled outlet port where it may interface with an optional humidifier, continuing through the patient circuit. The patient circuit consists of a 6 ft tube, an angled connection interface, and mask, before reaching the patient airway. Note that the air flow path referenced above is a broad generalization of each of the devices in scope of this report.
Factors that might mitigate risk (e.g., safety mechanisms present in the design, instructions for use, current label warnings, etc.):	Device inspection per device IFU: Exposure to the hazard may be partially mitigated through device, tubing and mask inspection. Device User Manuals instruct patients to “Periodically inspect electrical cords, cables, tubing, and accessories for damage or signs of wear.” Mask IFU’s instruct patients to “Inspect the mask parts

	regularly for damage or wear" and to clean the mask daily. However, patients may not detect the particles (e.g., because the particles are too small).
Would a user detect the hazardous situation prior to occurrence of harm? If so, describe how:	Detection of Foam Particulate: The particulate analysis (as detailed in CAPA 7211) demonstrates a variety of small and large particles that may or may not be detectable based on size and quantity. Small, black contaminants may become visible near the air outlet port or within the patient circuit. Daily cleaning of the mask and weekly cleaning of the tubing may remove trapped particles and increase the odds of detection.

Probability Estimate

Estimation of Probability that the Harm will occur:	Short/Intermediate-Term Hazard Exposure **2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend) This Hazard has 10 reports of harm from 2008 through March 2021 for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or PAP therapy in general. Long-Term Exposure **2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend) This Hazard has zero reports of harm from 2008 through March 2021.

Comments:	Probability of Hazardous Situation Occurring (P1)
(Probability of Harm Rationale)	While Philips Respironics' testing and investigation to date indicates that the PE-PUR foam within the devices is degrading, and the degradation may be due to device exposure to certain conditions (e.g., environmental, disinfection using unauthorized cleaning agents) over a period of time, Philips Respironics is in the process of conducting additional studies to better understand: (1) the specific conditions that cause the foam to degrade; and (2) the rate of foam degradation when the device experiences such conditions. For example, if the device must experience certain environmental conditions for an extended period of time for the foam to degrade (e.g., high humidity, high temperature), not all users may subject their device to such conditions. Therefore, completion of these ongoing and planned studies will help Philips Respironics better estimate the reasonable worst-case probability of the foam degrading within the device population. See ongoing and planned investigational activities described in Step III, Section C. Although the observed complaint rate is 0.007%, as noted above, the complaint rate may not accurately reflect the probability of the failure because patients may not detect the particles and/or report the event to Philips Respironics. Nonetheless, based on the available information and test data collected to date, Philips Respironics estimates that the reasonable worst-case probability of the foam degrading in the device to be *occasional* over the device's useful life. **Probability that Hazardous Situation will Lead to Harm (P2)** The probability that the hazardous situation will lead to harm is dependent upon the amount of degraded foam a patient may inhale and/or ingest and may be exacerbated by the patient's underlying comorbidities. As noted in Step II, Section B, further investigations are ongoing and detailed in Step III, Section C. Short and long-term exposure to the hazard may cause generalized inflammation in patients that could facilitate clinical deterioration in certain patient populations as dictated by the underlying disease or associated comorbidities. As an inhalational therapy, it is possible that patients with low cardio-pulmonary reserve (e.g. COPD, CHF) may experience a meaningful deterioration in their function that requires medical intervention. Clinical events of this nature may not be easily linked to the hazardous situation or device use in general. Based on lab testing, exposure to the degraded foam and its components may lead to cellular DNA mutations. Such mutations may lead to uncontrolled cellular replication given a sufficient dose and duration of exposure that have not been determined. Patient related factors including bodily defenses, target tissue deposition, and immune function will also likely impact the development of the reasonable worst-case scenario harm. Additionally, a presumed lag time from exposure to harm development may make it difficult for patients to attribute their individual harm to the device usage. No severity 3 (Crucial) harm has been reported to date. It should be noted that harm in this case may not be immediately recognizable and may not be something that the patient would/could report.

	Probability of Occurrence of Harm (P) Taking into consideration P1 and P2, it is challenging to accurately estimate the probability of harm quantitatively. A probability of 2 (Occasional) was chosen as the reasonable worst-case scenario.

Considering the factors above, assess the probability that use of, or exposure to, the affected devices will cause future harm during the product's lifetime. Consider segments of the population most at risk (e.g. infants, elderly, pregnant women, critically ill patients, etc.).

Check (X) applicable level*	***Example of probability of harm***
___ **4** **(Always)**	Occurs 'every time'*
___ **3** **(Likely)**	'Reasonable probability' that use will cause harm*; good chance/ considerable certainty to cause harm
X **2** **(Occasional)**	'Remote probability' that use will cause harm*; expected to cause harm rarely/ from time to time (e.g., with no clear trend)
___ **1** **(Unlikely)**	'Not likely' that use will cause harm*; possible but improbable
___ **0** **(Inconceivable)**	Inconceivable; not possible

*** Corresponds with probability levels set forth in FDA's CDRH HHE Form Version 3-1 01/12/2007.**

***Note: If harm has already occurred as a result of the issue under review, then:**

- Probability level zero (0) and one (1) can only be used if the investigation shows the harm was the result of an isolated incident and no other units are likely to be affected; a detailed rationale for why harm is not likely to occur again must be provided.
- Probability level 0 rarely applies to post-market risk evaluation in cases where harm has occurred.

Step III – Health Hazard Evaluation Conclusion

Probability	Severity			
	1	2	3	4
4	Unacceptable	Unacceptable	Unacceptable	Unacceptable
3	Acceptable	Unacceptable	Unacceptable	Unacceptable
2	Acceptable	Further Analysis Required[1)]	Unacceptable Short/Intermediate-Term Exposure Long-Term Exposure	Unacceptable
1	Acceptable	Acceptable	Further Analysis Required[1)]	Unacceptable
0	Acceptable	Acceptable	Acceptable	Acceptable

*These conclusions will be re-evaluated once the additional testing described in Section III.C is completed.

[1)] If the results of a risk evaluation fall into one of these two cells (3x1 or 2x2), then a risk/benefit analysis and/or appropriate justification must be documented in section C below.

Note:

- The original premarket risk/benefit analysis may be reused if still applicable as the evaluation to justify an acceptable risk.
- The above Risk Table helps assess whether the risk is acceptable or not; however, reviewer/approvers of this document make the final determination.
- Even if a risk is deemed "acceptable", action to address the issue may still be warranted.

A. Document the results of the Health Hazard Evaluation for each hazardous situation under review:

Short/Intermediate-Term Exposure

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

Long-Term Exposure

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

B. If the risk of the individual hazardous situation is acceptable, review the Risk Management File and consider combined impact of all the individual risks to evaluate whether overall residual risk of the device is still acceptable. Is the summary of all the risks acceptable or not acceptable?

UNACCEPTABLE (acceptable / unacceptable)

Dorma SystemOne DreamStation DreamStation Go	
C. Any additional information (if applicable):	The risk management files associated with these products will be evaluated and updated per the information above. As noted above, the Philips Respironics team is continuing to conduct additional investigational activities to better understand the myriad of variables and considerations related to the reported foam degradation. To ensure that we maintain our perspective and focus on our users, we have made conservative assumptions in identifying the severity and probability of the harms associated with this issue. As we complete the testing listed below, we will update this HHE (as required). ADDITIONAL TESTING CONSIDERATIONS: Accelerated PE-PUR Foam Life Testing • The goal of this testing is to develop a model to help us understand the foam degradation behavior at ambient conditions within the specified operating temperature and humidity ranges, in the presence or absence of ozone. • Preliminary results, at the experiments' mid-point, show visual separation between the ozone and non-ozone groups, within the operating temperature ranges, indicating that ozone does accelerate degradation at lower temperatures. These results are not yet final; therefore, this potential impact has not been considered in the overall residual risk rating. Ozone Cycling on PE-PUR Foam • The purpose of this benchtop testing is to understand how ozone impacts the visual and chemical breakdown of PE-PUR foam at ambient conditions. The outcome of this test could provide further confirmation on the hypothesis that ozone has a direct connection to the premature breakdown of device sound abatement foam. • Preliminary results indicate that PE-PUR foam exposed to various cycles of ozone at ambient temperatures show significant accelerated foam degradation, even after only one cycle. As these results are also not yet final, this potential impact has not been considered in the overall residual risk rating. Dosage Test • The goal of this test is to estimate the daily and total dosage of particulate being delivered to a patient over the device's expected use life.

	Foam Volatile Organic Compounds (VOC) Testing • As more details become known, additional information will be added to this section.
Health Hazard Evaluation Conclusion:	**Health Hazard Evaluation Medical Assessment** The Health Hazard Evaluation conducted by the Philips Respironics Team concluded that the Hazards described herein represent an unacceptable risk to patients. **Short/Intermediate-Term Exposure to Hazard: Severity 3; Probability 2** The severity of harm (level 3) recognizes the seriousness of any potential harm that may significantly impact the clinical status of patients and require additional medical intervention. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend). **Long Term Exposure to Hazard: Severity 3; probability 2** The severity of harm (level 3) recognizes the seriousness of any potential malignancy and the need for medical intervention to preclude permanent impairment. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend).

Step IV – Outcome approved by the following individuals:

Prepared By:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Design Quality Engineer / Safety Risk Management

Approved By Director of BIU QARA:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Head of Design Quality Engineering

Approved By VP of Corporate QA – HHS Q&R (or delegate):

Signature Date

See attached signature sheet

Print Name and Title

s22 – Head of Quality SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Leader SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 [redacted] – Medical Director Connected Care

Approved By Clinical Affairs Representative:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 [redacted] – Head of Clinical Affairs

Note: This form may be emailed or faxed to the person(s) above. Signature (electronic or fax) is required for all HHEs.

HEALTH HAZARD EVALUATION FORM

ER 2241622 – Foam Degradation in NIV Devices, Version 00

Step I – Identification of the Issue/Problem

CAPA Number:	**7211**	**HHE Date Open:**	11/16/2020	**HHE Date Closed:**	04/26/2021
- Product Data -					
Product Code:	MNT (continuous ventilator, minimal ventilatory support, facility use) MNS (continuous ventilator, non-life supporting)				
Model:	All finished good part numbers under the devices listed below fall within the scope of this HHE. For a comprehensive list of all finished good numbers, refer to CAPA 7211.				
Device Name:	DreamStation ASV DreamStation ST, AVAPS A-Series BiPAP A40 BiPAP A30 BiPAP Hybrid A30 BiPAP V30 Auto OmniLab Advanced+ SystemOne ASV4 C-Series ST/AVAPS				
Lot/Serial Numbers:	All devices in the field and released in inventory currently using the polyester-based polyurethane foam (PE-PUR) could be subject to this potential failure mode.				
Marketing Status (Include 510(k) or PMA Number, Specify if Class I Exempt from 510(k)):	K090248 • SystemOne ASV4 K090539 • SystemOne ASV4 • DreamStation ASV K092818 • C-Series ASV • C-Series ST, AVAPS K102465 • DreamStation ST, AVAPS K113053				

	• OmniLab Advanced+ • A-Series BiPAP A30 • A-Series BiPAP V30 Auto K121623 • A-Series BiPAP A40 Products Not Marketed in the US • A-Series BiPAP Hybrid A30 (Japan only)
Manufacturing/Recall Firm Address:	Respironics Inc. 1010 Murry Ridge Ln Murrysville, PA 15668
Product Description (Include Intended Use from Labeling):	***K090248 and K090539*** **SystemOne ASV4 Product Identification and Intended Use** **Regulation**: 21 CFR 868.5905 Identification: A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The BiPAP autoSV Advanced System One is intended to provide non-invasive ventilatory support to treat adult patients (>30 kg / 66 lbs) with Obstructive Sleep Apnea and Respiratory Insufficiency caused by central and/or mixed apneas and periodic breathing. This device may be used in the hospital or home. **Device Description:** The BiPAP autoSV device is intended to augment breathing by supplying pressurized air through a circuit. It senses breathing effort by monitoring airflow in the circuit and adjusts its output to assist with inhalation. This therapy is known as Bi-level ventilation. Bi-level ventilation provides a higher pressure, known as IPAP (Inspiratory Positive Airway Pressure), during inhalation and a lower pressure, known as EPAP (Expiratory Positive Airway Pressure), during exhalation. The higher pressure makes it easier to inhale, and the lower pressure makes it easier to exhale. A user interface displays clinical data and enables the operator to set and adjust certain clinical parameters. The devices are intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of a six-foot disposable or reusable tubing and a patient interface device. **DreamStation ASV Product Identification and Intended use**: **Regulation**: 21 CFR 868.5905 Identification: A noncontinuous ventilator (Intermittent positive pressure breathing - IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's

	breathing. Classification: Class II (performance standards) **Intended Use**: The BiPAP autoSV device is intended to provide non-invasive ventilatory support to treat adult patients (>30 kg/66 lbs) with Obstructive Sleep Apnea and Respiratory Insufficiency caused by central and/or mixed apneas and periodic breathing. This device may be used in the hospital or home. **Device Description:** The BiPAP autoSV device is intended to augment breathing by supplying pressurized air through a circuit. It senses breathing effort by monitoring airflow in the circuit and adjusts its output to assist with inhalation. This therapy is known as Bi-level ventilation. Bi-level ventilation provides a higher pressure, known as IPAP (Inspiratory Positive Airway Pressure), during inhalation and a lower pressure, known as EPAP (Expiratory Positive Airway Pressure), during exhalation. The higher pressure makes it easier to inhale, and the lower pressure makes it easier to exhale. A user interface displays clinical data and enables the operator to set and adjust certain clinical parameters. The devices are intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of a six-foot disposable or reusable tubing and a patient interface device. ***K092818*** **C-Series S/T and AVAPS Product Identification and Intended Use** **Regulation**: 21 CFR 868.5905 Identification: A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The BiPAP C Series device is intended to provide non-invasive ventilatory support to treat adult patients weighing over 30 kg (66 lbs) and pediatric patients 7 years or older and weighing over 18 kg (40 lbs) with Obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. This device may be used in the hospital or home. **Device Description:** The C-Series is a microprocessor controlled blower based positive pressure system with integrated heated humidifier. The BiPAP S/T and BiPAP AVAPS devices are intended to provide non-invasive ventilatory support to Obstructive Sleep Apnea (OSA) and Respiratory Insufficiency patients weighing over 18 kg. This device may be used in the hospital or home. A user interface displays clinical data and enables the operator to set and adjust certain clinical parameters. The BiPAP AVAPS and

	BiPAP S/T is fitted with alarms to alert the user to changes that will affect the treatment. Some of the alarms are pre-set (fixed), others are user adjustable. The devices are intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of a six-foot disposable or reusable tubing and a patient interface device. ***K102465*** **DreamStation S/T and AVAPS Product Identification and Intended use**: **Regulation**: 21 CFR 868.5905 Identification: A noncontinuous ventilator (IPPB) is a device intended to deliver intermittently, an aerosol to patient's lungs or to assist a patient's breathing. Classification: Class II (performance standards) **Intended Use**: The BiPAP S/T device is intended to provide non-invasive ventilatory support to treat adult and pediatric (> 7 years of age and > 40 lbs) patients with obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. The device may be used in the hospital or home. The BiPAP AVAPS device is intended to provide non-invasive ventilatory support to treat adult and pediatric (> 7 years of age and > 40 lbs) patients with obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. The device may be used in the hospital or home. **Device Description:** The DreamStation BiPAP S/T and DreamStation BIPAP AVAPS devices are a microprocessor controlled blower based positive pressure system with optional integrated heated humidifier. The BiPAP S/T and BiPAP AVAPS devices are intended to provide non-invasive ventilatory support to Obstructive Sleep Apnea (OSA) and Respiratory Insufficiency patients weighing over 18 kg. This device may be used in the hospital or home. A user interface displays clinical data and enables the operator to set and adjust certain clinical parameters. The DreamStation BiPAP AVAPS and BiPAP S/T is fitted with alarms to alert the user to changes that will affect the treatment. Some of the alarms are pre-set (fixed), others are user adjustable. The devices are intended for use with a patient circuit that is used to connect the device to the patient interface device (mask). A typical patient circuit consists of a six-foot disposable or reusable tubing and a patient interface device. ***K113053*** **BiPAP A30 Product Identification and Intended use**:

	Regulation: 21 CFR 868.5895 Identification: A continuous ventilator (respirator) is a device intended to mechanically control or assist patient breathing by delivering a predetermined percentage of oxygen in the breathing gas. Adult, pediatric, and neonatal ventilators are included in this generic type of device. Classification: Class II (performance standards) **Intended Use**: The BiPAP A30 ventilator is intended to provide non-invasive ventilatory support to treat adult and pediatric patients weighing over 10 kg (22 lbs) with Obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. It is intended to be used in both the home and clinical settings, such as hospitals, sleep laboratories, and sub-acute care institutions. **Device Description:** The ventilator augments patient breathing by supplying pressurized air through a patient circuit. The device senses the patient's breathing effort by monitoring airflow in the patient circuit and adjusts output to assist inhalation and exhalation. This therapy is known as Bi-level ventilation. Bi-level ventilation provides a higher pressure, known as Inspiratory Positive Airway Pressure (IPAP), when inhaling, and a lower pressure, known as Expiratory Positive Airway Pressure (EPAP), when exhaling. The device can also provide a single pressure level known as Continuous Positive Airway Pressure (CPAP). A user interface displays clinical data and enables the operator to set and adjust device parameters. These devices are fitted with alarms to alert the user to changes that will affect the treatment. Some of the alarms are pre-set (fixed), others are user adjustable. The devices are intended for use with a patient tubing circuit that connects the device to the patient interface (mask for non-invasive ventilation). A typical patient circuit consists of a six-foot disposable or reusable smooth lumen tubing, an exhalation device, and a mask. **V30 Product Identification and Intended use**: **Regulation**: 21 CFR 868.5895 Identification: A continuous ventilator (respirator) is a device intended to mechanically control or assist patient breathing by delivering a predetermined percentage of oxygen in the breathing gas. Adult, pediatric, and neonatal ventilators are included in this generic type of device. Classification: Class II (performance standards) **Intended Use**: The BiPAP V30 Auto ventilator is intended to provide non-invasive ventilatory support to treat adult and pediatric patients weighing over 10 kg (22 lbs.) with Obstructive Sleep Apnea (OSA) and Respiratory Insufficiency. The autoSV mode is intended for adult patients >30 kg (66 lbs.) with Respiratory Insufficiency and Obstructive Sleep Apnea caused by central and/or mixed apneas and periodic breathing.

	The device is intended to be used within an institution and/or hospital and is not intended for life support. It may be used during intra-facility transport. **Device Description:** The ventilator augments patient breathing by supplying pressurized air through a patient circuit. The device senses the patient's breathing effort by monitoring airflow in the patient circuit and adjusts output to assist inhalation and exhalation. This therapy is known as Bi-level ventilation. Bi-level ventilation provides a higher pressure, known as Inspiratory Positive Airway Pressure (IPAP), when inhaling, and a lower pressure, known as Expiratory Positive Airway Pressure (EPAP), when exhaling. The device can also provide a single pressure level known as Continuous Positive Airway Pressure (CPAP). A user interface displays clinical data and enables the operator to set and adjust device parameters. These devices are fitted with alarms to alert the user to changes that will affect the treatment. Some of the alarms are pre-set (fixed), others are user adjustable. The devices are intended for use with a patient tubing circuit that connects the device to the patient interface (mask for non-invasive ventilation). A typical patient circuit consists of a six-foot disposable or reusable smooth lumen tubing, an exhalation device, and a mask. **OmniLab Advanced + Product Identification and Intended Use** **Regulation**: 21 CFR 868.5895 Identification: A continuous ventilator (respirator) is a device intended to mechanically control or assist patient breathing by delivering a predetermined percentage of oxygen in the breathing gas. Adult, pediatric, and neonatal ventilators are included in this generic type of device. Classification: Class II (performance standards) **Intended Use**: The OmniLab Advanced + is intended to provide non-invasive ventilation for pediatric patients 7 years or older >18.2 kg (40 lbs) with Respiratory Insufficiency or Obstructive Sleep Apnea (OSA). It is also intended to treat adult patients >30 kg (66 lbs) with Respiratory Insufficiency or Obstructive Sleep Apnea caused by central and/or mixed apneas and periodic breathing. The OmniLab Advanced + is intended to provide non-invasive ventilation in a hospital or sleep lab setting. **Device Description:** This device augments patient breathing by supplying pressurized air through a patient circuit. It senses the patient's breathing effort by monitoring airflow in the patient circuit and adjusts its output to assist in inhalation and exhalation. This therapy is known as Bi-level therapy. Bi-level therapy provides a higher pressure, known as IPAP (Inspiratory Positive Airway Pressure), when the patient inhales, and a lower pressure, known as EPAP (Expiratory Positive Airway Pressure), when the patient exhales. The higher pressure makes it easier for the patient to inhale, and the lower pressure makes it

	easier for the patient to exhale. The device can also provide a single pressure level, known as CPAP (Continuous Positive Airway Pressure). ***K121623*** **BiPAP A40 Product Identification and Intended use**: **Regulation**: 21 CFR 868.5895 Identification: A continuous ventilator (respirator) is a device intended to mechanically control or assist patient breathing by delivering a predetermined percentage of oxygen in the breathing gas. Adult, pediatric, and neonatal ventilators are included in this generic type of device. Classification: Class II (performance standards) **Intended Use**: The BiPAP A40 ventilator is intended to provide invasive and non-invasive ventilatory support to treat adult and pediatric patients weighing over 22 lbs (10 kg) with Obstructive Sleep Apnea (OSA), Respiratory Insufficiency, or Respiratory Failure. It is intended to be used in home, institutional/hospital, and portable applications such as wheelchairs and gurneys. It is not intended to be used as a transport ventilator, and is not intended for life support. **Device Description:** The ventilator augments patient breathing by supplying pressurized air through a patient circuit. The device senses the patient's breathing effort by monitoring airflow in the patient circuit and adjusts output to assist inhalation and exhalation. This therapy is known as Bi-level ventilation. Bi-level ventilation provides a higher pressure, known as Inspiratory Positive Airway Pressure (IPAP), when inhaling, and a lower pressure, known as Expiratory Positive Airway Pressure (EPAP), when exhaling. The device can also provide a single pressure level known as Continuous Positive Airway Pressure (CPAP). A user interface displays clinical data and enables the operator to set and adjust device parameters. The BiPAP A40 Pro and BiPAP A40 EFL are fitted with alarms to alert the user to changes that will affect the treatment. Some of the alarms are pre-set (fixed), others are user adjustable. The devices are intended for use with a patient tubing circuit that connects the device to the patient interface (mask for non-invasive ventilation). A typical patient circuit consists of a six-foot disposable or reusable smooth lumen tubing, an exhalation device, and a mask. ***Products Not Marketed in the US*** **BiPAP Hybrid A30 Product Identification and Intended Use** **Regulation**: 21 CFR 868.5895 Identification: A continuous ventilator (respirator) is a device intended to mechanically control or assist patient breathing by delivering a predetermined percentage of oxygen in the breathing

	gas. Adult, pediatric, and neonatal ventilators are included in this generic type of device. Classification: Class II (performance standards) **Intended Use**: The BiPAP Hybrid A30 is intended to provide non-invasive ventilation for pediatric patients 7 years or older >18.2 kg (40 lbs) with Respiratory Insufficiency or Obstructive Sleep Apnea (OSA). It is also intended to treat adult patients >30 kg (66 lbs) with Respiratory Insufficiency or Obstructive Sleep Apnea caused by central and/or mixed apneas and periodic breathing. The device is intended for use in the hospital. **Device Description:** This device augments patient breathing by supplying pressurized air through a patient circuit. It senses the patient's breathing effort by monitoring airflow in the patient circuit and adjusts its output to assist in inhalation and exhalation. This therapy is known as Bi-level therapy. Bi-level therapy provides a higher pressure, known as IPAP (Inspiratory Positive Airway Pressure), when the patient inhales, and a lower pressure, known as EPAP (Expiratory Positive Airway Pressure), when the patient exhales. The higher pressure makes it easier for the patient to inhale, and the lower pressure makes it easier for the patient to exhale. The device can also provide a single pressure level, known as CPAP (Continuous Positive Airway Pressure).
Brief description of the issue/problem and how it was identified:	Philips Respironics received complaints in 2019 regarding SystemOne CPAP devices from Thailand (Complaint numbers RA 307829970 and 307806329) alleging the presence of black debris/particles within the airpath circuit (extending from the device outlet, humidifier, tubing, and mask). The patient's nephew expressed concerns that the black particulate was delivered to the patient's airway and could affect her health. The SystemOne devices were returned and visual inspection showed signs of foam degradation. Chemical analysis of the foam confirmed degradation, triggering the initiation of CAPA 7211 and additional investigational activities. The sound abatement foam is an open-cell polyester-based polyurethane (PE-PUR) foam that is widely used for sound dampening purposes in many industries. The PE-PUR foam is also used in Philips Respironics noninvasive ventilator (NIV) devices, the subject of this Health Hazard Evaluation (HHE). A complaint analysis performed as part of CAPA 7211 indicated that complaints for PE-PUR foam degradation were also identified for the NIV devices. Specifically, 42 complaints were identified suggesting the presence of degraded foam with NIV devices. In addition, the complaint analysis showed an overall increase in complaints related to alleged PE-PUR foam degradation across the PRI PAP devices, NIV, and ventilators. The majority of complaints were reported by Philips service personnel and were found subsequent to investigating the patients' primary complaints. As of the date of this

