I'm Melinda Irwin. I'm a professor in the School of Public Health with Vasilis and also deputy Director for the Cancer Center, overseeing population sciences research, which focuses on lifestyle, genetic and environmental risk factors for cancer etiology and outcomes. So we’re delighted today to have the Yale and National International expert in environmental carcinogens and cancer speak to us.
who is also he’s the Susan Dwight Bliss Professor of Environmental Health Sciences as well as Chair of our Department of Environmental Health Sciences in the Yale School of Public Health. He received his PhD in Biochemical Pharmacology from the University of Ioannina in Greece. He then trained in gene environment interactions, molecular toxicology and pharmacogenetics at the Department of Environmental Health and the College of Medicine at University of Cincinnati. He joined Yale almost 10 years ago in 2014 from the University.
00:01:09.368 --> 00:01:11.953 of Colorado School of Pharmacy,
NOTE Confidence: 0.6866663
00:01:11.960 --> 00:01:14.158 where he rose to the ranks to
NOTE Confidence: 0.6866663
00:01:14.158 --> 00:01:16.406 become professor and director of the
NOTE Confidence: 0.6866663
00:01:16.406 --> 00:01:18.476 toxicology graduate program and was
NOTE Confidence: 0.6866663
00:01:18.476 --> 00:01:20.440 professor also of ophthalmology.
NOTE Confidence: 0.6866663
00:01:20.440 --> 00:01:22.916 He’s established an internationally
NOTE Confidence: 0.6866663
00:01:22.916 --> 00:01:26.011 recognized research program that’s been
NOTE Confidence: 0.6866663
00:01:26.011 --> 00:01:28.459 continuously funded by NIH since 1997,
NOTE Confidence: 0.6866663
00:01:28.459 --> 00:01:30.554 and his research interests include
NOTE Confidence: 0.6866663
00:01:30.554 --> 00:01:32.754 the etiology and molecular mechanisms
NOTE Confidence: 0.6866663
00:01:32.754 --> 00:01:34.602 of environmentally induced human
NOTE Confidence: 0.6866663
00:01:34.602 --> 00:01:36.912 disease such as liver disease,
NOTE Confidence: 0.6866663
00:01:36.920 --> 00:01:40.232 obesity and diabetes, cancer,
NOTE Confidence: 0.6866663
00:01:40.232 --> 00:01:42.716 and neurodegenerative diseases.
NOTE Confidence: 0.6866663
00:01:42.720 --> 00:01:45.560 Vasilis is the director of the N i.e.
NOTE Confidence: 0.6866663
HS funded P 42, Yale Superfund Research Center and also the director of the NI AAA funded R24 Resource Center for Mouse Models and Metabolomics tools to investigate alcohol metabolism and tissue injury. This is really does translational research from preclinical work to clinical to community engaged research focusing on environmental risk factors in cancer. Thank you.

Thank you very much, Melinda.
And Melinda, thank you very much for the impressive introduction.

I don’t know if I anyway, so I wish. Let me start. Actually the talk of today’s lecture is exploring environmental health, the insights through our P42 Centre Research Centre on emerging contaminants and their effects on cancer. So one of the concerns that we have is, you know that 50% or maybe more than 50% of the cancers might not be due to the genetic effects,
might not be to mutations,
NOTE Confidence: 0.7186378
might not be to polymorphisms
NOTE Confidence: 0.7186378
or things like that.
NOTE Confidence: 0.7186378
So they have an environmental impact.
NOTE Confidence: 0.7186378
One of the things that has triggered
NOTE Confidence: 0.7186378
my attention the last five or you know
NOTE Confidence: 0.7186378
6-7 years is the early onsets of cancer,
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which actually there was a very
NOTE Confidence: 0.7186378
nice review in Natural Nature
NOTE Confidence: 0.7186378
Reviews in clinical oncology,
NOTE Confidence: 0.7186378
which posed the question if the early onset
NOTE Confidence: 0.7186378
of cancer is an emerging global epidemic.
NOTE Confidence: 0.7186378
And it has.
NOTE Confidence: 0.7186378
As you can see, the incidence of of
NOTE Confidence: 0.7186378
cancers in various organs in ages less
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than 50 and actually less than 40,
has been rising in many parts of the world since the 80s. The evidence suggests an ideological risk of risk factor exposures in early life. Young, under hood, and all those specific individual exposures remain to be largely unknown. So this is what my interests are, how this environmental exposures could lead not only to cancers but also to early onsets of cancers. And we can go from liver cancer to colorectal cancer with associations to alcohol, which I could give you.
another lecture on that.