	HHE, 766,587 NIV devices have been shipped. Accordingly, Philips Respironics initiated this HHE to evaluate potential foam degradation in the context of NIV devices based on available data generated to date. This Health Hazard Evaluation only assesses the risks associated with physical exposure to foam particulates. Emission of chemical compounds as a result of foam breakdown is recognized as a potential source of harm, however testing is ongoing to further investigate the potential harms associated with this. As additional information becomes available, this HHE will be updated to reflect any changes to the overall risk profile.
Affected Patient/User Population:	All patient groups that fall within the intended use of the devices referenced in the Product Description are within the affected patient population. The intended patient population across multiple NIV platforms broadly includes the following: adult and pediatric patients weighing over 22 lbs. (10 kg) with Obstructive Sleep Apnea, Respiratory Insufficiency, or Respiratory Failure. Higher risk populations within the intended patient population include pediatrics; the elderly; pregnant women; and patients with comorbidities such as heart failure, COPD, and obesity.
HHE Author (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management
HHE Contributors (Name/Function):	s22 [redacted] – Design Quality Engineer/Safety Risk Management s22 [redacted] – Design Quality, Sr. Manager s22 [redacted] –Quality Engineering, Manager s22 [redacted] – Head of Design Quality Engineering s22 [redacted] – Sustaining Engineering Manager s22 [redacted] – Sr. Quality Engineer s22 [redacted] – Sr. Bio Safety and Verification Engineer s22 [redacted] – Head of Global Clinical and Scientific Affairs s22 [redacted] – Medical Director, Connected Care s22 [redacted] – Director of Regulatory Affairs s22 [redacted] – Medical Leader, SRC s22 [redacted] – Medical Safety Manager, SRC

Step II – Analyze Post Release Health Risk Associated with Affected Units

Note: Assess the risk as if no corrective action will be taken and all affected devices will remain in the marketplace.

A. Identification of the Individual Hazard(s)

Hazard Category:	**Hazard Category:** Biological and Chemical **Hazard**: Biocompatibility / Toxicity of chemical constituents
Hazard Cause:	Polyester-based polyurethane foam (PE-PUR) is used as a sound abatement foam in the NIV device airpath. Based on all available data generated to date, Philips Respironics determined that the PE-PUR foam's reaction with water (hydrolysis) was a source of the foam degradation potentially caused and/or exacerbated by the following factors: • Device operation in higher heat and humidity environmental conditions; and/or • Use of unapproved cleaning and disinfection methods with the NIV device (e.g. ozone). *Environmental Conditions* The labeled environmental conditions for operating temperature are 5° to 35° C (41° to 95° F) with storage temperatures ranging from -20° to 60° C (-4° to 140° F). Preliminary test results conducted by Philips Respironics show that high temperature (90° C) contributes to significant degradation of the foam. Testing is ongoing to further investigate the impact of ambient temperature and humidity on foam degradation including: (1) models that may better simulate real world device operation conditions; and (2) lower temperatures within the labeled range. Refer to Section III,C for additional information on planned testing. *Unapproved Cleaning and Disinfection Methods* The NIV user manual cleaning instructions do not include ozone disinfection; rather, the instructions recommend water and a mild liquid dishwashing detergent for cleaning and DisCide Ultra Towelettes or a Chlorine Bleach solution for disinfection. The manual states that any deviation from these instructions or agents not listed in this guide may impact the performance of the product. Ozone disinfection devices appear to have become more readily available around the same time as Philips Respironics received complaints of foam degradation, however further investigation is ongoing. Foam degradation has also been reported even when ozone disinfection was not reported.
Hazardous Situation:	**Exposure to particulate by-products of foam degradation during use.** If PE-PUR foam degrades, small particulates (estimated size range of 2.69 µm-724 µm) may be expelled from the device blower box, through the motor and patient circuit and could enter the patient respiratory tract and/or Gastrointestinal (GI) tract. Based on our analysis of the degraded foam, the particles may include compounds such as diethylene glycol (DEG), toluene diamine isomers (TDA), and toluene diisocyanate isomers (TDI). Due to an inability to obtain a sufficient quantity of representative field

	samples for biocompatibility lab testing, we created lab degraded foam used for such testing, including: cytotoxicity, genotoxicity, irritation, and sensitization tests.

B. Estimation of Severity

Description of reported and/or potential harm:	**Harm resulting from Short-Term and Intermediate-Term Exposure:** exacerbation or worsening of the underlying patient condition Potential Harms: • Irritation (skin, eye, and respiratory tract) • Inflammatory response • Headache • Asthma • Effects to reproductive system • Neoplasia While no harm was reported for NIV devices, 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or the use of PAP therapy in general. **Harm resulting from Long-Term Exposure:** cytotoxic, genotoxic, and potential carcinogenic effects Zero cases of harm have been directly or indirectly linked to this failure mode.
Estimation of Severity of Harm	**3 (Crucial) – Short/Intermediate Term Exposure** Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment This is considering the reasonable worst-case scenario, per the rationale in the comments section below. **3 (Crucial) – Long Term Exposure** Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment Philips Respironics identified no significant difference in the estimated severity of harm when considering the general and higher risk patient populations.
Comments: (Severity of Harm Rationale)	A Bio Endpoint Analysis and toxicological risk assessment was performed on the specific chemical constituents and their potential impact to patients. This analysis is included as part of CAPA 7211; the testing is summarized below. Due to the difficulty in obtaining a sufficient quantity of representative field

samples for biocompatibility lab testing, laboratory accelerated aged foam was used to conduct the cytotoxicity, genotoxicity, irritation, and sensitization tests. The following results were noted:

- Cytotoxicity was noted for all extraction concentrations.
- Two genotoxicity assays confirmed a positive mutagenic response.
- Irritation results for the non-polar extract returned a passing result.
- Sensitization results from both polar and non-polar extracts returned a passing result.

Daily chemical dosages and concentrations are unknown at this time. Philips is in the process of constructing a model that calculates the start and rate of foam degradation. Further investigations are ongoing and detailed in Step III, Section C. Additionally, the literature does describe tolerable intake (TI) references for some of the major degradative by-products of the polyester polyurethane foam: TDA, TDI and DEG. Specifically:

- **Toluene diamine isomers (TDA)**, such as toluene-2,4-diamine, are primarily used in the synthesis of polyurethane, various dyes, and heterocyclic compounds.[1,2]
    - A chronic reference dose (RfD) for 2, 6 toluene diamine has been listed by the IRIS EPA at 0.03 mg/kg per day.[3]
- **Toluene diisocyanate isomers (TDI)** such as 2,4-toluene diisocyanate are chemical intermediates utilized in the production of polyurethane products.[4]
    - A reference concentration of 0.00007 mg/m^3 (0.07 µg/m^3) has been recommended for toluene diisocyanates by the EPA IRIS risk assessment.[5]
    - The U.S. Office of Environmental Health Hazard Assessment (OEHHA) has listed the Safe Harbor Levels at 20 µg/day for the no significant risk level (NSRL) to toluene diisocyanates.
- **Diethylene glycol (DEG)** is a polyol building block utilized in the synthesis of polyurethane.
    - Literature suggests a proposed human oral ingestion reference dose of 0.3 mg/kg for DEG.[6]
    - A WEEL occupational level of 10 mg/m^3 has been proposed by TERA for inhalational limits of DEG[7]- but this is not adequate or protective for sensitive patient populations and only accounts for an occupational worker exposure.
    - Per prior informal feedback from the FDA, 1% of the WEEL occupational value (10 mg/m^3) would be an adjusted tolerable intake of 0.1 mg/m^3.

Philips Respironics is working to complete the additional investigatory activities described in Step III, Section C to assess whether the amount of

degraded PE-PUR form inhaled and/or ingested by the patient may potentially exceed the TI references provided above.

In order to evaluate the risks posed by the PE-PUR foam particulates, exposure time and patient airway physiology must be considered. Data generated to date suggests that the PE-PUR foam degrades into particulates of varying sizes. The location of collected particulates in the respiratory tract and the body's response to them is partially dictated by size.

- For this HHE, the PE-PUR foam particulates are assumed to reach the patient airway (the amount or concentration in µg/m^3 is unknown).

  The location of where aerosolized particulates collect in the respiratory tract and the body's response to them is partially dictated by size.[1] A multitude of tissues compose the respiratory tract which includes the conducting airways that consist of the nose and mouth, pharynx, larynx, leading into the trachea, main bronchi, lobar, segmental bronchi, and terminal bronchioles.[2] The terminal bronchioles then lead into the respiratory bronchioles, alveolar ducts, and lastly alveolar sacs.[2] There are defense mechanisms in the respiratory system which help prevent particulates from entering into the lung, these include cilia and mucous layers. Cilia are hair-like projections of the cells that line the airway and propel the liquid layer of mucous which can trap pathogens and particulates prior to reaching the lungs.[3]

- The nose and accompanying respiratory tract is capable of filtering foreign particles dependent on particle size and airflow rate with a filtration efficacy decreasing with particulate size.[4] Small particles (<1-3 µm) are capable of diffusing into deep lung tissue and deposit into the alveoli whereas larger particulates (> 8 µm) will be deposited throughout the nasal passages and larger bronchioles.[1]

- Macrophages: one of the three types of alveolar cells, also known as dust cells, can eliminate foreign particles and bacteria through the process of phagocytosis

Philips Respironics particle size analysis identified that the majority of particulate (> 8 µm) is of a size that is unable to penetrate into deep lung tissue and thus will remain in the patient upper airway. A smaller fraction of the particulate (<1-3 µm) may still penetrate into the lower respiratory tract.

Our conclusions are as follows:

- Based on the cytotoxicity and genotoxicity results and toxicological risk assessment, combined with our conclusion that particles are likely to reach the upper airway and potentially the lower respiratory track, a reasonable worst-case estimate for the **general** and **higher risk** (e.g., patient populations with preexisting conditions or comorbidities) patient populations is a severity level 3 (Crucial) for both short/intermediate and long term exposure.

Reference Information:

Check (X) Applicable Level*	Examples

*	___ 4 **(Catastrophic)**	Directly results in death
	X 3 **(Crucial)**	Results in serious injury: life-threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment
	___ 2 **(Marginal)**	Results in moderate injury: temporary impairment, or self-limiting illness
	___ 1 **(Negligible)**	Results in less than moderate or no injury

Severity Levels 4 and 3 are “serious adverse health consequences” per FDA’s CDRH Health Hazard Evaluation Form Version 3-1 01/12/2007. Severity Levels 2 and 1 are not serious adverse health consequences per FDA’s HHE Form.

References:

1. Thomas, R. J. Particle size and pathogenicity in the respiratory tract. Virulence 4, 847–858 (2013).

2. Patwa, A. & Shah, A. Anatomy and physiology of respiratory system relevant to anaesthesia. Indian J. Anaesth. 59, 533–541 (2015).

3. Defense Mechanisms of the Respiratory System - Lung and Airway Disorders. Merck Manuals Consumer Version Available at: https://www.merckmanuals.com/home/lung-andairway-disorders/biology-of-the-lungs-and-airways/defense-mechanisms-of- the-respiratorysystem. (Accessed: 23rd May 2018)

4. Imre Salma, Imre Balásházy, Renate Winkler-Heil, Werner Hofmann, Gyula Záray,. Effect of particle mass size distribution on the deposition of aerosols in the human respiratory system, Journal of Aerosol Science, Volume 33, Issue 1, 2002, Pages 119-132, ISSN 0021-8502, https://doi.org/10.1016/S0021-8502(01)00154-9. (https://www.sciencedirect.com/science/article/pii/S0021850201001549)

5. Knowles, M. R. & Boucher, R. C. Mucus clearance as a primary innate defense mechanism for mammalian airways. J. Clin. Invest. 109, 571–577 (2002)

C. Estimation of Probability of Harm Resulting from Affected Units

Estimated quantity of affected devices (# in field, # in factory, # in distribution centers, etc.):	Between 2008 through March 2021, a total of 766,587 shipments of NIV System Devices (see list of devices above).
Number and type of injuries/number of deaths attributed to the problem with the device (if any):*	No instances of harm have been reported in NIV devices where foam degradation was alleged. Injuries = 0 Deaths = 0 In the case of long-term exposure, it should be noted that harm may not be immediately recognizable and may not be something that the customer would/could report. A total of 42 complaints were filed for foam degradation with NIV devices. The reported complaint rate for this failure mode is 0.005%. While no harm was reported for NIV devices, 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or PAP therapy in general.
Describe the factor(s) that need to occur to create the hazardous situation (reasonably foreseeable sequence or combination of events):	A hazardous situation is created when a patient uses an NIV device where the PE-PUR foam exhibits degradation. As described in Step II, Section A under Hazard Cause, foam may degrade when exposed to specific conditions. Once the foam starts to degrade, airborne particulates from degraded foam material could potentially enter the NIV system air flow path. The particulate must travel through the path outlined below. NIV Air Flow Path: Air enters through the inlet filter and into the blower box that contains the PE-PUR foam. From the blower box, the air continues through the angled elbow of blower and through the blower impeller. Air then travels through the angled outlet port where it may interface with an optional humidifier, continuing through the patient circuit. The patient circuit consists of a 6 ft tube, an angled connection interface, and mask, before reaching the patient airway. Note that the air flow path referenced above is a broad generalization of each of the devices in scope of this report.
Factors that might mitigate risk (e.g., safety mechanisms present in the design, instructions for use, current label warnings, etc.):	<u>Device inspection per device IFU</u>: Exposure to the hazard may be partially mitigated through device, tubing, and mask inspection. Device User Manuals instruct patients to “Periodically inspect electrical cords, cables, tubing, and accessories for damage or signs of wear.” Mask IFU’s instruct patients to “Inspect the mask parts regularly for damage or wear” and to clean the mask daily.

	However, patients may not detect the particles (e.g., because the particles are too small). Bacteria Filter: When used in a hospital or clinical setting (i.e. Sleep Lab), labeling recommends that an in-line bacteria filter (Part Number 342077) be placed in-line with the patient circuit whenever the device is used on multiple patients. When a bacterial filter is used within the patient circuit, particulate is unable to reach the patient. According to the Ambu 20801 performance sheet, the filter tested 99.97% effective on an inert test particle of 0.3µm. Based on the particle size report (detailed in Att 2), the bacteria filter will effectively filter out any foam particulate that could make its way up the patient circuit.
Would a user detect the hazardous situation prior to occurrence of harm? If so, describe how:	Detection of Foam Particulate: The particulate analysis (as detailed in CAPA 7211) demonstrates a variety of small and large particles that may or may not be detectable based on size and quantity. Small, black contaminants may become visible near the air outlet port or within the patient circuit. Daily cleaning of the mask and weekly cleaning of the tubing may remove trapped particles and increase the odds of detection.

Probability Estimate

Estimation of Probability that the Harm will occur:	Short/Intermediate-Term Hazard Exposure **2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend) This Hazard has zero reports of harm from 2008 through March 2021 for NIV devices. While no harm was reported for NIV devices, 10 reported cases of harm were reported for PAP devices. These complaints are detailed in CAPA 7211 and generally included complaints of headache, upper airway irritation, cough, chest pressure, and sinus infection. Attributable harm may be confounded by the additional use of ozone (alleged to be used in 5 of the 10 complaints) or PAP therapy in general. Long-Term Exposure **2 (Occasional)** 'Remote probability' that use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend) This Hazard has zero reports of harm from 2008 through March 2021
Comments: (Probability of Harm Rationale)	**Probability of Hazardous Situation Occurring (P1)** While Philips Respironics' testing and investigation to date indicates that the PE-PUR foam within the devices is degrading, and the degradation may be due to device exposure to certain conditions (e.g., environmental, disinfection using unauthorized cleaning agents) over a period of time, Philips Respironics is in the process of conducting additional studies to better understand: (1) the specific conditions that cause the foam to degrade; and (2) the rate of foam degradation when the device experiences such conditions. For example, if the device must experience certain environmental conditions for an extended period of time for the foam to degrade (e.g., high humidity, high temperature), not all users may subject their device to such conditions. Therefore, completion of these ongoing and planned studies will help Philips Respironics better estimate the reasonable worst-case probability of the foam degrading within the device population. See ongoing and planned investigational activities described in Step III, Section C. Although the observed complaint rate is 0.005%, as noted above, the complaint rate may not accurately reflect the probability of the failure because patients may not detect the particles and/or report the event to Philips Respironics. Nonetheless, based on the available information and test data collected to date, Philips Respironics estimates that the reasonable worst-case probability of the foam degrading in the device to be *occasional* over the device's useful life.

	Probability that Hazardous Situation will Lead to Harm (P2) The probability that the hazardous situation will lead to harm is dependent upon the amount of degraded foam a patient may inhale and/or ingest and may be exacerbated by the patient's underlying comorbidities. As noted in Step II, Section B, further investigations are ongoing and detailed in Step III, Section C. Short and long-term exposure to the hazard may cause generalized inflammation in patients that could facilitate clinical deterioration in certain patient populations as dictated by the underlying disease or associated comorbidities. As an inhalational therapy, it is possible that patients with low cardio-pulmonary reserve (e.g. COPD, CHF) may experience a meaningful deterioration in their function that requires medical intervention. Clinical events of this nature may not be easily linked to the hazardous situation or device use in general. Based on lab testing, exposure to the degraded foam and its components may lead to cellular DNA mutations. Such mutations may lead to uncontrolled cellular replication given a sufficient dose and duration of exposure that have not been determined. Patient related factors including bodily defenses, target tissue deposition, and immune function will also likely impact the development of the reasonable worst-case scenario harm. Additionally, a presumed lag time from exposure to harm development may make it difficult for patients to attribute their individual harm to the device usage. No severity 3 (Crucial) harm has been reported to date. It should be noted that harm in this case may not be immediately recognizable and may not be something that the patient would/could report. **Probability of Occurrence of Harm (P)** Taking into consideration P1 and P2, it is challenging to accurately estimate the probability of harm quantitatively. A probability of 2 (Occasional) was chosen as the reasonable worst-case scenario.

Considering the factors above, assess the probability that use of, or exposure to, the affected devices will cause future harm during the product's lifetime. Consider segments of the population most at risk (e.g. infants, elderly, pregnant women, critically ill patients, etc.).

Check (X) applicable level*	***Example of probability of harm***
___ **4** **(Always)**	Occurs 'every time'*
___ **3** **(Likely)**	'Reasonable probability' that use will cause harm*; good chance/ considerable certainty to cause harm
X **2** **(Occasional)**	'Remote probability' that use will cause harm*; expected to cause harm rarely/ from time to time (e.g., with no clear trend)
___ **1** **(Unlikely)**	'Not likely' that use will cause harm*; possible but improbable
___ **0** **(Inconceivable)**	Inconceivable; not possible

*** Corresponds with probability levels set forth in FDA's CDRH HHE Form Version 3-1 01/12/2007.**

***Note: If harm has already occurred as a result of the issue under review, then:**

- Probability level zero (0) and one (1) can only be used if the investigation shows the harm was the result of an isolated incident and no other units are likely to be affected; a detailed rationale for why harm is not likely to occur again must be provided.
- Probability level 0 rarely applies to post-market risk evaluation in cases where harm has occurred.

Step III – Health Hazard Evaluation Conclusion

Probability	Severity			
	1	2	3	4
4	Unacceptable	Unacceptable	Unacceptable	Unacceptable
3	Acceptable	Unacceptable	Unacceptable	Unacceptable
2	Acceptable	Further Analysis Required[1)]	Unacceptable Short/Intermediate-Term Exposure Long-Term Exposure	Unacceptable
1	Acceptable	Acceptable	Further Analysis Required[1)]	Unacceptable
0	Acceptable	Acceptable	Acceptable	Acceptable

*These conclusions will be re-evaluated once the additional testing described in Section III.C is completed.

[1)] If the results of a risk evaluation fall into one of these two cells (3x1 or 2x2), then a risk/benefit analysis and/or appropriate justification must be documented in section C below.

Note:

- The original premarket risk/benefit analysis may be reused if still applicable as the evaluation to justify an acceptable risk.
- The above Risk Table helps assess whether the risk is acceptable or not; however, reviewer/approvers of this document make the final determination.
- Even if a risk is deemed "acceptable", action to address the issue may still be warranted.

A. Document the results of the Health Hazard Evaluation for each hazardous situation under review:

Short/Intermediate-Term Exposure

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

Long-Term Exposure

Severity: **3** / Probability: **2** = UNACCEPTABLE (acceptable/unacceptable)

B. If the risk of the individual hazardous situation is acceptable, review the Risk Management File and consider combined impact of all the individual risks to evaluate whether overall residual risk of the device is still acceptable. Is the summary of all the risks acceptable or not acceptable?

UNACCEPTABLE (acceptable / unacceptable)

DreamStation ASV DreamStation ST, AVAPS A-Series BiPAP A40 BiPAP A30 BiPAP Hybrid A30 BiPAP V30 Auto OmniLab Advanced+ C-Series ASV C-Series ST/AVAPS	
C. Any additional information (if applicable):	The risk management files associated with these products will be evaluated and updated per the information above. As noted above, the Philips Respironics team is continuing to conduct additional investigational activities to better understand the myriad of variables and considerations related to the reported foam degradation. To ensure that we maintain our perspective and focus on our users, we have made conservative assumptions in identifying the severity and probability of the harms associated with this issue. As we complete the testing listed below, we will update this HHE (as required). ADDITIONAL TESTING CONSIDERATIONS: Accelerated PE-PUR Foam Life Testing • The goal of this testing is to develop a model to help us understand the foam degradation behavior at ambient conditions within the specified operating temperature and humidity ranges, in the presence or absence of ozone. • Preliminary results, at the experiments' mid-point, show visual separation between the ozone and non-ozone groups, within the operating temperature ranges, indicating that ozone does accelerate degradation at lower temperatures. These results are not yet final; therefore, this potential impact has not been considered in the overall residual risk rating. Ozone Cycling on PE-PUR Foam • The purpose of this benchtop testing is to understand how ozone impacts the visual and chemical breakdown of PE-PUR foam at ambient conditions. The outcome of this test could provide further confirmation on the hypothesis that ozone has a direct connection to the premature breakdown of device sound abatement foam. • Preliminary results indicate that PE-PUR foam exposed to various cycles of ozone at ambient temperatures show significant accelerated foam degradation, even after only one cycle. As these results are also not yet

	final, this potential impact has not been considered in the overall residual risk rating. Dosage Test • The goal of this test is to estimate the daily and total dosage of particulate being delivered to a patient over the device's expected use life. Foam Volatile Organic Compounds (VOC)Testing • As more details become known, additional information will be added to this section.
Health Hazard Evaluation Conclusion:	**Health Hazard Evaluation Medical Assessment – NIV** The Health Hazard Evaluation conducted by the Philips Respironics Team concluded that the Hazards described herein represent an unacceptable risk to patients. **Short/Intermediate-Term Exposure to Hazard: Severity 3; Probability 2** The severity of harm (level 3) recognizes the seriousness of any potential harm that may significantly impact the clinical status of patients and require additional medical intervention. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend). **Long Term Exposure to Hazard: Severity 3; probability 2** The severity of harm (level 3) recognizes the seriousness of any potential malignancy and the need for medical intervention to preclude permanent impairment. Probability of harm (level 2) indicates a remote probability that device use will cause harm; expected to cause harm rarely/ from time to time (e.g., with no clear trend).

Step IV – Outcome approved by the following individuals:

Prepared By:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Design Quality Engineer / Safety Risk Management

Approved By Director of BIU QARA:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Head of Design Quality Engineering

Approved By VP of Corporate QA – HHS Q&R (or delegate):

Signature Date

See attached signature sheet

Print Name and Title

s22 – Head of Quality SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Leader SRC

Approved By Credentialed Medical Professional:

Signature Date

See attached signature sheet

Print Name and Title

s22 – Medical Director Connected Care

Approved By Clinical Affairs Representative:

Signature Date

See EDMS for e-signature and date

Print Name and Title

s22 – Head of Clinical Affairs

Note: This form may be emailed or faxed to the person(s) above. Signature (electronic or fax) is required for all HHEs.

PRIVILEGED AND CONFIDENTIAL

DEGRADED POLYESTER-POLYURETHANE FOAM- BIOLOGIAL RISK ASSESSMENT

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December 10, 2020
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Medical Device Biocompatibility Assessment

Contents

1. Executive Summary

Philips Respironics Inc. (PRI) has received field reports of CPAP and ventilator units returned to service centers with degraded sound abatement foam. The sound abatement foam is a polyester-based polyurethane (PE-PUR) foam located in the gas pathway of the device. The PE-PUR foam from these field returns previously underwent FTIR analysis which confirmed degradation of the material *via* hydrolysis. In order to better quantify the potential biological and toxicological risk that exposure to degraded PE-PUR foam particulates pose, multiple biological endpoints were tested on representative degraded PE-PUR foam, per the ISO 10993-1:2018 guidance. Cytotoxicity was noted for all extraction concentrations and two genotoxicity assays confirmed a positive mutagenic response. Irritation results for the non-polar extract returned a passing result, as did the sensitization results from both polar and non-polar extracts. Overall, based on an understanding of the toxicological significance of the foam degradants and the results of the ISO 10993 testing to include mutagenic responses in both a bacterial and mammalian system, the degraded PE-PUR foam is not considered biocompatible and presents a significant biological risk to those patient populations who are exposed to degraded PE-PUR foam.

2. Introduction

2.1 Background

The polyester polyurethane (PE-PUR) foam of this risk assessment is representative of multiple platforms in the Philips Respironics (PRI) continuous positive airway pressure (CPAP) devices and ventilators. This material is an open-cell polyester-based polyurethane foam that is used as an acoustic foam for sound dampening in the CPAP and ventilator devices. The general chemical structure of polyester polyurethane (PE-PUR) is shown in Figure 1.[1] The main degradation mechanism of PE-PUR foams is hydrolysis, and they have shown sensitivity to thermal ageing in humid conditions.[2] The main degradative by-products of PE-PUR foam after a humid ageing experiment included diethylene glycol (DEG), toluene diamine isomers (TDA), and toluene diisocyanate isomers (TDI).[2] Thermal decomposition by-products of polyurethane also include TDA and TDI, and were quantified in air samples suggesting that these by-products are somewhat volatile.[3] General chemical structures for these degradative constituents are displayed in Figure 1b-d. An example hydrolysis reaction is also depicted in Figure 1.

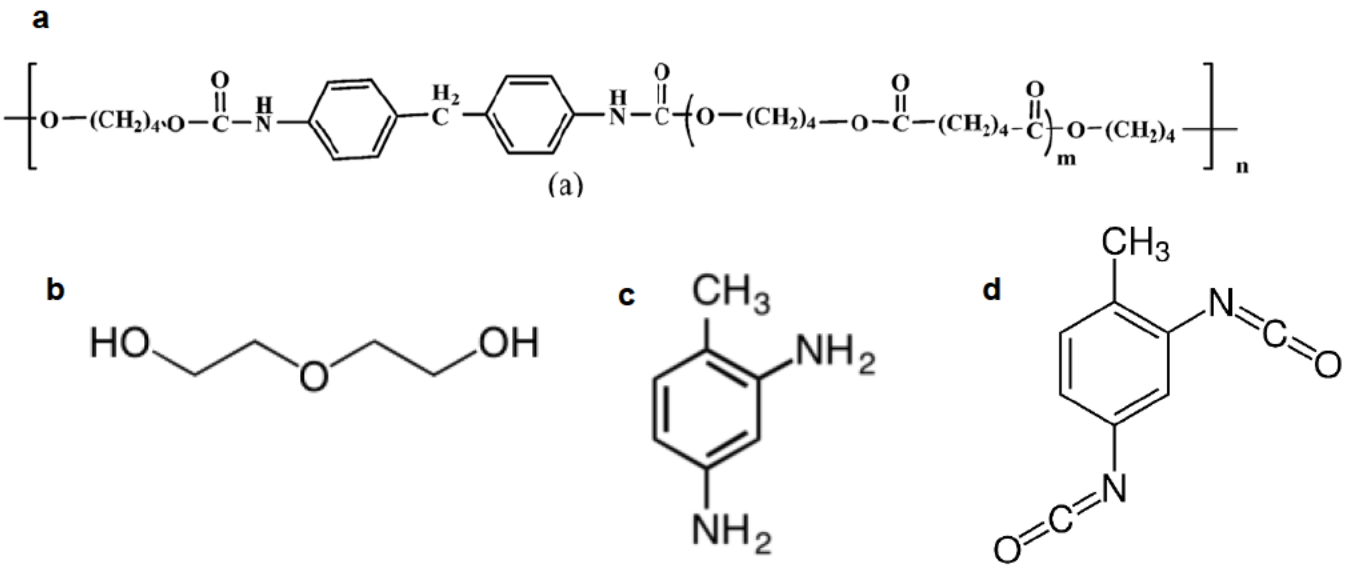

Figure 1. General chemical structure of (a) PE-PUR (b) diethylene glycol (c) representative toluene diamine (d) representative toluene diisocyanate

Due to the known degradative by-products of PE-PUR foam and the potential patient exposure to degraded foam particulates, an extractables/leachables study per ISO 10993-18 was initially conducted in order to evaluate toxicological risk. A field sample of degraded foam from a System One device was extracted in a physiologically relevant solvent (0.9% NaCl) at 37 ºC for 72 h and advanced chemical characterization techniques were employed to identify and quantify all analytes present. Over 35 leachables were identified and after a high-level toxicological risk analysis, 22 compounds were thoroughly investigated utilizing health-based thresholds and toxicology best practices. Compounds of concern were identified as analytes with Margin of Safety (MOS) values less than 10- many of these compounds had MOS values less than 1. Based upon the exposure to diethylene glycol, nickel, and 19 unknown compounds with potential for carcinogenicity, mutagenicity, and systemic toxicity, potential biological and toxicological risks from exposure to degraded PE-PUR foam were identified (see Report *"EXPOSURE TO POLYESTER-POLYURETHANE FOAM PARTICULATES FROM SYSTEM ONE FOAM DEGRADATION: BIOLOGICAL RISK ASSESSMENT"*). Per ISO 10993-1:2018 Clause B.3.4[4], an update to the biological risk assessment is necessary when new information from post market monitoring is made available pertaining to the safety in actual clinical use. In order to better understand the physiologically relevant risks to patients after exposure to degraded PE-PUR foam, biological endpoint testing to include both *in vivo* and *in vitro* assays was conducted per ISO 10993-1:2018.

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2.2 Purpose

The purpose of this report is to evaluate the potential biological risks posed by the degraded PE-PUR foam according to the risk management process outlined in FDA Guidance 2020 and ISO 10993-1:2018.[4,5] This biological risk assessment is informed by chemical characterization and toxicological risk assessment of degraded foam, the experimental results from the biological endpoint testing, additional information available from toxicological databases, national and international regulatory bodies, and published scientific literature.

2.3 Risk Assessment Guidelines

The biological risk assessment is guided by information from several regulatory bodies including:

- ISO 10993-1:2018 Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process[4]
- ISO 18562-1:2017 Biocompatibility evaluation of breathing gas pathways in healthcare applications- Part 1: Evaluation testing within a risk management process[6]
- ISO 14971:2019 Medical devices- Application of risk management to medical devices[7]
- ISO 10993-17:2002- Biological evaluation of medical devices- Part 17: Establishment of allowable limits for leachable substances[8]
- Use of International Standard ISO 10993-1, “Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process” Guidance for Industry and Food and Drug Administration Staff [9]

Utilizing these guidelines, the degraded PE-PUR foam was evaluated in order to understand the potential biological risks present for those patient populations for which the impacted devices are intended.

2.4 Acronyms

DMSO-dimethylsulfoxide
E/L- Extractables and Leachables
GEF- global evaluation factor
IMF- increased mutant frequency
MLA- Mouse Lymphoma Assay
MOS- Margin of Safety
NaCl- sodium chloride
PE-PUR- polyester polyurethane
PRI- Philips Respironics Inc.
RPMIi- RPMI medium, incomplete

SO- sesame seed oil
TFT-trifluorothymidine
$TK^{+/-}$ L5178Y - heterozygous thymidine kinase mutant mouse lymphoma cells

2.5 PRI References

WI 7.3-960 Biocompatibility Testing and Reporting
Report Beringer L, 7/2020 *"EXPOSURE TO POLYESTER-POLYURETHANE FOAM PARTICULATES FROM SYSTEM ONE FOAM DEGRADATION: BIOLOGICAL RISK ASSESSMENT"*

3. Device Description and Classification

The PE-PUR foam within the PRI portfolio of CPAP and ventilator devices is normally classified as a dry gas pathway component, and per ISO 10993-1:2018, is externally communicating with tissue/bone/dentin. The PE-PUR foam is upstream from purposeful humidification and thus was initially listed as a "dry" gas pathway component. This classification translates into respiratory device gas pathway testing dictated by the ISO 18562-1:2017[6] series of standards to include volatile organic emissions and particulates. However, this classification has been updated to reflect the degradation of PE-PUR foam noted in field returns an likelihood of patient exposure as a humidified gas pathway component. Biological endpoint testing consistent with this classification was initiated. The change in patient contact classification is due to the field complaints received regarding degradation of foam in PRI devices, and in at least one case confirmation of particulate collection in the patient circuit and mask. Furthermore, for CPAP devices utilized in home care environments, a bacterial/viral filter is not mandated for use and thus there is no formal barrier preventing particulates from getting to the patient.

The initial results from the E/L study and the accompanying toxicological risk assessment detected nineteen unknown compounds from the PE-PUR field sample. The majority of these unknown compounds were detected via techniques that identify either semi-volatile or non-volatile compounds which are of concern for both inhalational and oral modes of exposure. Many of the unknowns detected revealed high levels of exposure (in mg) and are likely degradants of the PE-PUR foam, increasing the potential toxicological risk. Based upon the chemistry of PE-PUR and typical degradative by-products[2], multiple chemical classes or their derivatives were proposed for the unknowns to include polyol (ethylene glycol) derivatives, toluene diamine isomers, and toluene diisocyanate isomers.

Due to the degradation of the PE-PUR foam and its typical chemical by-products, along with the updated patient contact classification for this medical device component, the biological risk assessment considered evaluation of multiple, clinically relevant biological endpoints listed in Tables 1.

Table 1. Biological Endpoints- Humidified Gas Pathway, Long Term Contact (>30 days)

Biological Endpoint	ISO Standard
Cytotoxicity	10993-5: Tests for *in vitro* cytotoxicity (2009)
Sensitization	10993-10: Tests for irritation and skin sensitization (2010)
Irritation	10993-10: Tests for irritation and skin sensitization (2010)
Genotoxicity	10993-3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (2014)

4. Experimental Testing Methods

4.1 Preparation of PE-PUR Degraded Foam Samples

Representative Soundcoat Sound 4PCF foam was subjected to elevated temperature and humidity within a controlled environmental chamber over a period of 28 days in order to replicate the degradation observed in various field complaints (Figure 2). The most degraded sample was chosen for all biological endpoint tests as it (1) is representative of a true worst-case scenario for patient exposure and (2) was visually representative of documented field complaints. An advanced chemical comparison between the field complaint utilized in the first risk assessment and the degraded foam samples utilized for the biological assays was not conducted.

Figure 2. (L) Return 307803629 is IN461S device with Serial Number P1165312101A5 built June 5, 2014 per the eDHR. (R) Representative PE-PUR foam degradation utilized for the biological endpoint studies.

4.2 *In vitro* Analysis

Cytotoxicity-ISO 10993-5:2009

In vitro cytotoxicity assays are widely utilized in evaluating the potential toxicities associated with devices or materials in medical devices. It is a very useful test in that it is rapid and can be predictive of potential harmful leachates and reactive/non-reactive analytes, but must be used in conjunction with other biological assays to understand clinically relevant biological risk.

All PE-PUR degraded foam samples were extracted at the physiologically relevant human temperature of 37 °C for 72 hours in cell culture medium (1 X MEM). Due to the nature of cell culture medium, it has capabilities of extracting both polar (hydrophilic) and non-polar (hydrophobic/lipophilic) compounds. This is important as the compounds of concern noted in the initial toxicological risk assessment (i.e., toluene diamines, ethylene glycols) are generally soluble in polar solvents,[16–18] whereas toluene diisocyanates are more miscible in organic (non-polar) solvents.[19–21]

Genotoxicity- ISO 10993-3:2014

There are several genotoxicity assays available per ISO 10993-3:2014[22] for the investigation and hazard classification of medical devices and their constituent materials. Genotoxicity is the ability of chemicals to damage genetic information within a cell which results in mutations and/or clastogenic effects which may lead to malignancies.[23]

Due to the initial risks of genotoxicity and carcinogenicity identified in the toxicological risk assessment, a battery of *in vitro* genotoxicity assays were employed for the PE-PUR degraded foam samples. A bacterial reverse mutation assay (Ames Assay) was conducted on the representative degraded PE-PUR foam with both 0.9 % NaCl and DMSO solvents in order to be inclusive of polar and non-polar substances. The physiologically relevant condition for patient exposure was consistent with the cytotoxicity assays, and each extraction occurred at 37 °C for 72 hours. Bacterial reverse mutation assays are able to detect relevant genetic changes produced by the majority of genotoxic carcinogens detected via rodent assays.[22]

In order to be compliant to the ISO 10993-3:2014 standard, and also utilize an additional test system for the measurement of genotoxicity because no single test is capable of detecting all relevant risks, the mouse lymphoma assay (MLA) was conducted on extracts of the degraded PE-PUR foam samples. RPMI incomplete cell culture medium and DMSO were utilized as the polar and non-polar solvent systems respectively, and foam samples were extracted at 37 °C for 72 h. The MLA utilizes mouse lymphatic mammalian cells which are deficient in thymidine kinase (TK) due to a mutation and are sensitive to mutagenic chemicals. The MLA has the potential to detect mutagenic and clastogenic events and based on colony size, can be predictive of gene mutation or chromosomal aberration.[26]

No additional genotoxicity assay were conducted. Per ISO 10993-3:214 Clause C.1, “for the majority of medical devices and/or materials for which genotoxicity testing is considered necessary a standard *in vitro* test battery is sufficient to provide evidence for genotoxic potential.”

4.3 *In vivo* Analysis

Irritation- ISO 10993-10:2010

The intracutaneous irritation assay is conducted with rabbits and involves an intradermal injection with specified extracts. Irritation is a non-specific inflammatory response to single, repeated, or continuous application of a substance/material that is reversible and mainly characterized by local erythema (ISO 10993-10:2014 Clause 3.10).

Both 0.9% NaCl and sesame seed oil (SO) were utilized to extract the PE-PUR degraded foam samples, at 37 °C for 72 h in accordance ISO 10993-12:2012[27] and ISO 10993-10:2010.

Sensitization- ISO 10993-10:2010

In contrast to irritation, sensitization is an immunologically mediated cutaneous reaction to a substance that can be characterized by erythema and edema (ISO 10993-10:2014 Clause 3.16). Sensitization is a result of an adapted immune system and is typically unique to individuals.[28] The Guinea Pig Maximization Test (GPMT) is capable of detecting a delayed type (Type IV) mediated hypersensitivity. Similar to irritation, guinea pigs are exposed to the specified solvent extracts via intradermal injection and topical application and then graded with an erythema and edema scale.

Animals are then challenged again with the solvent extracts in order to gauge the allergic/sensitizing potential.

Consistent with the rabbit intracutaneous assay, 0.9 % NaCl and sesame seed oil (SO) were utilized to extract the degraded PE-PUR foam 37 °C for 72 h in accordance ISO 10993-12:2012[27] and ISO 10993-10:2010.

5. Risk Assessment Method

The biological risk assessment was guided by ISO 10993-1:2018[4], FDA General Guidance 2020[5], and ISO 14971:2019.[7] According to ISO 14971:2019, a toxicological risk assessment should take into account the following:

- Physical and chemical characteristics of the materials
- History of clinical use or human exposure data
- Existing toxicological/biological safety data on product/component materials
- Test procedures

Additionally, per ISO 14971:2019, the nature and duration of patient contact with the device should be considered when choosing the methodology for the risk assessment. Due to the nature of patient exposure and the possibility for degraded foam particulates to be inhaled (small percentage) or ingested orally (majority), biological endpoints and experimental conditions were chosen to incorporate physiologically relevant fluids. Evaluation of the chemical nature of the materials and information characterizing the chemical identity and biological response of materials can be useful in assessing a medical device for its intended use on the patient. The initial toxicological risk assessment performed with the E/L data on the field samples of degraded PE-PUR informed the selection of biological endpoint tests. Additional factors that can affect biocompatibility of materials include the identity, concentration, availability, and toxicity of all constituents such as additives and processing aids, which was initially explored in the toxicological risk assessment. Per ISO 10993-1:2018 Clause 4.5, all known possible biological hazards shall be taken into account for every material and final product, but this does not imply that testing for all possible hazards will be necessary or practical.

This document contains an analysis of the biological risks posed to patients from exposure to degraded PE-PUR foam particulates and/or constituents either orally or due to inhalation. This analysis was based upon results from cytotoxicity, irritation, and genotoxicity assay results. At the time of this assessment, sensitization results were not available.

6. Results

6.1 *In vitro* and *in vivo* biological endpoints- Degraded PE-PUR Foam

In order to comply with ISO 10993-1:2018 guidelines as well as FDA Guidance 2020, multiple biological endpoints were evaluated to determine the relevant biological and toxicological risks

from exposure to degraded PE-PUR foam. An overview of the *in vitro* and *in vivo* testing results can be found in Table 2 to include cytotoxicity, irritation, and genotoxicity. Sensitization results were not available at the time of this analysis. Actual experimental results and GLP practices from accredited labs are documented in the respective listed documents.

As shown in Table 2, all results indicate that the PE-PUR foam in its degraded state is cytotoxic and mutagenic. Irritation revealed passing results, however only half of the assay was conducted due to an issue with sample extraction which is further discussed below. It is important to note that for each assay conducted, the extracts in every vehicle (0.9% NaCl, SSO, DMSO, 1x MEM, and RPMIi) needed to be strained to remove particulate and degradative debris in order for the test systems to be used (guinea pigs and rabbits or cell cultures). Each biological endpoint test utilized diluted solutions filtered first through a strainer of extracts.

Table 2. *In vivo* and *In vitro* Biological Endpoint Summary

Device Component	Biological Test	Notes	Acceptance Criteria	Pass/Fail	Report
Degraded PE-PUR Foam	Cytotoxicity ISO 10993-5:2009 MTT Assay	37 ºC for 72 h in 1X MEM w/ 10% FBS	No cytotoxic potential (Cellular viability ≥ 70 %)	Fail: Cellular viability = 11% and lower	20-03961-G1
	Sensitization ISO 10993-10:2010 Guinea Pig Maximization Test	Sesame seed oil (non-polar), NF 37°C for 72 h	No evidence of delayed dermal contact sensitization; graded erythema scale	Pass	20-03961-G3
	Irritation ISO 10993-10:2010 ISO Intracutaneous*	Sesame seed oil (non-polar), NF 50 °C for 72 h	No significant difference in erythema or edema mean score compared to control score	Pass	20-03961-G4
	Genotoxicity ISO 10993-3:2014 Bacterial Reverse Mutation Study	0.9 % NaCl Saline (polar) 37 °C for 72 h DMSO (non-polar) 37°C for 72 h	Non-mutagenic to *S. typhimurium* and *E. coli* tester strains in the presence and absence of S9 homogenate (metabolic activator)	Fail: TA98, TA100, WP2 strains indicate mutagenicity	20-03961-G2
	Genotoxicity ISO 10993-3:2014 Mouse Lymphoma Assay	RPMIi (polar) 37 °C for 72 h DMSO (non-polar) 37°C for 72 h	IMF is less than the GEF	Fail: IMF larger than GEF, indicate mutagenicity	20-03961-G5

*For the intracutaneous irritation assay and GPMT, the prevalence of degraded PE-PUR foam particulates and the color of the extract affected the quality of injection in the 0.9% NaCl solvent system. Because the extracts are injected within the skin, the darker pigment could obscure the results of the erythema and

edema scoring, and thus the decision was made to proceed only with the SSO extract which was a lighter pigment. 20

Cytotoxicity

All concentrations of the test sample, which was cell culture media extracts of the degraded PE-PUR foam after it had been strained to create a usable extract, demonstrated between 9-17% viability. All concentrations were listed as cytotoxic.