But anyway, the early onset cancer epidemic might be 1 manifestation of increasing the trends of the in the development of many chronic disease in the young and future generation. So what we come here is the early life exposure, it's the exposures of the mother. And actually now it's also exposure preconceptionally for both mother and father what they have been into and how this would affect the development of the embryo, the later studies.
So the exposome includes environmental exposure, Melinda talked about diet, lifestyle, obesity and microbiome and this exposome has changed completely in the last 40 or 50 years. So a lot of people looking into how this Eddy life exposures could have an effect. Of course we should not ignore the exposure we have on daily basis and talking about that one of the most important thing is drinking water. You drink your water and in most of the cases especially when you
come to emerging contaminants,

you don’t you have no idea what

So it’s it’s a lot of aspects in here.

So talking about drinking water

and protecting the environment.

So the federal government has the

Superfund Act and what that is refers
to a comprehensive environmental response.

Compensation and liability are

known as CLEFCLA since the 80s.

So what the federal government did

is they put a law that provides a

legal framework for clean up sites of

contaminate and hazardous substances.

Especially,
you know there are some states, Connecticut is a heavily industrialized, actually it’s a retired, it’s a retired state of heavily industrialized area. If I’ll show you the sites of superfunds, either federal or local, we might walk away and go and look for a job or another state. It’s everywhere and I will explain you why in I’ll give you some of these examples. Again, we have to be taking everything into consideration. So there is the federal law,
if there is a company that has a spill out, so they're getting a fine and that could be hundreds of millions of dollars. Some of this amount of money they go to the EPA and some of them go to National Institute of Environmental Health Sciences and what the environmental Health Sciences does takes this money and creates a centers. So you have we have here the Cancer Center at the same time we have the the Superfund research centers and essentially the centers focus on the understanding of health effects of
the exposures to hazardous substances, developing innovative technologies to mitigate essentially size, clean up and engaging communities affected by this environmental issues. So their research contributes to the overall goal of safeguarding the public health and environmental in areas of hazard or waste contamination. So this is what are the centers and this is as I said this is where the federal money from penalties from those cleanups go and they’re coming. We have 23 funded centers in the
the United States and as you can see on the top left is our Connecticut, it’s a Yale Superfund Reset centre. This is the first ever centre we’ve got in Connecticut and the focus of our centre is on emerging contaminants. I said the focus of our centre is on emerging contaminants. So what are water contaminants of emerging concern now these are chemicals that they’re detected in trace amount in our drinking water within global drinking supplies that their risk on human health is not fully understand or even not been evaluated at all. OK. And what are these emerging
concerns include that including industrial chemicals such as Pfas. Everybody has heard about the Pfas. Everybody you know today at least you will get educated on 1,4 dioxane on some volatile solvents that they exist. But in addition to that we have a lot of pharmaceuticals, personal care products and actually yesterday NIH had a webinar about the personal care products. You’ll be surprised how much they go down the drain and how much they end up in your drinking water. It’s truly amazing.
And of course you have pesticides and herbicides that come from the agriculture that eventually, you know they’re going to end up into the water table and they’re going to add up to our drinking water. So the overall objective of our Yale Superfund Research Center is to improve public health from the emerging water contaminants in the drinking waters. And what we’re trying to do with trying to develop not innovative research in terms of the mechanisms of toxicities that these emerging contaminants cause and also look at the ways that we can
mitigate that we can detect and inform the communities,

Our center has been focused on 1,4 dioxane. We and also it’s what we call, I’m Greg, I’m sorry that’s it’s in my sense this is in my genes, it’s not environmental. So it’s 1,4 dioxin and what we call its Co contaminants which is 1, its the dichloroethane, trichloroethane and also trichloroethylene.
Those are volatile solvents that they exist and I will explain you why and how this has come up with. But essentially, this is what our center is doing and this is what we’re focusing now. You can say why did you focus on that? So when I came here, it was 2014. I immediately went on, I think the next year immediately I met with the state authorities, the Department of Public Health and the Department of Energy. And I said I’d like to develop a Superfund research program.
NOTE Confidence: 0.52509516
00:11:12.884 --> 00:11:14.994 for the state of Connecticut.
NOTE Confidence: 0.52509516
00:11:15.000 --> 00:11:17.597 What is the issue that you have?
NOTE Confidence: 0.52509516
00:11:17.600 --> 00:11:18.662 At that time?
NOTE Confidence: 0.52509516
00:11:18.662 --> 00:11:20.786 PFS were not that hot and
NOTE Confidence: 0.52509516
00:11:20.786 --> 00:11:22.808 actually thank God because we
NOTE Confidence: 0.52509516
00:11:22.808 --> 00:11:24.884 took the direction of 1.4 dioxin.
NOTE Confidence: 0.52509516
00:11:24.884 --> 00:11:27.412 Had they know anything about 1.4 dioxin?
NOTE Confidence: 0.52509516
00:11:27.412 --> 00:11:27.718 No.
NOTE Confidence: 0.52509516
00:11:27.718 --> 00:11:30.266 But they told me that this was the
NOTE Confidence: 0.52509516
00:11:30.266 --> 00:11:32.597 major issue and the major issue was
NOTE Confidence: 0.52509516
00:11:32.597 --> 00:11:34.717 because of this solvents on this
NOTE Confidence: 0.52509516
00:11:34.717 --> 00:11:37.360 multiple sites in the state of Connecticut.
NOTE Confidence: 0.52509516
00:11:37.360 --> 00:11:40.400 And the problem with 1.4 dioxin
NOTE Confidence: 0.52509516
00:11:40.400 --> 00:11:42.800 is they could not filter it.
NOTE Confidence: 0.52509516
00:11:42.800 --> 00:11:46.556 It would go through every aspect.
And even in public water, they cannot filter it if the source is contaminated, it will end up in your drinking water. So that was a major issue and this is why we chose to go with 1.4 dioxane. And actually I'm really proud not because I got the grant, I'm really proud because I brought the four schools together and that is our school of public health, the School of Medicine, the engineering and the environment. And we developed this program.
as you can see, four research projects and four course. We have the administrative core, we have the training core, the DMAC which plays the data management and analytics. We also have the community engagement and of course we have the training, the training core that you're going. I'll go in a little bit more details when we move forward on this. So again, more time it was the concern of the public, of the public institutions was on
1.4 dioxin for a particular reason.

Because it is a possible human carcinogen.

It has been found that it causes cancer in animals,

but now there is no epidemiological studies yet in humans.

This is why it’s emerging contaminants

and it’s found with the other Co contaminants and has been prioritized

by US Environmental Protection

Agency on the 3rd Unregulated Monitoring role for testing in

2013 and 2015 and you will see

the map. It is spread

throughout United States.

So it’s been also characterized
as forever chemical just like the PFS because it cannot be filtered.
It’s very, it’s difficult to be, metabolized by bacterial species and so on and it goes there.
This is from the chemical Environmental news saying that this is really so when we wrote a big grant that we can oversee what it was available, what was the scientific evidence, what was the demological studies, what are the strategies to mitigate that. And we had that on a very nice review that actually helped
us to get the team together.

So 1.4 dioxane of course in three isomers, 1.41 point 2 and 1.3, but the concern and the most prevalent is the 1.4 dioxane.

Is it a new chemical?

No, it’s not. I’m just not going to go in all details of this because we can talk about for a long time, but it was first synthesized in 1863 and initially it was used as a stabilizer. It was used as a stabilizer for the solvents, the DCA TCE and DCA, and what happens is this, they were covered on.
They were.
They were transferred on aluminium containers and the aluminum containers, you know, they have a cover inside which is aluminum and they protect from being interacting with the metal. So what happened is after a certain period of time these solvents interact with the metal and they create even toxic products. So what they did is they found 1.4 dioxane, it could block the catalysis of this reaction.
So they were using 1.4 dioxane as a stabilizer of those chemicals not only to protect the toxicity but to stabilize the solvents for their use. And what we're using this everything that you can imagine, I'll show you. So it was used as a stabilizer to begin with, but later as you can see from this, it has been used in many in many areas. So this is the uses, I'm not going to go in great details but includes from the stabilizing to medical, pharmaceutical, rubber and plastic industry, printing in and paints, adhesives, brake fluids, brake cleaning fluids and also rust.
NOTE Confidence: 0.73635834
00:16:13.260 --> 00:16:16.590 remover and also antifreeze and deicing.

NOTE Confidence: 0.73635834
00:16:16.590 --> 00:16:19.460 The stuff that you they throwing on

NOTE Confidence: 0.73635834
00:16:19.532 --> 00:16:21.814 the airplanes before we take off on

NOTE Confidence: 0.73635834
00:16:21.814 --> 00:16:24.390 this it has 1.4 dioxide quite a bit

NOTE Confidence: 0.73635834
00:16:24.390 --> 00:16:27.617 and what we end up with on the ground.