Sensitization

The degraded PE-PUR foam was extracted in both 0.9% NaCl and SSO to represent both polar and non-polar solvent systems. Extracts were prepared and then an initial dose, followed by a challenge dose was administered to guinea pigs via intradermal injection. Scores from the Magnusson and Kligman Scale, along with the sensitization classification were utilized to describe erythema and edema presence compared to that of control animals. Both extracts were determined to be non-sensitizers.

Irritation

The degraded PE-PUR foam was extracted only in SSO due to vehicle suitability with 0.9% NaCl and its administration to the rabbits. Extracts were prepared and then an initial dose, followed by a challenge dose was administered to rabbits via intracutaneous injection. Erythema and edema was scored 24, 48, and 72 hours after injection of the test article and graded on a scale from 1-4. The extract was listed as non-irritating compared to that of the control animals.

Genotoxicity

Ames Assay

The Ames Assay utilized 5 different strains of bacteria which are either histidine (*his*) or tryptophan (*trp*) mutants and detect frame shifts and base pair substitutions to include:

- *S. typhimurium* TA98- frameshift
- *S. typhimurium* TA100- basepair substitution
- *S. typhimurium* TA 1535- basepair substitution
- *S. typhimurium* TA 1537- frameshift
- *E.coli* WP2- basepair substitution

The degraded PE-PUR foam was extracted in both 0.9% NaCl and DMSO to represent both polar and non-polar solvent systems. It was noted during the experiment that the DMSO extract appeared to completely dissolve the test article. This created an invalid extract as the intention

of the extraction process is to determine extractables/leachables and not dissolve the material. Therefore the DMSO results are not considered relevant for this risk assessment. The results for the polar extracts from the degraded PE-PUR foam samples included a significant increase in the number of revertant colonies and thus mutagenic potential as summarized in Table 3 below.

Table 3. Summary of Ames Assay Results- Degraded PE-PUR Foam

Strain	S9 Presence	Solvent	Significant Increase ($p < 0.05$)	Mutation Detected by Assay
TA98	-	37 °C for 72 h in 0.9% NaCl	Yes	Frameshift
TA98	+	37 °C for 72 h in 0.9% NaCl	Yes	Frameshift
TA100	-	37 °C for 72 h in 0.9% NaCl	Yes	Basepair substitution
TA100	+	37 °C for 72 h in 0.9% NaCl	Yes	Basepair substitution
TA1537	+	37 °C for 72 h in 0.9% NaCl	Yes	Frameshift
WP2	+	37 °C for 72 h in 0.9% NaCl	Yes	Basepair substitution

Mouse Lymphoma Assay

All mouse lymphoma cells were initially grown and treated with the tests agents in a suspension culture, including both with and without exogenous metabolic activation (S9). Cytotoxicity is measured in order to understand dosing ranges of the test article, since pronounced toxicity in this assay may lead to events that contribute to false-positive results.[29]

Mutant colony sizing is utilized in order to provide information concerning the ability for the chemical tested to induce point mutations and/or chromosomal events. The degraded PE-PUR foam was extracted in both RPMIi cell culture media and DMSO to represent both polar and non-polar solvent systems. It was noted during the experiment that the DMSO extract appeared to completely degrade the test article. This created an invalid extract as the intention of the extraction process is to determine extractables/leachables and not dissolve the material. Therefore the DMSO results are not considered relevant for this risk assessment.

The first phase of this experiment involved understanding the dosage concentrations for both extracts, which were verified by a cytotoxicity test using trypan blue exclusion. Only conditions with 20% or more viability were utilized in the assay, this included 1.56 and 0.781% concentrations for RPMIi without metabolic activation and 1.563%, and 0.78% with metabolic activation.

Cells were plated for selective growth and cloning efficiency calculations to include colony counting after incubation for 11 days. Both large and small colonies were observed in all conditions. However, the induced mutant frequency (IMF) was larger than the global evaluation factor (GEF) for RPMIi at 1.56% with metabolic activation indicating a mutagenic response.

Dilution of Extract (%)	S9 Presence	Solvent	Induced Mutant Frequency (IMF) x 10^{-6}	Greater than GEF? (126 x 10^{-6})	Mutation Detected by Assay
1.56	-	RPMIi	111	Baseline	Small colonies chromosomal damage/aberrations, Large colonies potential mutations
0.78	-	RPMIi	57	No	Small colonies chromosomal damage/aberrations, Large colonies potential mutations
1.56	+	RPMIi	219	Yes	Small colonies chromosomal damage/aberrations, Large colonies potential mutations
0.78	+	RPMIi	45	No	Small colonies chromosomal damage/aberrations, Large colonies potential mutations

Both the Ames Assay and MLA returned positive (mutagenic) responses for a variety of test concentrations of the degraded PE-PUR foam extracts, both with (Ames and MLA) and without (Ames) metabolic activation.

7. Evaluation of Risks

The estimation of biological and toxicity risks posed to patient populations exposed to degraded PE-PUR foam have been reviewed using the results from ISO 10993-1:2018 testing, along with methodologies prescribed in ISO 10993-3:2014 and FDA Guidance 2020 on the use of ISO 10993-1. Each biological endpoint test is discussed and evaluated in the context of patient risk below.

Cytotoxic potential

Cell viability of 11%, 7%, 4%, and 3% was noted at concentrations of the PE-PUR foam extracts of 100% (neat), 50%, 25%, and 12.5%, respectively, compared to cell viabilities of 100%, 85%, and 0% for the untreated, negative, and positive controls, respectively..

Based upon the results of the MTT assay, there is sufficient evidence that leachates from the degraded PE-PUR foam are cytotoxic and could affect local toxicity wherever degraded PE-PUR particulates make contact with patient tissue.

Sensitization

The Guinea Pig Maximization Test (GPMT) was performed with both the non-polar SSO extract, as well as the 0.9% NaCl extract. Both extracts returned no significant difference in erythema or edema scoring compared to the control animals, and thus the extracts were classified as non-sensitizers.

Irritation

The irritation assay was only able to be conducted with the non-polar SSO extract, and therefore any hydrophilic/water soluble chemistries could not be determined. Nonetheless, the nonpolar extract resulted in a passing score.

Genotoxic potential

Ames Assay

The bacterial reverse mutation assay or Ames Assay is the initial screen utilized to detect mutagenic potential of chemicals. Mutagenicity is the ability for a chemical or mixture of chemicals to induce a permanent and transmissible change in the amount or structure of genetic material within cells or organisms.[38] Genotoxicity is the ability of a chemical or agent to cause DNA or chromosomal changes.[39] Genotoxic carcinogens are able to interact with DNA and induce mutations, leading to a variety of downstream biological effects.

Both the *S. typhimurium* and *E. coli* strains produced statistically significant revertant colonies, including during the presence of metabolic activation. The presence of S9 is particularly important because it is a fraction obtained from rodent liver to include microsomal and cytosolic fractions in order to enable metabolic activation.[41] These are included because many carcinogens are inactive until they become transformed *via* metabolic activation[42], and thus the presence of S9 is more indicative of what could occur in a living system, such as the human body.

Although genotoxic occurrences and their corresponding biological signaling cascades are incredibly complex and often involve co-factors, genetic susceptibility, environmental implications, *etc*. the Ames Assay is predictive of mutagenicity and a gold standard in regulatory toxicology.[43] Potential severity of harm to patients exposed to degradative products of PE-PUR foam could include carcinogenicity based upon the Ames Assay results. Frameshift mutations have been implicated in colorectal and gastrointestinal cancer.[46–48] Basepair substitutions have been associated with breast cancer, uterine cancer, and oncogenic mutation in leukocytes. [49–51]

Mouse Lymphomas Assay

The mouse lymphoma assay was utilized as another tool to better understand the mutagenic risk in a mammalian test system.. Although the Ames Assay is indicated in ISO 10993-1:2018 within the biological risk management process, there are limitations. There is evidence that some non-carcinogens are capable of producing positive results and Walmsley and Billinton have concluded that the Ames Assay is specific but not very sensitive, whereas the mammalian assays such as MLA are sensitive with poor specificity.[52] Therefore, in order to be inclusive of the limitations posed by bacterial methodologies and incorporate a battery of tests as indicated by ISO 10993-3:2014, both the Ames and MLA assay results were utilized for overall risk characterization. It should be noted that numerous PRI products and materials that have undergone genotoxicity assays prior to the degraded PE-PUR foam testing have never returned a positive mutagenic result.

The MLA utilizes a mutant mouse lymphoma cell with a mutation in the thymidine kinase (TK) locus of L5178Y. The MLA is capable of detecting gene mutations to include point mutations and chromosomal events.[25] Mutants that display significant genetic damage have longer doubling times and create smaller colonies, which also may indicate chromosomal aberrations.[53] Larger colonies may be indicative of gene mutation[26], but overall this phenomenon and its correlations are still being explored.

The MLA confirmed that in the presence of metabolic activation, small and large colonies were confirmed, and a mutagenic response was noted in the RPMIi extract at 1.56 %. This testing only accounted for the polar solvent system however, as the non-polar system of DMSO was deemed unsuitable to due to almost complete degradation of the foam sample. There are “non-polar” environments in the body and thus the MLA conducted is not a complete representation of all potential experimental results.

Potential severity of harm to patients exposed to degradative products of PE-PUR foam could include carcinogenicity based upon the MLA results. Chromosomal aberrations have been implicated in gliomas and other types of tumors and genetic mutations are confirmed causes of chemical carcinogenesis.[54–57]

8. Discussion

During the synthesis of polyurethane, toluene diamine and toluene diisocyanates are utilized. Typical metabolic distribution of toluene diamine isomers include distribution in the gastrointestinal tract, liver, kidneys, and adrenal glands as determined by animal studies.[59,60] Multiple Ames' tests and *in vivo* studies have confirmed 2,4, 2,5 and 2,6 diaminotoluene (toluene diamine isomers) are mutagenic.[61–64] Toluene diisocyanate has been designated as carcinogenic via the oral route due to its conversion to toluene diamine in the gastrointestinal tract. However, it is typically labeled as non-carcinogenic via inhalation.[73] *In vivo* and *in vitro* tests indicate both mutagenic and non-mutagenic outcomes.[74] In order to encompass the mutagenicity and carcinogenicity risk posed by these two by-products, while also incorporating local biological endpoints to include sensitization and irritation endpoints, *in vitro* and *in vivo* assays were used to test representative degraded PE-PUR foam.

The cytotoxicity and positive genotoxicity results observed from degraded PE-PUR foam samples indicate a potential patient risk. Potential cytotoxicity and genotoxicity leading to carcinogenicity are possible outcomes from degraded PE-PUR foam exposure.

Overall, based on an understanding of the toxicological significance of the foam degradants and the results of the ISO 10993 testing to include mutagenic responses in both a bacterial and mammalian system, the degraded PE-PUR foam is not considered biocompatible and presents a significant biological risk to those patient populations who are exposed to degraded PE-PUR foam.

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PRIVILEGED AND CONFIDENTIAL

EXPOSURE TO POLYESTER-POLYURETHANE FOAM PARTICULATES FROM SYSTEM ONE FOAM DEGRADATION: BIOLOGICAL RISK ASSESSMENT

ER 2241475 v00

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Contents

1. Executive Summary

Philips Respironics Inc. (PRI) was made aware in May 2019 that four CPAP units were returned to a service center with degraded sound abatement foam. The sound abatement foam a polyester based polyurethane (PE-PUR) foam located in the gas pathway of the device. The PE-PUR foam from these field returns underwent FTIR analysis which confirmed degradation of the material *via* hydrolysis. In order to better quantify the potential biological and toxicological risk that exposure to degraded PE-PUR foam particulates pose, a clinically relevant extraction of the degraded foam was conducted per ISO 10993-12:2012. The field sample of degraded foam was extracted in a physiologically relevant solvent (0.9% NaCl) at 37 ºC for 72 h and advanced chemical characterization techniques were employed to identify and quantify all analytes present. Over 35 leachables were identified and after a high level toxicological risk analysis, 22 compounds were risk assessed utilizing health based thresholds and toxicology best practices. A variety of exposure scenarios were calculated to include inhalational and oral exposure and modifications of compound and estimated exposure concentration. Compounds of concern were identified as analytes with Margin of Safety (MOS) values less than 10- many of these compounds had MOS values less than 1. Based upon the exposure to diethylene glycol, nickel, and 19 unknown compounds with potential for carcinogenicity, mutagenicity, and systemic toxicity, the biological and toxicological risks from exposure to degraded PE-PUR foam are of concern and the severity of harm is crucial with respect to both the 30 kg and 70 kg patient populations of the System One medical device.

2. Acronym List

COC- Compound of Concern
CEF-Concomitant Exposure Factor
DBT- Dose Based Threshold
DNEL- Derived No Effect Level
E/L- Extractables and Leachables
GC-MS- Gas Chromatography Mass Spectroscopy
MF- Modifying Factor
MOS- Margin of Safety
NOAEC- No Observed Adverse Effect Level Concentration mg/m^3
NOAEL- No Observed Adverse Effect Level
NOEL- No Observed Effect Level
PEF- Proportional Exposure Factor
PRI- Philips Respironics Inc.
RfD- Reference Dose (Oral)
RfC-Reference Dose (Inhalation)
UTF- Utilization Factor
TE-Tolerable Exposure
TI- Tolerable Intake
TTC- Threshold of Toxicological Concern

UPLC-MS- Ultra Performance Liquid Chromatography-Mass Spectroscopy
VOC- Volatile Organic Compounds

3. Background

3.1 Device Description

The DreamStation and System One devices are designed to provide continuous positive airway pressure (CPAP) support through a mask worn on the face in both home and institutional/hospital setting for patients diagnosed with obstructive sleep apnea (OSA) weighing > 30 kg. Four CPAP units in total, three DreamStations and a System One, REMstar Pro were returned and confirmed to contain degraded sound abatement foam. The subject of this biological risk assessment is the System One, REMstar Pro. The sound abatement foam is located in the gas pathway of the device. Degradation of foam, the risks that the degradative by-products pose to the patient, and the potential for particulates making contact with the patient airway was evaluated in order to consider the potential biological risk this situation posed.

The System One foam is Soundcoat Sound 4PCF foam. This material is an open cell polyester based polyurethane foam (PE-PUR) that is used as an acoustic foam for sound dampening in the CPAP devices. The foam was tested in its production equivalent form for biocompatibility according to ISO 10993-1:2018 and passed cytotoxicity, irritation, and sensitization (ER 2200198 v16). ***Although the initial PE-PUR foam has evidence of biocompatibility for long term duration skin contact biological endpoints, this risk assessment will consider patient exposure to the degraded PE-PUR foam and its particulates, as this is what was reported in the field complaint***. ***Furthermore, inhalation and oral modes of exposure are the most clinically relevant risks- skin contact endpoints are not appropriate for this type of patient contact.***

Figure 1 shows representative images of the degraded foams from two System One CPAP units. These devices were being used in and the product complaints were received from Thailand. Return 307829970 is 461P device with Serial Number P164783468DA1 built May 24, 2016, per the electronic Design History Record (eDHR). Return 307803629 is IN461S device with Serial Number P1165312101A5 built June 5, 2014 per the eDHR. Both units were within the device lifespan window of five years when the complaints were initially filed.

Figure 1. Degraded PUR foam from patient devices

The PE-PUR foam degraded into particulates of varying sizes and was confirmed to undergo hydrolysis via a third party laboratory (RJ Lee Report PA060520190006) in this instance. Additional field complaints with different PRI devices housing degraded PE-PUR foam have confirmed degradation *via* hydrolysis (Trilogy HHE ER 2227646 v06).

3.2 PE-PUR Polymer Degradation

Polymer properties and functions can be impacted by degradation and is dependent on the type of degradation (i.e. chemical, physical, mechanical).[1–3] Water induced degradation (hydrolysis) of polymers can affect physiochemical properties.[4–6] Furthermore, polymers can be biocompatible in their original form but show toxicity upon degradation.[7] The System One PE-PUR foam was confirmed by a third party lab to have undergone hydrolysis as evidenced by the carbonyl band shifting after FTIR analysis. This full report is available in Attachment 1 of "2019-04-24, CPAP Foam Degradation." A representative image of the degraded foam is shown in Figure 1, including a portion of the deposition path of the particulates. Because the foam particulates are visible in the picture, it is likely that their sizes include a range of diameters both larger and smaller than 50 µm, as this is generally accepted as the limit of human eye visibility. Preliminary analysis on multiple experimental PE-PUR foam samples artificially aged revealed particulate distribution sizes that included diameters of 82 µm and 387 µm. Field samples of the actual degraded PE-PUR foam were difficult to obtain and measure, as the degraded foam adheres to surfaces and itself, making sample preparation difficult for SEM or other microscopy

analysis. The general chemical structure of polyester polyurethane (PE-PUR) is shown in Figure 2.[8] The main degradation mechanism of PE-PUR foams is hydrolysis, and they have shown sensitivity to thermal ageing in humid conditions.[9] The main degradative by-products of PE-PUR foam after a humid ageing experiment included diethylene glycol (DEG), toluene diamine isomers (TDA), and toluene diisocyanate isomers (TDI).[9] A mammary implant fabricated out of polyester polyurethane was also shown to undergo hydrolysis with TDA as a major degradative by-product.[10] Thermal decomposition by-products of polyurethane also include TDA and TDI, and were quantified in air samples, suggesting that these by-products are somewhat volatile.[11] General chemical structures for these degradative constituents are displayed in Figure 2b-d. An example hydrolysis reaction is also depicted in Figure 3.

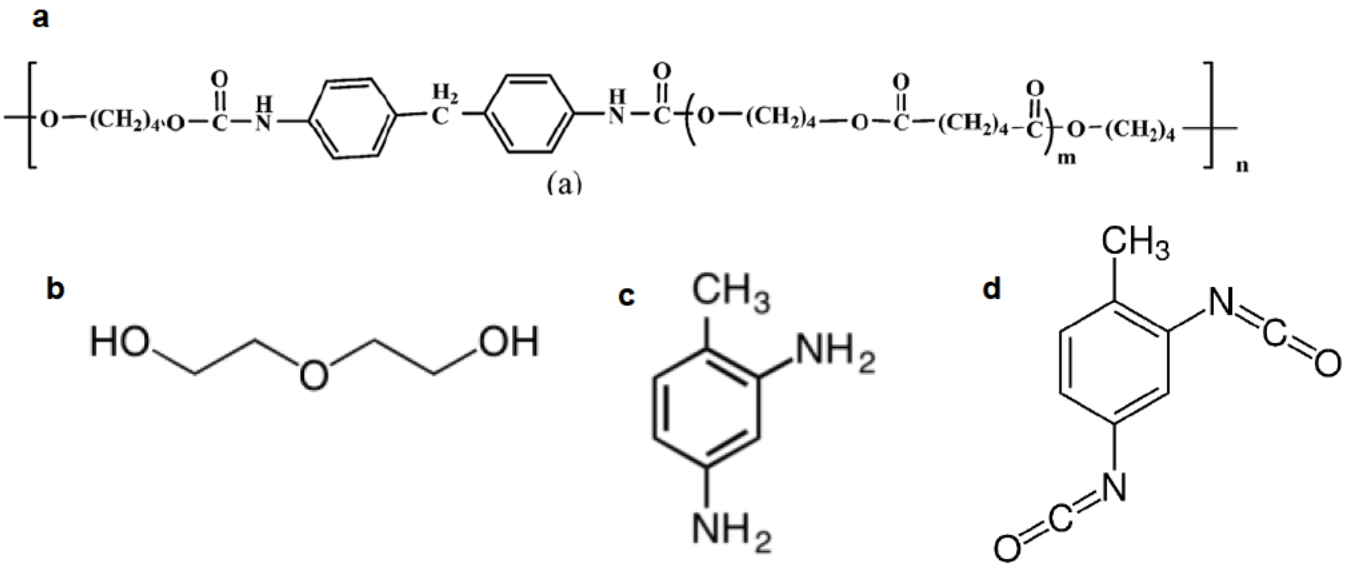

Figure 2. General chemical structure of (a) PE-PUR (b) diethylene glycol (c) representative toluene diamine (d) representative toluene diisocyanate

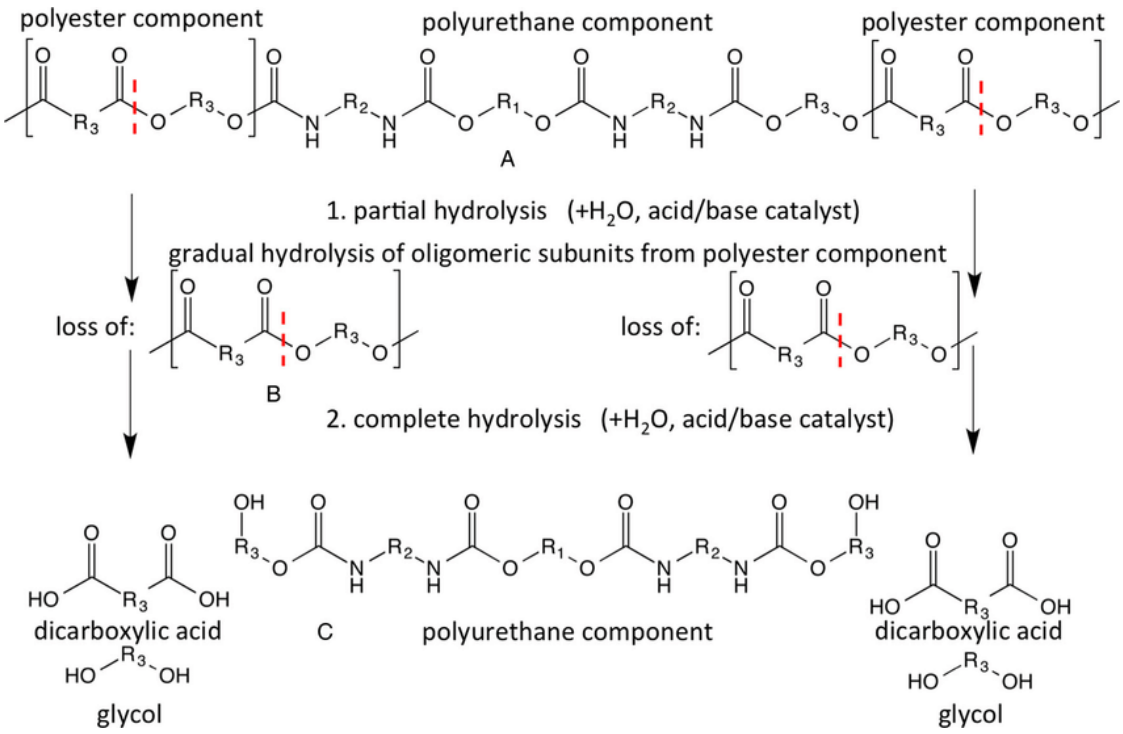

Figure 3. Example of polyester polyurethane hydrolysis reaction taken from Marjo *et al.*[12]

3.3 Physiology of Patient Airway and Particulate Exposure Pathway

In order to evaluate the risks that the PE-PUR degraded foam poses for devices in the field and for the patients affected by these two field complaints, patient airway physiology must be considered.

Particulates originating from the breakdown of the PE-PUR foam within the System One that were inhaled by the patient would undergo a variety of processes and would be deposited in accordance with interception, impaction, sedimentation, and diffusion.[13] The location of collected aerosolized particulates in the respiratory tract and the body's response to them is partially dictated by size.[14] Deposition of particles within the respiratory tract is also a function of patient breathing pattern.[15]

A multitude of tissues composes the respiratory tract which includes the conducting airways that consist of the nose, mouth, and pharynx, leading into the trachea, main bronchi, lobar, segmental bronchi, and terminal bronchioles.[16] The respiratory zone includes terminal bronchioles, respiratory bronchioles, alveolar ducts, and lastly alveolar sacs.[16] There are defense mechanisms in the respiratory system which help prevent particulates from entering into the lung and aid in respiratory clearance.[17] This includes the superficial epithelium which lines the nose, paranasal

sinuses, trachea, and lower airways and harbors ciliated cells and goblet cells.[18,19] Cilia are hair-like projections of the cells that line the airway and propel the liquid layer of mucous which can trap pathogens and particulates prior to reaching the lungs.[18] This mechanism is known as the mucociliary escalator, wherein mucus produced by goblet cells can trap particulates and transport them within a mucus blanket to the gastrointestinal tract.[19]

The nose and accompanying respiratory tract is capable of filtering foreign particles dependent on particle size and airflow rate with a filtration efficacy decreasing with particulate size.[20] Small particles (<1-3 µm) are capable of diffusing into deep lung tissue and deposit into the alveoli whereas larger particulates (> 8 µm) will be deposited throughout the nasal passages and larger bronchioles.[14] Furthermore, the lower airways and nasal cavity can also benefit from clearance with a cough or sneeze reflex respectively.[19]

In order to perform a quantitative toxicological risk assessment based upon assumed particulate deposition percentages throughout the patient airway and concentrations of detected analytes in the degraded foam/particulates, boundary conditions were calculated. These boundary conditions enabled calculations to be performed assuming specific scenarios. Although additional experiments under simulated conditions revealed particulates that were 82 µm and larger, the possibility that smaller particulates are present in the clinical use case cannot be ruled out as this time.

3.4 Boundary Conditions for Quantitative Toxicological Risk Assessment

For this risk assessment, the PE-PUR foam particulates are assumed to reach the patient airway because (1) a bacterial/viral filter is not mandated for use with the System One device and (2) particulates were confirmed to have collected in at least one patient circuit while being used with device P1165312101A5 (the amount or concentration of particulates inhaled in µg/m^3 and the distribution of particle size is unknown). It should also be noted that no alarm sounds if a filter is not in-line with the circuit and there is no user interface (UI) prompt concerning bacterial/viral filter placement.

The total weight of the foam in a newly manufactured System One device is 9.1 g with an overall top surface area of 119 cm^2. The field sample that was returned to PRI was approximately 26 cm^2 and it is assumed that 93 cm^2 of foam was degraded. The deposition of particulates and degree of degradation throughout the device, patient circuits, and mask are unknown. This pathway is illustrated below in Figure 4.

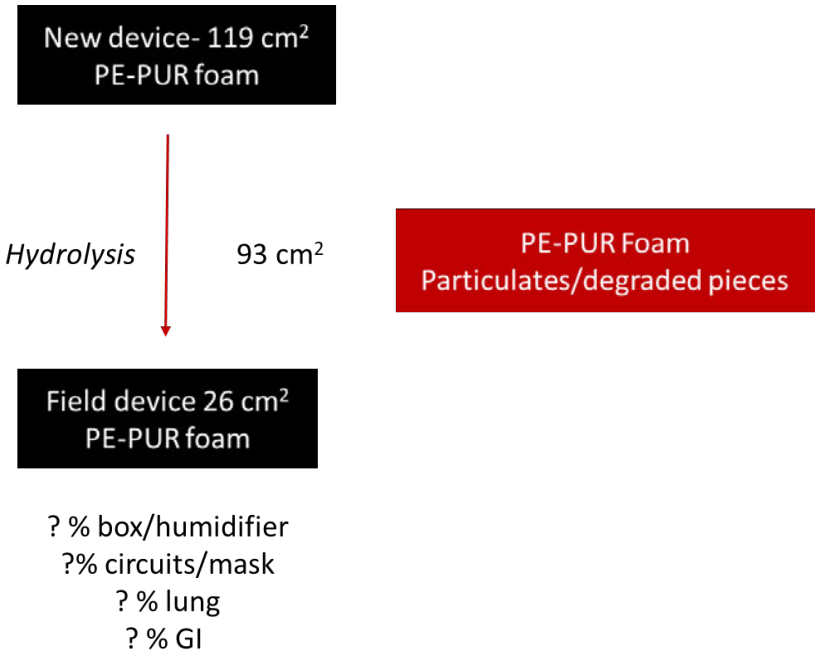

Figure 4. Illustration representing PE-PUR foam dimensions and percentage distribution

Figure 5 below is a modified schematic from the National Research Council regarding exposure assessments.[21] There are two proposed major routes of exposure to the degraded PE=PUR foam particulates that are considered clinically relevant- inhalation and oral ingestion.

Inhalation exposure to the particulates would begin at the upper respiratory tract where the mouth and nose warm and humidify the air, while also functioning as a filter to trap larger sized particulates. The dose to the patient is transformed from a potential dose to the applied dose after going through the upper respiratory tract towards the mid and lower respiratory tract, where an internal dose is present after particulates have been exposed to the lung tissue, including macrophages, dendritic cells, lymphocytes, and eosinophils which aid in the immune reaction to foreign material.[22] The particulates and the leachates coming out will undergo metabolism/biotransformation. This in turn leads to targeted organ effects and downstream acute and chronic biological effects.

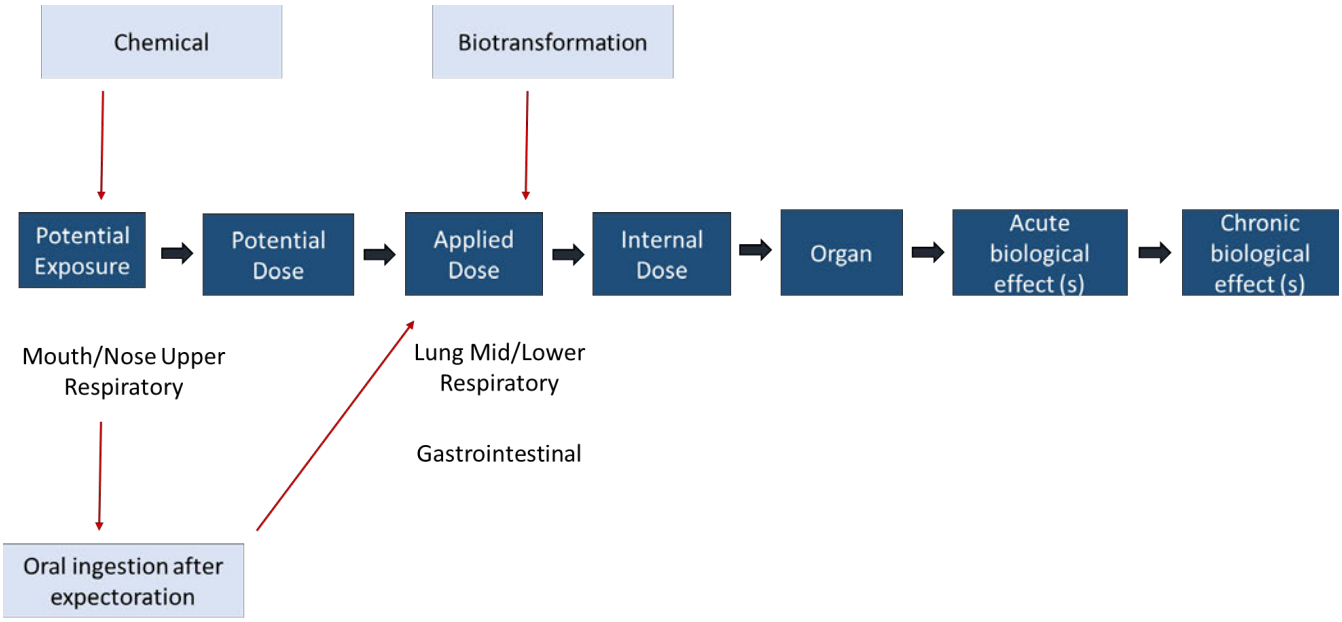

Figure 5. Modified schematic of exposure assessment route

The percentage of particulates that were distributed along the exposure pathway from device to patient are unknown but the below clinical boundary conditions are proposed.

Computational fluid dynamics (CFD) models have been developed of the human airway in order to better understand aerosol deposition for optimizing aerosolized drug delivery.[23–26] Attempts to better understand and quantify fractional deposition of particulates along the upper and lower respiratory tract have been well documented in scientific literature.[27–30] Numerous factors affect particle deposition in the conducting zone airways versus the respiratory zone (i.e. upper and lower bronchioles, alveolar ducts, and the alveoli) including tidal volume, inspiratory time and flow rate, respiratory rate, particle diameter, and particle density.[31] Figure 6 below illustrates the deposition differences based upon particle diameter and location within either the conducting zone (extra-thoracic) or respiratory zone (intra-thoracic) airways or of the respiratory system.

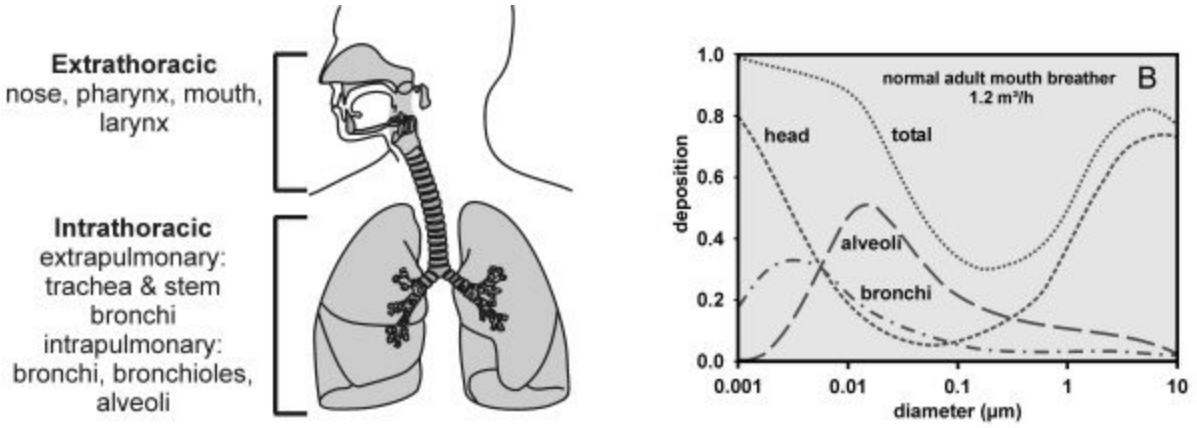

Figure 6. Reproduced figure of deposition of inhaled particles in the human respiratory tract in normal adult mouth breathing (male subject at rest)[28]

In order to accurately represent the worst-case scenario of patients inhaling degraded PE-PUR foam particulate while maintaining a clinically relevant scenario, data from scientific publications that utilize particulate deposition models was explored for use in the exposure calculations detailed in Section 4. The below analysis setup was initially utilized in the toxicological risk assessment, which is also detailed in Appendix 1 Pathway A of this document.

Hvelplund *et al*. have developed a three-dimensional respiratory tract CFD model based upon Computed Tomography (CT) scans of the human airway.[32] This study was chosen for its anatomical relevance and the predicted particulate deposition fractions based upon anatomical regions. Assumptions about the velocity and particle trajectory included differences in flow between the left and right lungs. Table 1 below is a reproduction of the percentages of particulate deposition based upon size from Hvelplund as well as several other CFD/CT model publications. Hvelplund *et al.* have shown that that simulated particles are deposited based upon size with differences in the left and right lungs. Lambert *et al.* reported a CT based human airway model predicted approximately 75% particle distribution in the oral region and additional models have predicted particles of smaller sizes to deposit in the alveoli.[29,33]

Table 1. Particulate Deposition Percentages in Respiratory Tract

	Sturm	Ma and Lutchen	Xi *et al.*	Hvelplund *et al.*	Lambert *et al.*
Deposition	0.1 µm 20-45% deposit in all regions[34]	1 µm 9% deposit in all regions [35]	1 µm 10-39% deposit in alveoli dependent on alveolar size, breathing rate[36]	10 µm 43% deposit in left and right bronchi and trachea[32]	>30 µm 75% deposit in "oral regions" [33]

Using the results from various CFD publications, the below boundary assumptions are proposed for the initial toxicological exposure calculations (Appendix 1, Pathway A):

- The degraded PE-PUR foam particulates are size distributed, particulates could include diameters greater than, equal to, or smaller than 30 µm, 10 µm, 1 µm, and 0.1 µm.
- Based upon the above analysis, **75%** of the particulates could be trapped in the oral, nasal, and pharyngeal regions (these would be the larger particulates and foam pieces) and ingested, undergoing biotransformation within the GI tract.
- Based upon the above analysis, a large percentage range of particulates could be trapped within the lower portions of the conducting airway zone and the respiratory zone airways. To be inclusive of the worst-case scenario, **43%** will be used as the boundary condition for inhalational exposure based upon the 10 µm predictions with percentage of tracheal and bronchiole depositions from Hvelpund *et al*.
- This analysis is independent of a foreign body response, immune reaction, or cytokine storm that could be prompted by the presence of a foreign particulate in the upper and/or lower airways.

In order to encompass multiple scenarios to account for the numerous unknowns that surround the PE-PUR foam degradation in patient devices, another evaluation pathway was proposed with the below boundary assumptions. These were used for additional toxicological exposure calculations (Appendix 1, Pathway B):

- The degraded PE-PUR foam and particulates have an equal distribution of chemical analytes leaching out and can be calculated based upon the surface area (cm^2).
- The foam does not catastrophically fail to enable a bolus of particulates that reach the patient in a single day, the exposure is continual and over an extended period of time (over 30 days of exposure).
- Although particulates will get continual clearance within the body due to normal mucociliary escalator and elimination functions, a patient experiences continual exposure after the onset of foam degradation.
- Inhalational tolerable exposure limits will be utilized, as they are typically lower than oral limits.

- Particulate size distribution was not considered in order to create a more simplistic analysis due to the large number of unknown conditions:
    - All foam is lost, all foam reaches the patient (not realistic)
    - 80% foam is lost, 100%, 50%, and 25% reach the patient
    - 10% foam is lost, 100%, 50%, and 25% reach the patient (more clinically relevant)

4. Experimental Methods

In order to appropriately capture the toxicological risk posed to patients that have been exposed to the degraded PE-PUR foam particulates, additional advanced chemical characterization after extractables/leachables was performed on the field samples of degraded PE-PUR foam. Utilizing guidance from ISO 10993-12:2012 and ISO 10993-17:2002, a clinically relevant extraction was performed. Extraction conditions were chosen to be physiologically relevant and mimic the lung tissue/lung environment, as this is a primary route of exposure and also somewhat captures oral exposure, prior to transformation in the gastrointestinal tract (GI). Song *et al.* have reported that airway surface liquid (ASL), which forms the interface between luminal membranes of airway epithelial cells and inspired/expired gas, has an average pH of 7.28 ± 0.07 and a [Na^+] of 122 ± 2 mM and [Cl^-] of 123 ± 4 mM.[1] Ng *et al.* have reported that ASL and alveolar subphase fluid (AVSF) are more acidic than the average blood pH (typically 7.4)[2.] Extraction of the degraded PUR foam (from the field) was conducted in a 0.9 % NaCl solution with a pH of approximately 7.3, at 37ºC for 72 h. No additional enzymes or constituents were considered in order to reduce the complexity of the analysis, while still obtaining vital data for use in the assessment.

Every effort was made to maintain and extract both the particulates and the solid pieces of foam and extraction samples were not filtered. Gas Chromatography-Mass Spectrometry (GC-MS), and High Resolution Accurate Mass-Ultra High Performance- Mass Spectrometry (HRAM UHPLC-MS) as well as Inductively Coupled Plasma- Mass Spectrometry (ICP-MS) were techniques utilized to identify the analytes. An LC chromatogram with UV-Vis detector was also employed. Analysis and risk assessment methodologies were applied in accordance with ISO 10993-1:2018, ISO 10993-17:2002, and ISO 14971:2012. A summary of the various analytical methods for chemical characterization and the general class of compounds they can detect is shown below, along with the experimental test matrix in Table 2:

- ICP-MS- Elements/metals
- GC-MS- Semi-volatile organic compounds (SVOC) and volatile organic compounds (VOCs)
- HRAM UHPLC-MS and LC/UV-Non-volatile organic compounds (NVOC)

Detailed information about the experimental setup, limits of detection per analytical test, and controls are available in Attachment 1 of this document. Lower limit of quantitation (LLOQ) for each technique varied and included 10 ug/L and 0.5 ug/mL, depending upon the analyte. *It is important to note that this experiment was purposefully designed to mimic clinically relevant*

physiological conditions and as such, the analytes detected are true leachables- there is a high probability that patients are exposed to the detected compounds in some form.

Leachables are a subset of extractables (any and all compounds that may be detected in an E/L experiment, even if they are not clinically relevant). Although the experiment was conducted for 72 h, this is representative of a "snapshot" of the chemicals and degradative byproducts within the PE-PUR foam that are leached. This does not necessarily equate to a true diffusion of all leachables, and the representative concentration each day that the patient is exposed to. In reality, the kinetics and concentration versus time profiles for analytes diffusing out of polymer systems and any analytes metabolized by the body are traditionally not static.[37–39]

Table 2. Experimental Test Matrix

Test System	Extraction Solvent	Extraction Condition	GC/MS	GC/MS	HRAM-UHPLC/MS	LC/UV	ICP
			VOC	SVOC	NVOC	NVOC	Metals
PE-PUR degraded CPAP foam	0.9% NaCl, pH 7.3	37ºC for 72 hours	X	X	X	X	X

Based upon the above experimental setup the below boundary assumptions are proposed for the toxicological exposure calculations that were conducted in Pathway A and B of Appendix 1:

- The concentration of analytes detected from the experiment over 72 h is representative of the amount released each day and bioavailable to the patient for the lifespan of the device.
- The state of degradation from the sample foam (field sample from Thailand) is representative of the System One devices in the field.

5. Risk Assessment Method- Toxicological Evaluation

The evaluation of the leachables that are clinically relevant from the PE-PUR degraded foam and their specific biological risk assessment was guided by ISO 10993-1:2018, ISO 18562-1:2017, EN ISO 14971:2012, and 10993-17:2002.

In order to evaluate the toxicology profile of the leachables identified during experimental testing, an allowable limit of human exposure to the chemical identified needed to be established using both inhalation and ingestion routes of exposure. Guided by ISO 10993-17:2002, ISO 18562-1:2017, ISO/TS 21726, and ISO 18562-3:2017, various factors were considered or calculated to include:

- Critical health endpoints

- Tolerable intakes (TI)- mg/kg/day
- Tolerable exposure (TE) of the patient to the substance using appropriate patient body mass (m_B) and device utilization factor (UTF)
- Reference dose (RfD)
- Threshold of Toxicological Concern (TTC) approach
- ICH M7 Guidelines

Reviewing the toxicological data aids in establishment of the NOAEL or "no observed adverse effect level," which can then be used in order to assess if a biological risk exists to the patient from the compounds leached or extracted from the device. Different NOAEL values typically exist for a toxicological profile of a chemical compound, including oral acute and chronic toxicity, inhalation acute and chronic toxicity, carcinogenicity, and reproductive/developmental toxicity. In order to provide the most physiologically relevant toxicological analysis, either chronic oral toxicity or inhalation toxicity data was used in order to calculate TI and TE endpoints. Additionally, if a NOAEL could not be established, the lowest adverse effect level (LOAEL) or a reference dose/reference concentration (RfD or RfC) was used in calculations.

The toxicity data for this assessment were originally referenced in the National Institutes of Health (NIH) chemistry database –PubChem, but if compound information did not exist or was not available, additional published literature was used.[40] The Organization for Economic Co-operation and Development (OECD) is an international organization with numerous member countries that puts together chemical safety assessments in order to provide information about potential risks or health hazards posed to humans from certain chemicals.[41] These Screening Information Dataset (SIDS) and Assessment Reports (SIAR) contain references to numerous published scientific experiments where toxicology profiles were established. Oftentimes, the SIDS or SIAR documents provide a more tailored toxicological profile for human exposure. These reports are in conjunction with the U.S. Environmental Protection Agency (EPA) and the Existing Substances Regulation of the European Union (Regulation (EC) 793/93). For several compounds that did not have a toxicological profile on a national database such as PubChem, the SIDS or SIAR document was used to calculate the TE values. If other peer reviewed scientific literature was available that contained animal toxicology studies, this information was also used in deriving the TI and TE endpoints. Because the device indirectly interfaces with the patient respiratory tract (gas pathway), if inhalation toxicological profiles were available they were used from organizations such as the American Conference of Governmental Industrial Hygienists (ACGIH)[42], the Occupational Safety and Health Administration (OSHA),[43,44] the National Institute of Occupational Safety and Health (NIOSH)[45], the European Chemicals Agency (ECHA)[46], and the Integrated Risk Information System (IRIS).[47]

In order to maintain a conservative approach, for each compound that had an inhalational corresponding reported health-based threshold limit, 1% of the value was utilized in the tolerable intake (TI) calculation. This was determined to be sufficiently protective of all patient classes, as TLVS, RELs, PELs, etc. are based on chronic exposure of 40 hours per week typically (these values are developed for occupational/industrial hygiene assessments). For inhalational toxicity

evaluation, tolerable exposure (TE) was calculated for each patient class by multiplying the health-based tolerable intakes by an adult breathing volume of 20 m^3 and a volume of 8.57 m^3 for 30 kg patients, per ISO 18562-1:2017.

Margin of Safety (MOS) values were calculated per Section 5.3.

5.1 Tolerable Intake (TI)

The TI value is established in order to identify an acceptable amount of exposure to an identified chemical or substance that the patient could be exposed to from the medical device. TI is expressed in milligrams per kilogram body mass per day (mg/kg/day) using a modifying factor (MF) approach shown in equation (1).

$$(1)\ \mathrm{TI} = \frac{NOAEL\ (or\ LOAEL)}{MF}$$

The modifying factor can be calculated as MF =UF1×UF2×UF3, where UF1 is the variation among humans in response to a toxic agent- this can be set to a default of 10 per ISO 10993-17:2002 and was used during the toxicological risk assessment of the data. UF2 accounts for the fact that numerous toxicological profiles and critical health data come from species other than humans, and as such a 10-fold safety factor could be used in the absence of the knowledge of detailed interspecies variation. For the purpose of this biological risk assessment UF2 = 10. UF3 accounts for the quality and relevance of the experimental data obtained, with 1 being good quality, relevant data. In order to simulate worst-case scenario, while taking into consideration patients weighing ≥ 30 kg, UF3 was set to 10. As stated in clause 5.4.3 in ISO 10993-17:2002, a modifying factor (MF) between 10 and 1000 should be sufficiently protective unless poor or inappropriate data are known to be used in the calculation of TI.