NOTE Confidence: 0.73635834
00:16:27.617 --> 00:16:30.550 OK so pesticides and some of the

NOTE Confidence: 0.73635834
00:16:30.641 --> 00:16:34.720 pesticides they have up to 50% of

NOTE Confidence: 0.73635834
00:16:34.720 --> 00:16:38.632 1.4 dioxide 50% anyway and also

NOTE Confidence: 0.73635834
00:16:38.632 --> 00:16:40.752 the consumer products we talked

NOTE Confidence: 0.73635834
00:16:40.752 --> 00:16:43.153 about before what is environmental

NOTE Confidence: 0.73635834
00:16:43.153 --> 00:16:46.117 concerns first of all ground water

NOTE Confidence: 0.73635834
00:16:46.117 --> 00:16:48.044 contamination resistance it’s as I

NOTE Confidence: 0.73635834
00:16:48.044 --> 00:16:50.980 told you it’s it’s there it cannot be

NOTE Confidence: 0.73635834
00:16:50.980 --> 00:16:53.680 really degraded easily and can travel.

NOTE Confidence: 0.73635834
00:16:53.680 --> 00:16:56.280 It can travel everywhere toxicity.

NOTE Confidence: 0.73635834
It’s been classified, as I told you, as a possible human carcinogen by both the USEPA and the National engine for Recession. Regulatory concerns are plenty of concerns. There is no federal regulation. Well, we don’t have federal regulation yet, even for PFAS. And I don’t know if you watch the movie Dark Waters, which I recommend that you do, you realize what I’m talking about? About PFAS and regulatory issues. So as I told you before,
what do you find, 1.4 Dioxane. You find all the other solvents or vice versa. It has happened in many places in the United States around the Air Force or you know, army bases and everywhere. And it's not only in the United States, even in German Japan, China they have found whatever you find DC or DCA you will find 1.4 dioxin. So you expect to have it also in the rivers, in fish and in the drinking water. Here is the map from the CMR 3 and you can see there are white dots,
I mean dots,

Gray dots and red dots and essentially this is above,

below and or around the recommendation concentration which is .36 micro grams per liter.

This is a reference dose that this is the dose that it can cause one cancer per million.

And again this is advisory nothing regulatory.

The areas we have chosen as it was here, you cannot believe if you live in Long Island, you live in Long Island, public water from Long Island
00:18:40.915 --> 00:18:42.639 comes from well water.

00:18:44.080 --> 00:18:47.118 they’re really high levels of 1,4 dioxide.

00:18:47.120 --> 00:18:48.160 And what happened on that?

00:18:51.010 --> 00:18:54.303 Actually Governor Cuomo was very strong and put the legislation and

00:18:54.303 --> 00:19:07.119 there is a law in New York now

00:18:59.520 --> 00:19:03.188 to put 1.4 dioxane in detergents

00:19:03.188 --> 00:19:04.919 and household items.

00:19:04.920 --> 00:19:06.509 Now there is a lawsuit from the

00:19:06.509 --> 00:19:07.720 industry against the government,

00:19:07.720 --> 00:19:09.295 but you know,

00:19:09.295 --> 00:19:10.260 at least they put that and they

00:19:10.319 --> 00:19:12.239 recognize that because everything,
and I don’t have time to go through that,

your tide, your shampoo,

it has 1.4 dioxane and everything is
going to go down to the water table.

And especially in Long Island,

the public water comes from well water.

So it’s a major concern.

Another area,

which was one of the reasons that
NIH had a very strong also thing

NIH locates in North Carolina,

is fully contaminated

and you know it’s still getting
a lot of discharges in there.

Is it only there?

No, we have the case of Michigan, which I'll explain you later.

We're working on that.

Ann Arbor has a major plan of
1.4 dioxane sitting right there
and there's a lot of concern.

New Jersey found out last couple of
years that the public water had 1.4 dioxane.

And what happened there is a lawsuit.

I haven't followed up the details,
but in March 23 of 2023.

The water companies shoot the
manufacturers for putting 1.4
dioxin into the river, which eventually ended up into
the drinking water. So there's a lot of things going on and this
is happening just right now.
That was again in a different area in North Carolina where they found again 1.4 dioxin 1300 times higher compared to the reference level.
So what I'm saying is there is a lot of issues in there simply because was not nobody was paying attention before and this is something that due to the difficulties in determining that and having the assays but eventually right now there is a major concern.
00:21:04.600 --> 00:21:08.394 So in terms of toxicity in general

00:21:08.400 --> 00:21:10.472 most of the toxicity what we know

00:21:10.472 --> 00:21:12.940 or what we knew and what we’re going

00:21:12.940 --> 00:21:15.600 to do is from liver and kidney OK.