5.2 Tolerable Exposure (TE)

TE takes into account how the medical device is used and the body mass of the patient. TE can be calculated from the following equation (2).

$$(2)\ \mathrm{TE}=\mathrm{TI}\times m_B \times \mathrm{UTF}$$

UTF is the utilization factor to take into account the frequency that the patient uses the device and the number of devices utilized in a lifetime. UTF can be calculated using the equation UTF = CEF×PEF, where concomitant exposure factor (CEF) can be set to 1.0 if few devices that can release the leachable substance are used within a calendar year. The proportional exposure

factor (PEF) can be set to a default of 1. For the toxicological assessment of the System One foam that underwent leachables testing, UTF was set to 1 (1 x 1). This assessment considers both pediatric and adult patients-toxicological profiles and calculations used 70 kg to represent adult weight and 30 kg to represent the worst-case scenario that the device is rated for. Any compounds in the data that were of a similar chemical class/family, or reported multiple times were combined to yield a single "exposure per device" number, which was used to evaluate the TI and TE endpoints.

If a NOAEC value or derived no effect level (DNEL) was found in mg/m^3, it was subjected to the TI calculation listed above before being multiplied by either the adult breathing volume (20 m^3/day) or breathing volume corresponding to worst-case lowest patient weight (30 kg, 8.57 m^3/day) to derive a final TE value, based upon guidelines in ISO 18562-1:2017.

5.3 Margin of Safety (MOS)

In order to aid in the identification of potential biological risks from the compounds detected in the extractables/leachables assay, margins of safety (MOS) were calculated to screen out compounds of potential concern. The MOS approach is standard in toxicological practice and risk based assessments and in general a MOS >1 indicates that the substance is not likely to be of concern.[48–51] The following equation was utilized for MOS calculations in (3):

$$(3)\ \text{MOS} = \frac{TE}{Actual\ Exposure\ Per\ Device}$$

However, in some toxicological assessments, MOS calculations are considered concerning if they are under 100.[52,53] In order to be protective of all patient classes that utilize System One but inclusive of the limitations and assumptions this toxicological risk assessment is guided by, any MOS calculations that fell below 10 were highlighted and labeled as compounds of concern (COC).

5.4 Threshold of Toxicological Concern

The threshold of toxicological concern (TTC) is a systematic approach to determining what are deemed "safe" levels for exposure to a certain chemical or substance.[52] The calculation of specific TTC values is guided by initial research and recommendations from Cramer *et al.,* modified over the last three decades in order to apply new experimental data and techniques.[50,54] The current standards and practices for TTC calculations can be found in "Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree."[55] These

practices have been adopted and refined by the European Food Safety Authority and the World Health Organization and take into account data from hundreds of chemicals and structures, metabolism and toxicity data, and published toxicological profiles.

Cramer classes can be used in order to determine acceptable toxicological thresholds of concern (TTC) for exposure to materials. The rules originally established by Cramer and refined by Munro et al. predict potential toxicological hazard when orally administered based upon the molecular structure of the chemical/material.[56] Below are the class definitions:

- Low (Class I): Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity.
- Intermediate (Class II): Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.
- High (Class III): Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.

It is important to note that a Class III substance is not always an unacceptable risk or a cause for concern, but a negative result or structural alert should be further analyzed and the biological risk assessed.

Currently accepted TTC values for various categories of chemicals and substances are shown in Table 3. In order to calculate a TTC value for a compound without a published toxicological profile, Table 4 was utilized for the risk assessment. It should be noted that for this assessment when a TTC approach was applied, the TE equation which factors in TI, weight, and the UTF value, was not used. Instead the TTC threshold was multiplied by patient weight (kg) to get tolerable exposure levels per day.

Table 3. TTC values and Cramer classes[57]

Type of TTC Value	TTC (µg/person/day)	TTC (µg/kg/day)
Structural alert for genotoxicity	0.15	0.0025
OPs and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1800	30

5.5 M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH M7)

The ICH M7 document is authored by the U.S Department of Health and Human Services and the FDA and contains guidelines to assess chemical impurities that may be present in drugs and drug substances. An impurities classification scheme guided by threshold of toxicological concern, along with acceptable daily intakes dependent upon duration of exposure, have been proposed.[58] Both ISO 21726:2019 and ISO 10993-1:2018 which are biocompatibility standards for medical devices, reference ICH M7 as an appropriate document for assessing unknown compounds that could be mutagenic (DNA reactive) that originate from a medical device. Although multiple situations and acceptable intakes are proposed for various scenarios, the acceptable intake for long term exposure to an individual impurity was chosen as the threshold for each unknown compound identified. This is based upon the worst-case exposure scenario for a CPAP user (greater than or equal to 10 years) and the potential that one or more of the unknown compounds could be carcinogenic and/or mutagenic.

5.6 Scientific Literature Review

In order to review the applicable chemical characterization and toxicological data on the various extractables/leachables identified during testing, a number of scientific literature databases were searched including: PubMed, Elsevier, and Science Direct, as well as the toxicology database TOXNET®, which indexes information from TOXLINE, ChemIDplus, and HSDB (Hazardous Substances Data Bank) among others. In order to explore additional potential biological risks posed by the extractables/leachables identified from the System One foam, toxicity, genotoxicity, and carcinogenicity were explored *in silico* using the JRC (Joint Research Centre) commissioned, free toxicological decision tree and database software ToxTree (v3.1.0.1851) available at http://toxtree.sourceforge.net/) if applicable.[59] ToxTree runs through a series of decision trees based upon the internationally accepted Cramer Classification Scheme, along with data sourced from various mutagenicity and carcinogenicity databases.[60]

6. Results

Multiple compounds were detected in the extraction of the field degraded PE-PUR foam in 0.9% NaCl at 37 ºC for 72 h. These analytes are listed in Tables 5-7 and represent non-volatile, semi-volatile, and volatile compounds as well as metals. Based upon the experimental exposure amounts in mg, several additional calculations were performed in order to represent the area of missing foam assumed to be degraded in both the Thailand field returns, as well as the total foam surface area of 119 cm^2 (Section 5.3). These values are useful in establishing boundary conditions for exposure to the detected analytes when conducting the toxicological risk assessment. The numbers listed in Tables 4-6 have not yet been modified to account for the exposure routes (inhalation vs. oral ingestion) and the average usage per day of a CPAP (8 hours).

Compounds that were identified as not expected to originate from the degradation of PE-PUR foam or were detected and analyzed as having a lower toxicological risk are explained in additional detail in Appendix 2 of this document.

Table 4. Metals in Degraded PE-PUR Foam after 0.9% NaCl extraction

Compound	Exposure Per Foam Sample 26 cm^2 (mg)	Estimated Exposure Per Missing Foam 11.1 cm^2 (mg)	Estimated Exposure Per Missing Foam 93 cm^2	Estimated Exposure Per Total Foam 119 cm^2 (mg)
antimony	0.0003	0.0001	0.001	0.001
nickel	0.0004	0.0002	0.001	0.002

Table 5. Volatiles and Semi-Volatiles in Degraded PE-PUR Foam after 0.9% NaCl extraction

Compound	Exposure Per Foam Sample 26 cm^2 (mg)	Estimated Exposure Per Missing Foam 11.1 cm^2 (mg)	Estimated Exposure Per Missing Foam 93 cm^2	Estimated Exposure Per Total Foam 119 cm^2 (mg)
acetone	0.0001	0.0001	0.0004	0.0005
diethylene glycol	0.731	0.292	2.6	3.4
adipic anhydride	0.322	0.129	1.1	1.5
Unknown 1	0.475	0.190	1.71	2.19
Unknown 2	3.8	1.53	13.7	17.5
Unknown 3	0.116	0.05	0.4	0.5
Unknown 4	2.36	0.94	8.5	10.9
Unknown 5	1.252	0.501	4.5	5.8

Table 6. Non-volatile Compounds in Degraded PE-PUR Foam after 0.9% NaCl extraction

Compound	Exposure Per Foam Sample 26 cm^2 (mg)	Estimated Exposure Per Missing Foam 11.1 cm^2 (mg)	Estimated Exposure Per Missing Foam 93 cm^2	Estimated Exposure Per Total Foam 119 cm^2 (mg)
pipemidic acid	0.457	0.18	1.65	2.10
5-methoxy AMT	0.209	0.084	0.75	0.96
bis(2-butoxyethyl) adipate	0.312	0.125	1.123	1.435
n-dimethyldodecamide	0.023	0.009	0.083	0.106
erucamide	0.026	0.010	0.093	0.120
lauramide	0.021	0.008	0.075	0.096
Unknown 6	0.054	0.021	0.193	0.247
Unknown 7	0.079	0.032	0.284	0.363
Unknown 8	0.081	0.033	0.293	0.374
Unknown 9	0.066	0.027	0.239	0.305
Unknown 10	0.057	0.023	0.204	0.261
Unknown 11	1.673	0.669	6.023	7.696
Unknown 12	0.995	0.398	3.582	4.577
Unknown 13	0.041	0.016	0.148	0.190
Unknown 14	0.259	0.104	0.932	1.191
Unknown 15	0.627	0.251	2.257	2.884
Unknown 16	0.341	0.136	1.228	1.569
Unknown 17	0.025	0.010	0.089	0.113
Unknown 18	0.125	0.050	0.450	0.575
Unknown 19	0.065	0.026	0.233	0.298

All compounds underwent an initial risk screen based upon their chemistry and if existing toxicological data and defined RfC, RfD, DNEL, or human specific thresholds were available. High risk analytes were identified if they were suspected or confirmed carcinogens, mutagens, reproductive toxicants, systemically toxic, or had specific respiratory effects. Table 7 displays results of the initial risk screen after analysis of the chemistries and exposure amounts as detected in the degraded field sample of PE-PUR foam. Three identified compounds (IC) revealed known

or suspected toxicities and serious health hazards whereas 19 unknown analytes were detected with no presumption of safety.

Table 7. Toxicological Effects Summary Compounds of Concern- High Risk

Compound	Inhalational/Air way Deposition	GI tract	Other	Typical PUR Component?	Severity of Harm*
antimony	chronic bronchitis, emphysema, irritation, pneumoconiosis[6 1,62]	Not confirmed	Suspected reproductive toxicant[63]	Yes, flame retardant and/or organometallic catalyst[64]	Crucial
nickel	lung inflammation, lung fibrosis[65,66]	Binds to albumin, no metabolism/bio transformation [67]	Potential carcinogen in some forms after inhalation, contact dermatitis[68–70]	Yes, organometallic catalyst[71]	Crucial
diethylene glycol	Not confirmed	Rapidly absorbed and converted to toxic metabolite 2-hydroxyethoxy acetic acid (HEAA)[72]	Metabolic acidosis, renal injury, neurotoxicity, fatal at estimated exposure of 1 mL/kg for adults, potential developmental toxicant [73–75]	Yes, used to synthesize polyurethane[76]	Crucial
19 unknowns with several mg of exposure-low molecular weights (< 1000 Da)	Unknown effects	Unknown effects	Potential for carcinogenicity, mutagenicity, reproductive toxicant, systemic toxicity	Unknown	Unknown, potential for crucial

*Crucial as defined by ER 2214194 Risk Matrix meaning *"Results in severe injury: life threatening, or permanent impairment or necessitates medical intervention to preclude permanent impairment"*

In order to quantify the toxicological risk, exposure scenarios needed to be calculated utilizing ISO 10993-17:2002 and ISO 18562-1:2017 as guidelines. Unknown compounds were screened for both carcinogenic and non-carcinogenic endpoints, using ICH M7 Guidance[58] on Impurities, ISO/TS 21726[77], and Cramer Class III compound limits to account for a worst-case scenario.

Based upon polyester polyurethane chemistry, there are several chemicals of concern (COC) that can be present in the event of polyester polyurethane degradation. The nineteen unknown compounds detected are listed as potential for crucial severity of harm partially as a result from the high probability of the two below compounds (or their constituents) to be present in these unknowns:

- toluene diamine isomers
- toluene diisocyanate isomers

This probability is supported by nitrogen (N) groups detected in the unknown molecular formulas available in Attachment 1 of this document, as a hallmark characteristic of isocyanates is the N=C=O group or N grouping for amines. An overview of diisocyanate and diamine toxicological significance is available in Appendix 2 of this document.

7. Evaluation of Risks

The System One foam was found to be degraded in two documented cases from Thailand, with three additional CPAP units (DreamStation) tagged with the same issue. Because the foam is a polyester based polyurethane material, it is susceptible to hydrolysis. The two primary concerns for the foam degradation and resultant particulates are (1) particulates present in the System One device that are inhaled or otherwise ingested by the patient and the resulting typical cascade of physiological events to foreign material in the respiratory tract and (2) exposure to the potential degradative by-products and chemistries of PE-PUR in particulate form. *This toxicological risk assessment is solely focused on (2) but does not presume that the inhalation of foreign particulate matter is an acceptable biological risk.* This specific sequence of events regarding particulate matter has not been evaluated in this risk assessment, however per ISO 18562-2:2017, smaller particulates of 2.5 µm and 10 µm have concentration thresholds at which going above presents a health risk. Based on the preliminary analysis done on simulated degraded PE-PUR foam and several field samples, it appears the particulates are above this diameter, but this is not conclusive.

During the synthesis of polyurethane, toluene diisocyanate (which is manufactured using toluene diamine) is used during the polymerization process. Potential degradative by-products of polyurethane include these two compounds in addition to diethylene glycol (a polyol used in

polymerization). In order to better understand the degradative profile of the PE-PUR foam and particulates, a Thailand foam sample from a patient device was subjected to extraction in 0.9% NaCl with appropriate pH at 37 ºC for 72 h to mimic the respiratory environment/lung tissue. Extensive chemical characterization on the leachables profile was performed, revealing presence of diethylene glycol, among other analytes. Toxicological analysis based upon a variety of exposure scenarios (2 actual field return surface areas and 2 calculated worst-case scenarios among others) was conducted using boundary conditions including an 8 hour per night device usage, 30 and 70 kg patient populations, and modification of bioavailability of chemicals in oral and inhalational exposure routes. Over 35 compounds were detected during the chemical characterization analysis but only 22 compounds were risk assessed. The additional compounds identified were either listed as unexpected chemistry from PE-PUR foam or presented a very low toxicological risk. Of the 22 compounds risk assessed, two known compounds and 19 unknown compounds presented MOS calculations of <10 for various exposure routes and patient populations (some MOS values <1). The most concerning of the analytes include the unknowns, some of which showed a propensity for being diisocyanates or diamine constituents. **The biological/toxicological risks from exposure to degraded PE-PUR foam analyzed in this risk analysis originating from PRI System One devices utilizing the assumptions and boundary conditions listed have been deemed concerning due to the following**:

- Over 90% of the unknown compounds, along with diethylene glycol and nickel are present in exposure amounts that equate to MOS values of less than 10 and in some exposure and patient scenarios of less than 1 (Appendix 1, Pathway A and B analysis).
- All 19 unknown compounds are present in amounts that are orders of magnitudes larger than the ICH M7 guidance for prolonged/lifetime exposure (> 10 years) to potential carcinogenic or mutagenic impurities of 1.5 µg/day. These unknown compounds also exceed the tolerable exposure limit per day for inhalation of diisocyanate derivatives for an adult.
- Several of the unknown compounds have nitrogen included in their molecular formula, indicative of diisocyanates or diamines which are anticipated human carcinogens and mutagens.
- Nickel and nickel particulate exposure via inhalation are reasonably anticipated human carcinogens.
- Diethylene glycol was detected in large amounts (0.7 mg) from the PE-PUR foam field sample, has been implicated in numerous human poisoning incidents, and is estimated to be fatal at exposures of 1 mL/kg. Poisoning incidents stem from acute exposures mainly, but it is reasonable to anticipate adverse health related effects with long term exposure to DEG.

8. Discussion

The toxicological risk assessment conducted on the Thailand field sample from a System One CPAP device was guided by ISO 10993 biocompatibility and toxicological standards and established toxicological best practice. Thailand weather is typically described as tropical, with high heat and high humidity. These environmental conditions may have affected the hydrolytic reaction kinetics regarding the foam of the System One device. It is acknowledged that in this situation information was missing that may have aided in this analysis. This includes:

- Measurements of degraded foam particulate distribution throughout the System One device, the patient circuit, and the mask.
- The amount of time the patient was utilizing the device while the foam was actively degrading (i.e. months or years).
- The actual exposure in $\mu g/m^3$ of foam particulates each night.
- The size distribution of particulates that entered the patient mouth/upper airway/lower airway with multiple field returns to calculate an average.
- The device age when the foam first underwent hydrolysis.
- Amount of diisocyanates that are actually reactive and bioavailable in the degraded foam, as this can help predict toxicity.

Additional conditions that affected this analysis included estimation of degraded foam bioavailability between oral and inhalational exposures. Other situations that were not factored into this risk assessment include patient comorbidities that could exacerbate exposure effects from the detected chemicals. Boundary conditions were proposed in this risk analysis in order to perform a quantitative toxicological assessment in order to establish MOS values, which are important values that aid in categorizing risk. Based upon the high level toxicological analysis, and the exposure calculations after adjustment for route of exposure and different foam degradation scenarios, there is evidence of toxicological risk from exposure to degraded PE-PUR foam and particulates.

9. APPENDIX 1 –TOXICOLOGICAL RISK ASSESSMENT SCENARIOS

9.1 Estimated Actual Exposure- Pathway A

In order to encompass the range of biological risk to be inclusive of varying degrees of foam degradation, boundary conditions for evaluating exposure to PE-PUR foam particulates were proposed. These are represented in Table 8 below to be inclusive of the two System One field issues in Thailand, along with an absolute worst case scenario with total foam degradation involving 119 cm^2 and the absolute best case of zero foam degradation. It should be noted that the detected concentration for each analyte is assumed to be the concentration per day, uniformly, which is the worst-case assumption.

Table 8. Calculated Boundary Conditions for Exposure

Exposure Scenario for Calculations	Boundary Condition	Estimated Surface Area Left (cm^2)	Estimated Surface Area for Calculations (cm^2)	Ratio to multiply
N/A	Zero foam degradation (0 cm^2 available)	119	0	0
Scenario 1	Severe foam degradation from sample 307803629	26	26- E/L experimental results run on this sample	1
Scenario 2	Some foam degradation from sample 307829970 (90% intact estimated from picture)	107.9	11.1	0.4
Scenario 3	Hypothetical- Severe foam degradation from sample 307803629	26	93 – Missing surface area from the degraded sample	3.6

Scenario 4	Worst-case foam degradation	0	119	4.6

All exposure calculations were calculated using the results from the leachables experiment (based upon the 26 cm^2 field return sample) and the three other boundary conditions offset by the calculated ratios in order to represent a range of risk. Based upon the remaining surface area received from the degraded field sample, 93 cm^2 is unaccounted for of which the patient could have been exposed to. It is important to note that in the current PRI released biological testing of the System One device, no biological risks were identified for the newly manufactured foam and therefore no analysis was conducted for foam that was not degraded.

This initial exposure scenario also incorporated a scalar multiplier ratio for 1/3 (8 hours/24 hours) to account for an average CPAP usage of 8 hours per day. In reality patients are able to use devices for longer or shorter durations and thus could be exposed to higher or lower concentrations depending upon usage of the device.

Exposure scenarios 1-4 as labeled in Tables 9-10 were calculated based upon the ratio conversions to account for 26, 11.1, 93, and 119 cm^2 of foam exposure respectively and modified by 0.75 (75%) for oral exposure and 0.43 (43%) for inhalational exposure. For example if a compound was detected at a concentration of 0.010 mg, it was first multiplied by either 0.75 or 0.43, then multiplied by the scenario scalar ratios. Finally, the adjusted inhalational and oral exposures were modified to account for the average use duration of a CPAP device for 8 hours per night (multiplication by 1/3).

It is important to note that MOS calculations were based upon the inhalational and oral distribution modifiers after exposure to the various chemicals detected in the degraded foam field sample. Although every effort was made to represent a realistic clinical scenario with physiological modeling as the basis for deposition of particulates and an average usage of 8 hours per night, there are limitations to these calculations. Based upon ICH M7 guidelines for a device that is used over the lifetime of the patient, the mutagenic/carcinogenic impurities limit was utilized in the unknown compound analysis in order to encompass worst-case scenario and be inclusive of the probable degradative by-products of PE-PUR (see Appendix 2).

Tables 11-14 include the final inhalational and oral exposure calculations and the margin of safety (MOS) values for each compound for both the 30 kg and 70 kg patient populations. Scenario 1 and MOS Scenario 1 are the actual experimental results from the leachables experiment conducted on the field foam sample.

Based upon the high level risk analysis of the compounds of concern and acknowledgement of the assumptions utilized for the toxicological risk assessment detailed in previous sections in this document, MOS calculations may be over or underestimated for each compound. In some human health exposure assessments, MOS calculations are considered concerning if they are under 100.[52,53] In order to be protective of all patient classes that utilize System One but inclusive of the limitations and assumptions this toxicological risk assessment is guided by, any compound with MOS < 10 was highlighted red and labeled as a compound of concern.

As shown in Tables 11-14 over 90% of the unknown compounds had MOS values less than 10 in each exposure scenario detailed in Table 8 for both 30 kg and 70 kg patient populations for oral and inhalational routes of exposure. Furthermore, nickel and diethylene glycol had MOS values less than 10 for 30 kg patient populations for both exposure scenarios. Nickel MOS was less than 10 for 30 kg patient populations via inhalational exposure. Over 90% of the unknown compounds were at unacceptable exposure levels when risk assessed using mutagenic/carcinogenic ICH M7 boundary conditions of 1.5 µg/day for lifetime exposure.

Table 9.PE-PUR Foam Particulates- Oral Exposure Toxicological Calculations

Compound	Scenario 1 mg Actual Experimental	Scenario 2 mg	Secnario 3 mg	Scenario 4 mg	NOAEL (mg/kg/day)	ICH M7 Mutagenic/ Carcinogenic Impurities mg[a]	TTC Class III µg/kg/day[b]
antimony	0.0001	0.00003	0.0003	0.0003	0.0004[78]	N/A	N/A
nickel	0.0001	0.00004	0.0003	0.0004	0.02[79]	N/A	N/A
diethylene glycol	0.18	0.07	0.66	0.84	0.3[80]	N/A	N/A
Unknown 1	0.12	0.05	0.43	0.55	N/A	0.0015	1.5
Unknown 2	0.95	0.38	3.43	4.38	N/A	0.0015	1.5
Unknown 3	0.03	0.01	0.10	0.13	N/A	0.0015	1.5
Unknown 4	0.59	0.24	2.12	2.71	N/A	0.0015	1.5
Unknown 5	0.31	0.13	1.13	1.44	N/A	0.0015	1.5
Unknown 6	0.01	0.01	0.05	0.06	N/A	0.0015	1.5
Unknown 7	0.02	0.01	0.07	0.09	N/A	0.0015	1.5
Unknown 8	0.02	0.01	0.07	0.09	N/A	0.0015	1.5
Unknown 9	0.02	0.01	0.06	0.08	N/A	0.0015	1.5
Unknown 10	0.01	0.01	0.05	0.07	N/A	0.0015	1.5
Unknown 11	0.42	0.17	1.51	1.92	N/A	0.0015	1.5
Unknown 12	0.25	0.1	0.90	1.14	N/A	0.0015	1.5
Unknown 13	0.01	0.004	0.04	0.05	N/A	0.0015	1.5
Unknown 14	0.06	0.03	0.23	0.30	N/A	0.0015	1.5
Unknown 15	0.16	0.06	0.56	0.72	N/A	0.0015	1.5
Unknown 16	0.09	0.03	0.31	0.39	N/A	0.0015	1.5
Unknown 17	0.006	0.003	0.02	0.03	N/A	0.0015	1.5
Unknown 18	0.03	0.01	0.11	0.14	N/A	0.0015	1.5
Unknown 19	0.02	0.01	0.06	0.07	N/A	0.0015	1.5

a ICH M7 2018 Guidance value for an individual impurity for lifetime exposure (> 10 years)

b Cramer Class III compound, resulting in 0.045 mg/day for 30 kg patient and 0.105 mg/day for 70 kg patient

Table 10.PE-PUR Foam Particulates- Inhalational Exposure Toxicological Calculations

Compound	Scenario 1 mg Actual Experimental	Scenario 2 mg	Scenario 3 mg	Scenario 4 mg	NOAEC (mg/m^3)	ICH M7 Mutagenic/ Carcinogenic Impurities[a]	TTC Class III ug/kg/day[b]
antimony	0.00004	0.00002	0.0002	0.0002	0.0002[78]	N/A	N/A
nickel	0.00006	0.00002	0.0002	0.0003	0.00004[79]	N/A	N/A
diethylene glycol	0.10	0.04	0.38	0.48	0.1[75]	N/A	N/A
Unknown 1	0.07	0.03	0.25	0.31	N/A	0.0015	1.5
Unknown 2	0.55	0.22	1.97	2.51	N/A	0.0015	1.5
Unknown 3	0.02	0.01	0.06	0.08	N/A	0.0015	1.5
Unknown 4	0.34	0.14	1.22	1.56	N/A	0.0015	1.5
Unknown 5	0.18	0.07	0.65	0.83	N/A	0.0015	1.5
Unknown 6	0.01	0.003	0.03	0.04	N/A	0.0015	1.5
Unknown 7	0.01	0.005	0.04	0.05	N/A	0.0015	1.5
Unknown 8	0.01	0.005	0.04	0.05	N/A	0.0015	1.5
Unknown 9	0.01	0.004	0.03	0.04	N/A	0.0015	1.5
Unknown 10	0.01	0.003	0.03	0.04	N/A	0.0015	1.5
Unknown 11	0.24	0.10	0.86	1.10	N/A	0.0015	1.5
Unknown 12	0.14	0.06	0.51	0.66	N/A	0.0015	1.5
Unknown 13	0.01	0.00	0.02	0.03	N/A	0.0015	1.5
Unknown 14	0.04	0.01	0.13	0.17	N/A	0.0015	1.5
Unknown 15	0.09	0.04	0.32	0.41	N/A	0.0015	1.5
Unknown 16	0.05	0.02	0.18	0.22	N/A	0.0015	1.5
Unknown 17	0.00	0.00	0.01	0.02	N/A	0.0015	1.5
Unknown 18	0.02	0.01	0.06	0.08	N/A	0.0015	1.5
Unknown 19	0.01	0.004	0.03	0.04	N/A	0.0015	1.5

a ICH M7 2018 Guidance value for an individual impurity for lifetime exposure (> 10 years)

b Cramer Class III compound, resulting in 0.045 mg/day for 30 kg patient and 0.105 mg/day for 70 kg patient

65 Toxicology Excellence for Risk Assessment OARS Workplace Environmental Exposure Level (WEEL) for DEG modified by taking 1% of inhalational limit in order to be protective of 30 kg patient population- this modification of 1% of an established health based occupational level approach was previously approved in FDA pre-submission meetings with Philips Respironics Inc.

70 Nickel is a reasonably anticipated human carcinogen via inhalational exposure and therefore 0.04 µg/m3 per day represents a theoretical lifetime risk of no more than a one in one hundred thousand chance of developing cancer.

Table 11. Toxicological Margin of Safety 30 kg – Oral Endpoints, ICH M7[58]

Compound	Scenario 1 mg	MOS Scenario 1	Scenario 2 mg	MOS Scenario 2	Scenario 3 mg	MOS Scenario 3	Scenario 4 mg	MOS Scenario 4
antimony	0.0001	160	0.00003	400	0.0003	44	0.0003	35
nickel	0.0001	6486	0.00004	16216	0.0003	1802	0.0004	1410
diethylene glycol	0.18	49	0.07	123	0.66	14	0.84	11
Unknown 1	0.12	≤ 0.6	0.05	≤ 0.6	0.43	≤ 0.6	0.55	≤ 0.6
Unknown 2	0.95	≤ 0.6	0.38	≤ 0.6	3.43	≤ 0.6	4.38	≤ 0.6
Unknown 3	0.03	≤ 0.6	0.01	≤ 0.6	0.10	≤ 0.6	0.13	≤ 0.6
Unknown 4	0.59	≤ 0.6	0.24	≤ 0.6	2.12	≤ 0.6	2.71	≤ 0.6
Unknown 5	0.31	≤ 0.6	0.13	≤ 0.6	1.13	≤ 0.6	1.44	≤ 0.6
Unknown 6	0.01	≤ 0.6	0.01	≤ 0.6	0.05	≤ 0.6	0.06	≤ 0.6
Unknown 7	0.02	≤ 0.6	0.01	≤ 0.6	0.07	≤ 0.6	0.09	≤ 0.6
Unknown 8	0.02	≤ 0.6	0.01	≤ 0.6	0.07	≤ 0.6	0.09	≤ 0.6
Unknown 9	0.02	≤ 0.6	0.01	≤ 0.6	0.06	≤ 0.6	0.08	≤ 0.6
Unknown 10	0.01	≤ 0.6	0.01	≤ 0.6	0.05	≤ 0.6	0.07	≤ 0.6
Unknown 11	0.42	≤ 0.6	0.17	≤ 0.6	1.51	≤ 0.6	1.92	≤ 0.6
Unknown 12	0.25	≤ 0.6	0.1	≤ 0.6	0.90	≤ 0.6	1.14	≤ 0.6
Unknown 13	0.01	≤ 0.6	0.004	≤ 0.6	0.04	≤ 0.6	0.05	≤ 0.6
Unknown 14	0.06	≤ 0.6	0.03	≤ 0.6	0.23	≤ 0.6	0.30	≤ 0.6
Unknown 15	0.16	≤ 0.6	0.06	≤ 0.6	0.56	≤ 0.6	0.72	≤ 0.6
Unknown 16	0.09	≤ 0.6	0.03	≤ 0.6	0.31	≤ 0.6	0.39	≤ 0.6
Unknown 17	0.006	≤ 0.6	0.003	≤ 0.6	0.02	≤ 0.6	0.03	≤ 0.6
Unknown 18	0.03	≤ 0.6	0.01	≤ 0.6	0.11	≤ 0.6	0.14	≤ 0.6
Unknown 19	0.02	≤ 0.6	0.01	≤ 0.6	0.06	≤ 0.6	0.07	≤ 0.6

Table 12. Toxicological Margin of Safety 70 kg- Oral Endpoints ICH M7[58]

Compound	Scenario 1 mg	MOS Scenario 1	Scenario 2 mg	MOS Scenario 2	Scenario 3 mg	MOS Scenario 3	Scenario 4 mg	MOS Scenario 4
antimony	0.0001	373	0.00003	933	0.0003	104	0.0003	81
nickel	0.0001	15135	0.00004	37837	0.0003	4202	0.0004	3290
diethylene glycol	0.18	114	0.07	287	0.66	32	0.84	25
Unknown 1	0.12	≤ 0.6	0.05	≤ 0.6	0.43	≤ 0.6	0.55	≤ 0.6
Unknown 2	0.95	≤ 0.6	0.38	≤ 0.6	3.43	≤ 0.6	4.38	≤ 0.6
Unknown 3	0.03	≤ 0.6	0.01	≤ 0.6	0.10	≤ 0.6	0.13	≤ 0.6
Unknown 4	0.59	≤ 0.6	0.24	≤ 0.6	2.12	≤ 0.6	2.71	≤ 0.6
Unknown 5	0.31	≤ 0.6	0.13	≤ 0.6	1.13	≤ 0.6	1.44	≤ 0.6
Unknown 6	0.01	≤ 0.6	0.01	≤ 0.6	0.05	≤ 0.6	0.06	≤ 0.6
Unknown 7	0.02	≤ 0.6	0.01	≤ 0.6	0.07	≤ 0.6	0.09	≤ 0.6
Unknown 8	0.02	≤ 0.6	0.01	≤ 0.6	0.07	≤ 0.6	0.09	≤ 0.6
Unknown 9	0.02	≤ 0.6	0.01	≤ 0.6	0.06	≤ 0.6	0.08	≤ 0.6
Unknown 10	0.01	≤ 0.6	0.01	≤ 0.6	0.05	≤ 0.6	0.07	≤ 0.6
Unknown 11	0.42	≤ 0.6	0.17	≤ 0.6	1.51	≤ 0.6	1.92	≤ 0.6
Unknown 12	0.25	≤ 0.6	0.1	≤ 0.6	0.90	≤ 0.6	1.14	≤ 0.6
Unknown 13	0.01	≤ 0.6	0.004	≤ 0.6	0.04	≤ 0.6	0.05	≤ 0.6
Unknown 14	0.06	≤ 0.6	0.03	≤ 0.6	0.23	≤ 0.6	0.30	≤ 0.6
Unknown 15	0.16	≤ 0.6	0.06	≤ 0.6	0.56	≤ 0.6	0.72	≤ 0.6
Unknown 16	0.09	≤ 0.6	0.03	≤ 0.6	0.31	≤ 0.6	0.39	≤ 0.6
Unknown 17	0.006	≤ 0.6	0.003	≤ 0.6	0.02	≤ 0.6	0.03	≤ 0.6
Unknown 18	0.03	≤ 0.6	0.01	≤ 0.6	0.11	≤ 0.6	0.14	≤ 0.6
Unknown 19	0.02	≤ 0.6	0.01	≤ 0.6	0.06	≤ 0.6	0.07	≤ 0.6

Table 13. Toxicological Margin of Safety 30 kg – Inhalational Endpoints*

Compound	Scenario 1 mg	MOS Scenario 1	Scenario 2 mg	MOS Scenario 2	Scenario 3 mg	MOS Scenario 3	Scenario 4 mg	MOS Scenario 4
antimony	0.00004	40	0.00002	99	0.0002	11	0.0002	8.7
nickel	0.00006	6.0	0.00002	14.9	0.0002	1.6	0.0003	1.3
diethylene glycol	0.10	8.2	0.04	20.5	0.38	2.3	0.48	1.8
Unknown 1	0.07	0.3	0.03	0.6	0.25	0.07	0.31	0.05
Unknown 2	0.55	0.03	0.22	0.08	1.97	0.009	2.51	0.007
Unknown 3	0.02	1.0	0.01	2.6	0.06	0.3	0.08	0.2
Unknown 4	0.34	0.05	0.14	0.1	1.22	0.01	1.56	0.01
Unknown 5	0.18	0.09	0.07	0.2	0.65	0.03	0.83	0.02
Unknown 6	0.01	2.2	0.003	5.5	0.03	0.6	0.04	0.5
Unknown 7	0.01	1.5	0.005	3.8	0.04	0.4	0.05	0.3
Unknown 8	0.01	1.5	0.005	3.7	0.04	0.4	0.05	0.3
Unknown 9	0.01	1.8	0.004	4.5	0.03	0.5	0.04	0.4
Unknown 10	0.01	2.1	0.003	5.2	0.03	0.6	0.04	0.5
Unknown 11	0.24	0.07	0.10	0.2	0.86	0.02	1.10	0.02
Unknown 12	0.14	0.1	0.06	0.3	0.51	0.03	0.66	0.03
Unknown 13	0.01	2.9	0.00	7.2	0.02	0.8	0.03	0.6
Unknown 14	0.04	0.5	0.01	1.1	0.13	0.1	0.17	0.1
Unknown 15	0.09	0.2	0.04	0.5	0.32	0.05	0.41	0.04
Unknown 16	0.05	0.3	0.02	0.9	0.18	0.1	0.22	0.08
Unknown 17	0.00	4.7	0.00	11.9	0.01	1.3	0.02	1.0
Unknown 18	0.02	0.9	0.01	2.4	0.06	0.3	0.08	0.2
Unknown 19	0.01	1.8	0.004	4.6	0.03	0.5	0.04	0.4

*18562-1:2017 thresholds for unknown VOCs of permanent contact duration were utilized- 40 µg/day per Clause 7.4 which equates to an excess cancer risk of 1 in 2.7 × 10–4 . This limit was modified for a 30 kg patient utilizing a ratio calculation (30 kg/70 kg modifier), which is equivalent to 17 µg/day.

Table 14. Toxicological Margin of Safety 70 kg – Inhalational Endpoints*

Compound	Scenario 1 mg	MOS Scenario 1	Scenario 2 mg	MOS Scenario 2	Scenario 3 mg	MOS Scenario 3	Scenario 4 mg	MOS Scenario 4
antimony	0.00004	93	0.00002	233	0.0002	26	0.0002	20
nickel	0.0006	13.9	0.0002	34.9	0.002	3.9	0.003	3.0
diethylene glycol	0.10	19	0.04	48	0.38	5.3	0.48	4.1
Unknown 1	0.07	0.5	0.03	1.5	0.25	0.2	0.31	0.1
Unknown 2	0.55	0.07	0.22	0.2	1.97	0.02	2.51	0.02
Unknown 3	0.02	2.4	0.01	6.0	0.06	0.7	0.08	0.5
Unknown 4	0.34	0.1	0.14	0.3	1.22	0.03	1.56	0.03
Unknown 5	0.18	0.2	0.07	0.6	0.65	0.06	0.83	0.05
Unknown 6	0.01	5.2	0.003	13	0.03	1.5	0.04	1.1
Unknown 7	0.01	3.5	0.005	8.8	0.04	1.0	0.05	0.8
Unknown 8	0.01	3.5	0.005	8.6	0.04	1.0	0.05	0.7
Unknown 9	0.01	4.3	0.004	10.6	0.03	1.2	0.04	0.9
Unknown 10	0.01	4.5	0.003	12.2	0.03	1.4	0.04	1.0
Unknown 11	0.24	0.2	0.10	0.4	0.86	0.05	1.10	0.04
Unknown 12	0.14	0.2	0.06	0.7	0.51	0.08	0.66	0.06
Unknown 13	0.01	6.8	0.00	17.0	0.02	1.9	0.03	1.5
Unknown 14	0.04	1.0	0.01	2.7	0.13	0.3	0.17	0.2
Unknown 15	0.09	0.5	0.04	1.1	0.32	0.1	0.41	0.1
Unknown 16	0.05	0.8	0.02	2.0	0.18	0.2	0.22	0.2
Unknown 17	0.00	11.2	0.00	28	0.01	3.1	0.02	2.4
Unknown 18	0.02	2.2	0.01	5.6	0.06	0.6	0.08	0.5
Unknown 19	0.01	4.3	0.004	10.7	0.03	1.2	0.04	0.9

*18562-1:2017 thresholds for unknown VOCs of permanent contact duration were utilized- 40 µg/day per Clause 7.4 which equates to an excess cancer risk of 1 in 2.7 × 10−4 . This limit was modified for a 30 kg patient utilizing a ratio calculation (30 kg/70 kg modifier), which is equivalent to 17 µg/day.

9.2 Estimated Actual Exposure- Pathway B

A second pathway for exposure and toxicological risk was explored, independent of particulate size in order to account for the magnitude of unknowns occurring with this situation. In order to encompass another facet of biological risk, calculations assuming equal distribution of the detected leachable analytes were conducted and then used in various exposure scenarios. These are represented below in Table 15 and assume concentration after calculation of concentration per cm^2. For example, if diethylene glycol was detected at 10 µg in the E/L experiment, it was first divided by 26 cm^2 (the entire field sample) to get a concentration of 0.38 $\mu g/cm^2$ prior to undergoing the foam percentage and surface area multipliers. Similar to Pathway A, in this scenario it should be noted that the detected concentration for each analyte is assumed to be the concentration per day available to the patient, which is the worst-case assumption. No adjustment for CPAP use per night or particulate distribution were assumed in this analysis. Furthermore, only inhalational exposure was considered as the tolerable exposure limits for an inhalational mode of exposure are in general lower than those for oral exposure, and would encompass a worst-case scenario.

Table 15. Exposure Scenarios and Boundary Conditions Pathway B

Exposure Scenario for Calculations	Boundary Condition	Foam% Reaches Patient	Foam Surface Area Available (cm^2)	Final Scalar
Scenario 1	All foam lost (100%)	100	119	119
Scenario 2	Severe foam degradation, majority lost (80%)	100	95.2	95.2
Scenario 3	Some foam degradation, some lost (10%)	100	11.9	11.9
Scenario 4	All foam lost (100%)	50	119	59.5
Scenario 5	Severe foam degradation, majority lost (80%)	50	95.2	47.6
Scenario 6	Some foam degradation, some lost (10%)	50	11.9	5.95
Scenario 7	All foam lost (100%)	25	119	29.8
Scenario 8	Severe foam degradation, majority lost (80%)	25	95.2	23.8
Scenario 9	Some foam degradation, some lost (10%)	25	11.9	2.98

Based upon ICH M7 guidelines for a device that is used over the lifetime of the patient, the mutagenic/carcinogenic impurities limit was again considered in the unknown compound analysis. This limit also coincides with the limits of the probable degradative by-products of PE-PUR, which include health based thresholds for diisocyanate exposure[81] (see Appendix 2).

Table 16 represents the exposure calculations after modification to account for amount of foam lost and amount of foam that reaches the patient. Table 17 includes the margin of safety (MOS) values for the adult patient population (70 kg).

Based upon the high level risk analysis of the compounds of concern and acknowledgement of the assumptions utilized for the toxicological risk assessment detailed in previous sections in this document, MOS calculations may be over or underestimated for each compound. In some human health exposure assessments, MOS calculations are considered concerning if they are under 100.[52,53] In order to be protective of all patient classes that utilize System One but inclusive of the limitations and assumptions this toxicological risk assessment is guided by, any compound with MOS < 1 was highlighted red and any compound with MOS <10 but greater than 1 was labelled yellow. Both red and yellow compounds are of concern.

As shown in Table 17, all unknown compounds had MOS values less than 10 in each exposure scenario detailed in Table 15 for the 70 kg patient population for an inhalational route of exposure. This was based on a tolerable exposure of 7×10^{-5} mg/m^3 of a diisocyanate for an adult exposure. In the most likely clinical scenario of 25% of the foam reaches the patient after 10% degrades, the DEG, antimony, and nickel exposures are acceptable with MOS >10. MOS calculations for a 30 kg patient population were not conducted because they are a smaller weight and breathing volume, tolerable exposures are lower, and therefore anything that would be of concern for an adult would also apply to the 30 kg patient class.

Table 16. Exposure Calculations for Foam Lost and Foam Availability- Inhalational Tolerable Exposure

Compound	Concentration (Field Sample) mg	Amount/cm2 ug	TE ug/day INH	All Foam Lost	80% Foam Lost	10% Foam Lost	50% Foam Reaches Patient			25% Foam Reaches Patient		
	26 cm2			119 cm 2	95.2 cm2	11.9 cm2	119 cm 2	95.2 cm2	11.9 cm2	119 cm 2	95.2 cm2	11.9 cm2
antimony	0.00030	0.01154	4.0	1.4	1.1	0.1	0.7	0.5	0.1	0.3	0.3	0.0
nickel	0.00037	0.01423	0.8	1.7	1.4	0.2	0.8	0.7	0.1	0.4	0.3	0.0
DEG	0.73100	28.11538	2000.0	3345.7	2676.6	334.6	1672.9	1338.3	167.3	836.4	669.1	83.6
unknown1	0.47500	18.26923	1.5	2174.0	1739.2	217.4	1087.0	869.6	108.7	543.5	434.8	54.4
unknown2	3.81300	146.65385	1.5	17451.8	13961.4	1745.2	8725.9	6980.7	872.6	4363.0	3490.4	436.3
unknown3	0.11600	4.46154	1.5	530.9	424.7	53.1	265.5	212.4	26.5	132.7	106.2	13.3
unknown4	2.36000	90.76923	1.5	10801.5	8641.2	1080.2	5400.8	4320.6	540.1	2700.4	2160.3	270.0
unknown5	1.25200	48.15385	1.5	5730.3	4584.2	573.0	2865.2	2292.1	286.5	1432.6	1146.1	143.3
unknown6	0.05400	2.07692	1.5	247.2	197.7	24.7	123.6	98.9	12.4	61.8	49.4	6.2
unknown7	0.07900	3.03846	1.5	361.6	289.3	36.2	180.8	144.6	18.1	90.4	72.3	9.0
unknown8	0.08100	3.11538	1.5	370.7	296.6	37.1	185.4	148.3	18.5	92.7	74.1	9.3
unknown9	0.06600	2.53846	1.5	302.1	241.7	30.2	151.0	120.8	15.1	75.5	60.4	7.6
unknown10	0.05700	2.19231	1.5	260.9	208.7	26.1	130.4	104.4	13.0	65.2	52.2	6.5
unknown11	1.67300	64.34615	1.5	7657.2	6125.8	765.7	3828.6	3062.9	382.9	1914.3	1531.4	191.4
unknown12	0.99500	38.26923	1.5	4554.0	3643.2	455.4	2277.0	1821.6	227.7	1138.5	910.8	113.9
unknown13	0.04100	1.57692	1.5	187.7	150.1	18.8	93.8	75.1	9.4	46.9	37.5	4.7
unknown14	0.25900	9.96154	1.5	1185.4	948.3	118.5	592.7	474.2	59.3	296.4	237.1	29.6
unknown15	0.62700	24.11538	1.5	2869.7	2295.8	287.0	1434.9	1147.9	143.5	717.4	573.9	71.7
unknown16	0.34100	13.11538	1.5	1560.7	1248.6	156.1	780.4	624.3	78.0	390.2	312.1	39.0
unknown17	0.02500	0.96154	1.5	114.4	91.5	11.4	57.2	45.8	5.7	28.6	22.9	2.9
unknown18	0.12500	4.80769	1.5	572.1	457.7	57.2	286.1	228.8	28.6	143.0	114.4	14.3
unknown19	0.06500	2.50000	1.5	297.5	238.0	29.8	148.8	119.0	14.9	74.4	59.5	7.4

antimony RfC IRIS EPA 78

nickel 1 in 100,000 cancer risk, derived from nickel subsulfide EPA 79

DEG 1% OARS WEEL 75

unknown 1-19 ICH M7 2018 Guidance value for an individual impurity for lifetime exposure (> 10 years) and RfC for 2,4-2,6 toluene diisocyanate mixture are very similar 81

Table 17. MOS Calculations 70 kg for Foam Lost and Foam Availability- Inhalational Tolerable Exposure

Compound	All Foam Reaches Patient 70 kg MOS			50% Foam Reaches Patient 70 kg MOS			25% Foam Reaches Patient 70 kg MOS		
	119 cm 2	95.2 cm2	11.9 cm2	119 cm 2	95.2 cm2	11.9 cm2	119 cm 2	95.2 cm2	11.9 cm2
antimony	2.91	3.64	29.13	5.83	7.28	58.26	11.65	14.57	116.53
nickel	0.47	0.59	4.72	0.94	1.18	9.45	1.89	2.36	18.90
DEG	0.60	0.75	5.98	1.20	1.49	11.96	2.39	2.99	23.91
unknown1	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.03
unknown2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
unknown3	0.00	0.00	0.03	0.01	0.01	0.06	0.01	0.01	0.11
unknown4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01
unknown5	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01
unknown6	0.01	0.01	0.06	0.01	0.02	0.12	0.02	0.03	0.24
unknown7	0.00	0.01	0.04	0.01	0.01	0.08	0.02	0.02	0.17
unknown8	0.00	0.01	0.04	0.01	0.01	0.08	0.02	0.02	0.16
unknown9	0.00	0.01	0.05	0.01	0.01	0.10	0.02	0.02	0.20
unknown10	0.01	0.01	0.06	0.01	0.01	0.11	0.02	0.03	0.23
unknown11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01
unknown12	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.01
unknown13	0.01	0.01	0.08	0.02	0.02	0.16	0.03	0.04	0.32
unknown14	0.00	0.00	0.01	0.00	0.00	0.03	0.01	0.01	0.05
unknown15	0.00	0.00	0.01	0.00	0.00	0.01	0.00	0.00	0.02
unknown16	0.00	0.00	0.01	0.00	0.00	0.02	0.00	0.00	0.04
unknown17	0.01	0.02	0.13	0.03	0.03	0.26	0.05	0.07	0.52
unknown18	0.00	0.00	0.03	0.01	0.01	0.05	0.01	0.01	0.10
unknown19	0.01	0.01	0.05	0.01	0.01	0.10	0.02	0.03	0.20

10. APPENDIX 2 - LEACHABLES NOT INCLUDED IN TOXICOLOGICAL RISK ASSESSMENT

10.1 Leachables from PE-PUR Foam- Unexpected Chemistry

Multiple analytes were detected in the 0.9% NaCl extracts of the field sample PE-PUR foam at 37 °C for 72 h. Metals that were detected in the extract that are not expected from typical polyurethane synthesis and PUR chemistry are shown below in Tables 15-16. These were not toxicologically risk assessed and instead attributed to environmental or external factors with use of the device. Both field returns were from Thailand, which has been reported to have levels of arsenic, vanadium, chromium and lead in ground water.[82–86] The water source that served as the humidification for the CPAP systems is unknown, but because these metals are not typical organometallics, alkali metal salts, or typical catalyst agents utilized in PUR foam synthesis, they were not grouped as being degradative leachable products that reached the patient. Interestingly, polyurethane foams have actually been proposed as filters to remove groundwater contaminants such as arsenic.[87] Lead has been documented as an air pollutant in Thailand, and thus may be a contributing factor of the lead detected in the degrade PE-PUR foam.[88–90]

Table 15. Unexpected Metals from PE-PUR foam

Compound	Exposure Per Foam Sample 26 cm^2 (mg)	Typically included in PUR synthesis as a catalyst, alkali metal salts, agent, etc.?	Documented in Groundwater in Southeast Asia
arsenic	0.0003	No	Yes
vanadium	0.0005	No	Yes
chromium	0.0003	No	Yes
lead*	0.001	No	Yes

* Very low exposure limits of lead concentrations have not been fully explored and in general, there is no safe level of lead exposure[91], however the PE-PUR foam acting as a reservoir for environmental contaminants has is not evaluated in this risk assessment.

Table 16. Unexpected Compounds from PE-PUR foam

Compound	Exposure Per Foam Sample 26 cm^2 (mg)	Typically included in PUR synthesis as a catalyst, alkali metal salts, agent, etc.?	Documented Pharmaceutical?
pipemidic acid	0.457	No	Broad spectrum antibiotic for GI, biliary, and urinary infections[92]
5-methoxy AMT	0.209	No	Tryptamine derivative that affects serotonin receptor[93]

10.2Leachables from PE-PUR Foam- Low Toxicity Risk Based on Detected Amounts or Chemistry

Table 17 includes compounds that were detected in the PE-PUR degraded foam but were classified as a lower toxicity risk due to their tolerable exposure levels per day. Several tolerable exposure limits were calculated following methodology described in Section 5. All tolerable exposure levels or tolerable intake levels were at least one order of magnitude larger than the exposure detected from the foam sample. In order to focus the toxicological risk assessment on the compounds of concern and those of clinical significance, these analytes were not subjected to the full analysis.

Table 17. Lower Toxicity Risk from Degraded Foam

Compound	Exposure Per Foam Sample 26 cm^2 (mg)	Included in PUR synthesis as a catalyst, alkali metal salts, agent, etc.?	Tolerable Exposure (mg/day) (mg/m^3) or Toxicological Effects
calcium	0.213	No	1000-1300[94]
magnesium	0.030	Potential organometallic catalyst[95]	240-420[96]
manganese	0.003	No	1.5-2.3[97]
potassium	0.080	No	2300-3400[98]
aluminum	0.022	Potential organometallic catalyst[95]	1 mg/kg/day[99]
barium	0.007	Yes, organometallic catalyst[100]	0.2 mg/kg/day[101]
lauramide	0.020	Potential use as surfactant[102]	0.05 mg/kg/day[103]
erucamide	0.026	Potential use as foam stabilizer[104]	0.05 mg/kg/day[94]
acetone	0.0001	Potential use as a solvent[105]	5.9 mg/m^3 [106] Irritation of mucous membranes including nose and throat[107]
n-dimethyldodecanamide	0.023	Potential use as surfactant[108]	0.05 mg/kg/day[94]
bis (2-butoxyethyl) adipate	0.312	Yes, parent chemistry used in urethane intermediate reactions[109]	adipic acid parent chemistry- 19 mg/kg/day[110,111]
adipic anhydride	0.322	Yes, parent chemistry adipic acid used to	adipic acid parent chemistry- 19 mg/kg/day[110,111]

		synthesize polyester bonds[112,113]	

APPENDIX 2- POTENTIAL UNKNOWN COMPOUNDS

There were nineteen unidentified compounds detected in the leachables experiment from the PE-PUR field sample. The majority of these unknown compounds were detected via techniques that identify either semi-volatile or non-volatile compounds. Many of the unknowns detected revealed high levels of exposure (in mg), increasing the potential toxicological risk. Based upon the chemistry of PE-PUR and typical degradative by-products[9], the following chemical classes or their derivatives are proposed for the unknowns, ranked in increasing order of their toxicological potential:

- Adipate derivatives
- Adipic acid derivatives
- Long chain amides
- Polyol (ethylene glycol) derivatives
- Toluene diamine isomers
- Toluene diisocyanate isomers

There is potential for the nineteen unknowns to be lower toxicity analytes, even though toxicological best practice dictates unknown chemistries to be risk assessed as a worst-case scenario. This is a limitation of this risk assessment- it is possible that a subset of the unknown compounds are derivatives of adipate or adipic acid, which as a general chemical class have much higher tolerable exposure limits compared to toluene diamine or toluene diisocyanate isomers. Two adipic acid derivatives were positively identified in the leachable experiment, and thus there is potential for additional derivatives to be present in the unknown compounds. Long chain amides (i.e. erucamide, lauramide) were also positively identified as leachable analytes, and additional related compounds could be among the ninenteen unknowns. It is possible that these unknowns could result in MOS calculations above 10, which would affect the overall risk profile of exposure to degraded PE-PUR foam particulates. This risk profile would only affect the nineteen unknown compounds, it would not change the risk from the other identified analytes classified as a toxicity risk.

Although less toxic analytes were detected in the leachables experiment, there were several compounds identified that present a toxicological risk. Diethylene glycol was predicted as a degradative by-product and was detected in large amounts from the PE-PUR foam field sample. There is potential for other predicted degradative by-products such as toluene diamine and toluene diisocyanate to be present.

Toluene diamine

Toluene diamine isomers, such as toluene-2,4-diamine, are primarily used in the synthesis of polyurethane, various dyes, and heterocyclic compounds.[114,115] Figure 7 displays typical chemical structures of toluene diamine isomers.

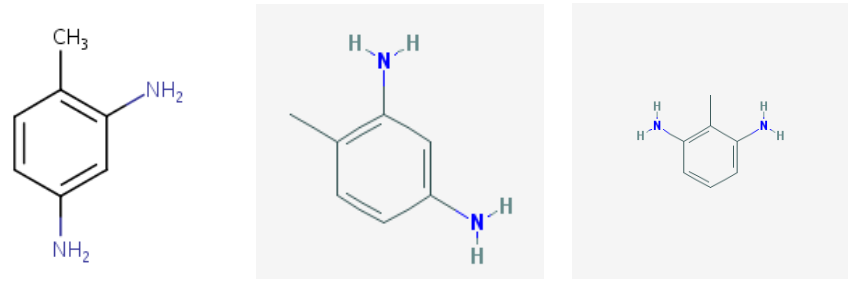

Figure 7. Representative chemical structures of various toluene diamine isomers

ADME: C14 labeled 2,4-diaminotoluene was administered to male Fisher rats via intraperitoneal injection. Blood and plasma radioactivity peaked at 1 hour and then decreased rapidly with 98.6% of the diamine excreted after 5 days via urination and defecation.[116] Distribution after exposure to diaminotoluenes varies depending upon the species, however the organs that contain the highest concentrations include the gastrointestinal tract, liver, kidneys, and adrenal glands.[117]

ACUTE TOXICITY: CFY rats were dosed with 0, 64, 100, 160, and 250 mg/kg bodyweight of toluene-2,5-diamine by oral gavage. Ataxia, increased salivation, piloerection, and lethargy were noticed in all dose groups after administration and 3 males died at the 64 mg/kg dose.[118] No NOAEL or NOEL value was proposed.

CHRONIC/SUB-CHRONIC TOXICITY: Sub-chronic toxicity studies reveal that 2,6-diaminotoluene fed to rats in their diet over a course of 13 weeks caused lower weight gain at 100 ppm in male rats and 1000 ppm in female rats.[119] This same type of effect was also noted in mice. Rats developed thyroid hyperplasias at 3000 ppm.[119] A 7 week study with both rats and mice administered 2,4-diaminotoluene also revealed lower body weights at 75 mg/kg bodyweight per day, elevated hematopoiesis, and liver deviations.[119]

REPRODUCTIVE/DEVELOPMENTAL TOXICITY: 2,4 toluenediamine was shown to effect mating frequency and infertile mating rate of Sprague-Dawley rats at high dose exposures.[120] Maternal toxicity after oral exposure to *o*-toluenediamine was noted in Sprague-Dawley rats at 300 mg/kg bodyweight per day and 100 mg/kg per day in rabbits.[121]

GENOTOXICITY/CARCINOGENICITY: Multiple Ames' tests and in vivo studies have confirmed 2,4, 2,5 and 2,6 diaminotoluene are mutagenic.[119,122–124] The CDC has labeled diaminotoluenes in general as probably carcinogens, and NIOSH has labeled 2,4-diaminotoluene as a probable human carcinogen.[125,126] Additional animal toxicity studies have confirmed that various diaminotoluene isomers possess different carcinogenic properties.[127,128]

A chronic reference dose (RfD) for human exposure to 2,6 diaminotoluene has been proposed by the U.S. EPA at 0.03 mg/kg per day.[128] This RfD takes into account the potential for carcinogenicity. An MAK of 0.1 mg/m^3 has been established for 2,4-diaminetoluene inhalation.[129]

Toluene diisocyanate isomers:

Toluene diisocyanate isomers such as 2,4-toluene diisocyanate are chemical intermediates utilized in the production of polyurethane products.[130] Figure 7 reveals some typical chemical structures of toluene diisocyanate isomers.

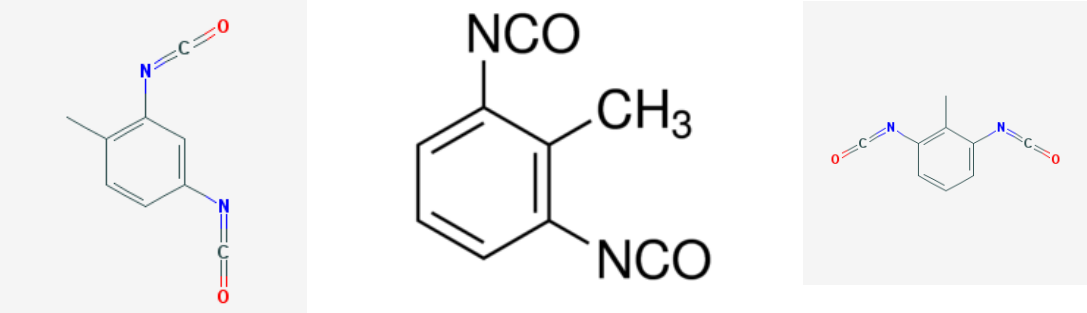

Figure 8. Chemical structures of toluene diisocyanate isomers

ADME: Toluene 2,4- diisocyanate was labeled with C14 and in Fischer 344 rats, 48 h post oral dosing 81% of radioactivity was found in the feces, 8% was found in urine and the remainder collected in tissues/gastrointestinal tract.[131] This was in contrast to the inhalation exposure of Fischer 344 rats to 14.2 mg/m^3 of C14 labeled toluene 2,4-diisocyante where the percentages after 48 h were 47, 15, and 34 % in the feces, urine, and GI tissues.[131] These results suggest different metabolism kinetics for the diisocyanate depending upon its route of administration, with more chemical passing through the GI tissues. A case study of 11 chronically exposed occupational workers to both 2,4 and 2,6- toluene diisocyanate from flexible polyurethane foam production plants has revealed differences in metabolism based upon exposure. Chronic exposure of workers from 0.0004 to 0.12 mg/m^3 of the various toluene diisocyanates produced

prolonged half-lives of the compound in plasma compared to people who have incurred short-term exposure.[131] Additional data suggests that inhalation of toluene diisocyanates range from pulmonary irritation to immunological sensitization and that uptake on the blood is dependent upon exposure concentration.[132] Furthermore, 15 plants have reported bronchitis, bronchospasm, and upper respiratory irritation with exposure to toluene diisocyanate and a recommended exposure level for humans was suggested to be 0.01 ppm.[133]

ACUTE TOXICITY: Acute exposure of mice to 10 sensitizing agents including 2,4 toluene diisocyanate produced nasal lesions and a decreased respiratory rate at 0.4 ppm.[134] Additional acute toxicity tests reveal that toluene diisocyanates are irritants and sensitizers, and the severity of additional pathologies is dependent upon route of administration with inhalation effects predominant among the pathologies.[135]

CHRONIC/SUB-CHRONIC TOXICITY: Guinea pigs exposed to 29 ppb of toluene diisocyanate vapors for 20 consecutive days showed effects on tracheal smooth muscle, however a NOAEL was not established.[136]

REPRODUCTIVE/DEVELOPMENTAL TOXICITY: There is limited evidence of minimal fetotoxicity but no reproductive toxicity in rats when exposed to inhaled toluene diisocyanate.[137]

GENOTOXICITY/CARCINOGENICITY: Toluene diisocyanate has been designated as carcinogenic via the oral route due to its conversion to toluene diamine in the gastrointestinal tract. However, it is typically labeled as non-carcinogenic via inhalation.[138] In vivo and in vitro tests indicate both mutagenic and non-mutagenic outcomes.[135]

A reference concentration of 0.07µg/m^3 has been recommended for toluene diisocyanates by the EPA IRIS risk assessment.[81] The U.S. Office of Environmental Health Hazard Assessment (OEHHA) risk analysis recommends a REL of 0.08 µg/m^3 to toluene diisocyanates. These values were used to derive TE limits for both the 30 kg and 70 kg patient populations using the appropriate inhalation volumes, which translates into 0.0016 mg and 0.00003 mg respectively.

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From: s22
To: s22
Cc: s22 ; s22 ; s22
Subject: RE: Philips CPAP/BPAP/Ventilator Recall - potential infringement notices [SEC=OFFICIAL, ACCESS=Legal-Privilege]
Date: Tuesday, 31 May 2022 8:34:22 AM
Attachments: image001.png
image002.png
image003.gif
image004.png
image005.gif
[D22-5527525] Philips Electronics Australia Ltd - Infringement notice- ARTG 327227.DOCX
[D22-5527525] Philips Electronics Australia Ltd - Infringement notice- ARTG 327227.tr5
[D22-5526553] Philips PE-PUR Infringement notices - DRAFT - Cover letter.DOCX
[D22-5526553] Philips PE-PUR Infringement notices - DRAFT - Cover letter.tr5

Hi s22

As just discussed, attached is the cover letter and one of the 10 infringement notices; there is one infringement notice for each ARTG entry that has devices with the defective foam. All of the infringement notices are found in E21-327521.

For your further consideration is the date (26 or 28 April 2021?) that you reasonably believe Philips Australia became aware of the devices being defective; this will be reflected in the cover letter and the infringement notices. A summary is provided below but happy to speak to you further regarding this.

Thanks

s22

Concerning conditions of inclusion, providing required information and if there was continued supply (or use) of knowingly defective goods

- The recall action impacted all product manufactured prior to 26 April 2021.
- On 26 April 2021 Philips published a statement in which they identified the risk to users of these devices with degradation of foam (attached).
- The 26 April announcement was followed on by a letter dated 28 April from Philips to their Australian customers advising of the foam degradation issue (attributing it to multiple factors) and that they would be in contact again as they address the issue - D21-2723486.
- This is the webpage where Philips Australia's announcements have been published https://www.philips.com.au/healthcare/e/sleep/communications/src-update?_ga=2.162671036.1209090897.1620711304-797588883.1586916367&_gl=1*1o8i7pq*_ga*Nzk3NTg4ODgzLjE1ODY5MTYzNjc.*_ga_2NMXNNS6LE*MTYyMDcxMTMwNC4xMC4xLjE2MjA3MTE3MTEuNjA).
- The earlier published advice about Philips applying a 'ship hold' to all stock has been superseded /overwritten with this current information, which I note commences with –

  "On April 26, 2021, Philips globally provided an important update to the market regarding proactive efforts to address identified issues with a component in certain products of our Sleep & Respiratory Care portfolio".
- On 28 June, Philips Australia referred to this earlier published advice as a 'ship hold' announcement (see D21-2783288 – row 5 in the table).
- We have no evidence that Philips Australia continued to supply affected units after 26 April.

s22
Director – Devices Post Market Reforms & Reviews Section

Medical Devices and Product Quality Division | Health Products Regulation Group
Medical Devices Surveillance Branch

Australian Government Department of Health
T: s22 M: s22 | E: s22 @health.gov.au
Location: Perth
PO Box 100, Woden ACT 2606, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: s22
Sent: Friday, 27 May 2022 9:11 AM
To: s22 @health.gov.au>
Cc: s22 @Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: Philips CPAP/BPAP/Ventilator Recall - potential infringement notices [SEC=OFFICIAL, ACCESS=Legal-Privilege]

Hi s22

As previously discussed, the INs have been drafted as per your instructions.

I would be grateful for your consideration on the date (26 or 28 April 2021?) that you reasonably believe Philips Australia became aware of the devices being defective to enable final drafts for each of the INs to be generated. A summary is provided below.

Thanks

s22

Concerning conditions of inclusion, providing required information and if there was continued supply (or use) of knowingly defective goods

- The recall action impacted all product manufactured prior to 26 April 2021.
- On 26 April 2021 Philips published a statement in which they identified the risk to users of these devices with degradation of foam (attached).
- The 26 April announcement was followed on by a letter dated 28 April from Philips to their Australian customers advising of the foam degradation issue (attributing it to multiple factors) and that they would be in contact again as they address the issue - D21-2723486.
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- The earlier published advice about Philips applying a 'ship hold' to all stock has been superseded /overwritten with this current information, which I note commences with –

  "On April 26, 2021, Philips globally provided an important update to the market regarding proactive efforts to address identified issues with a component in certain products of our Sleep & Respiratory Care portfolio".
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Director – Devices Post Market Reforms & Reviews Section

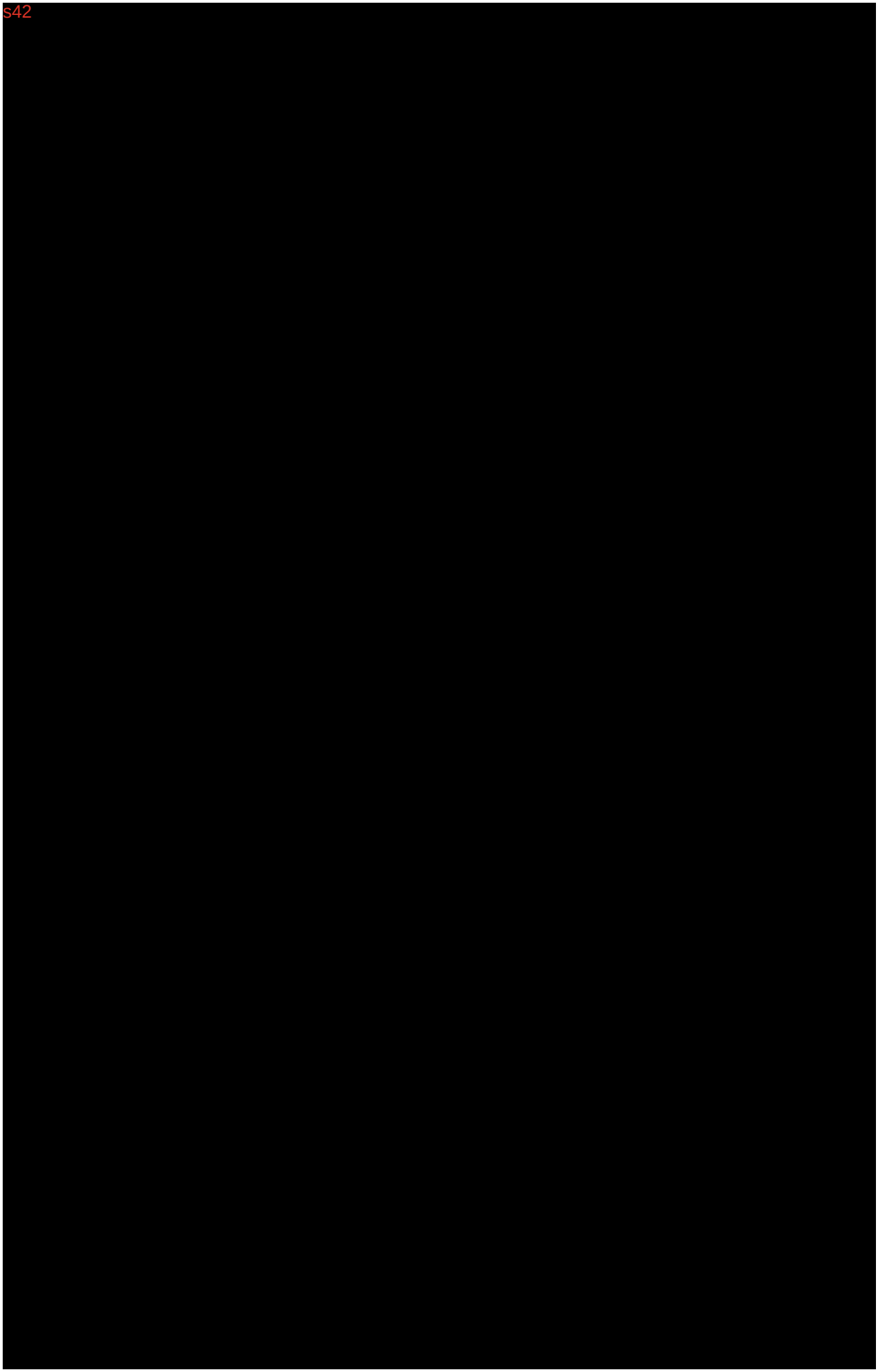
Medical Devices and Product Quality Division | Health Products Regulation Group
Medical Devices Surveillance Branch

Australian Government Department of Health
T: s22 M: s22 | E: s22 @health.gov.au
Location: Perth
PO Box 100, Woden ACT 2606, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

s42

s42



s42

[redacted]

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