00:21:15.600 --> 00:21:18.400 But however they have been found that

00:21:18.400 --> 00:21:21.220 there is some effects also in nasal

00:21:21.220 --> 00:21:24.730 and eye liver toxist is dose dependent

00:21:24.730 --> 00:21:26.914 characterized by cell degeneration,

00:21:26.920 --> 00:21:30.070 preneoplastic lesion development,

00:21:30.070 --> 00:21:33.139 acid lobular swelling, necrosis,

00:21:33.139 --> 00:21:35.158 increased DNA synthesis,

00:21:35.160 --> 00:21:37.692 all the prenea plastic damages that

00:21:37.692 --> 00:21:40.581 you can see in chromosomal damage

00:21:40.581 --> 00:21:43.356 and and enzyme leakage.

00:21:43.360 --> 00:21:45.766 The kidney toxicity manifests as a
00:21:45.766 -- 00:21:48.159 generation of the cortical tube cells.
00:21:48.160 -- 00:21:52.080 tubular tubular necrosis and
00:21:52.080 -- 00:21:54.040 chloro nephritis.
00:21:54.040 -- 00:21:56.364 So the other thing that we have
00:21:56.364 -- 00:22:01.110 discovered in our and which I think
00:22:01.110 -- 00:22:03.315 it could be very disturbing but is
00:22:03.315 -- 00:22:05.762 that we found out that there is
00:22:05.762 -- 00:22:08.834 a potential disruption of glucose
00:22:08.840 -- 00:22:10.880 homeostasis at least in our mice.
00:22:08.840 -- 00:22:10.880 But again, it’s not published.
00:22:10.880 -- 00:22:13.664 We have it here.
00:22:13.664 -- 00:22:16.160 So the studies and I’m not going to go,
00:22:16.160 -- 00:22:19.156 I can bypass because time is running.
00:22:19.160 -- 00:22:20.040 There are a lot of,
00:22:20.040 -- 00:22:22.609 a lot of experiments both in mice
00:22:22.609 -- 00:22:25.582 and rats in over the two years that
it is a proven liver carcinogen.

And you know it has been shown that you know it is occurring in various labs throughout the year, throughout the globe and they found the same thing.

So one of the thing though that it was a little bit puzzling is when they took, they did the genotoxicity. In other words they did the aims test or sister comma the exchange test.

They couldn’t find any genotoxicity for this 1.4 dioxin.

So they said well it’s not the mutagen, maybe it’s a promoter.
As you can see on the 4th bullet, there is a published study published last year by a Japanese group that indicates that 1,4 dioxin can induce DNA adducts as well. OK, and they're going on that. But what really triggered my interest and this is what really reflects essentially the mode of action of 1,4 dioxane is what they did is they took genotoxic carcinogens not genotoxic carcinogens in 1,4 dioxane and they did the studies in both mice and rats. They measured the RNA sick and
NOTE Confidence: 0.6750126
00:23:39.798 --> 00:23:42.734 they try to make sense if 1.4
NOTE Confidence: 0.6750126
00:23:42.734 --> 00:23:45.723 dioxin belongs to one or the other
NOTE Confidence: 0.6750126
00:23:45.723 --> 00:23:48.518 group based on gene expression.
NOTE Confidence: 0.6750126
00:23:48.520 --> 00:23:50.172 And what they found as you can
NOTE Confidence: 0.6750126
00:23:50.172 --> 00:23:52.200 see from the from the slides
NOTE Confidence: 0.6750126
00:23:52.200 --> 00:23:54.840 1.4 dioxin is a distinct form.
NOTE Confidence: 0.6750126
00:23:54.840 --> 00:23:57.616 So in other words it’s it’s does not
NOTE Confidence: 0.6750126
00:23:57.616 --> 00:24:00.128 belong to any of these two models
NOTE Confidence: 0.6750126
00:24:00.128 --> 00:24:02.776 which I thought it was very interesting
NOTE Confidence: 0.6750126
00:24:02.776 --> 00:24:05.226 and it was worth of exploring.
NOTE Confidence: 0.6750126
00:24:05.226 --> 00:24:08.588 So let’s go and see what we’re doing.
NOTE Confidence: 0.6750126
00:24:08.588 --> 00:24:11.270 So our Project 1 briefly goes
NOTE Confidence: 0.6553215
00:24:11.361 --> 00:24:14.076 on liver cancer and biomarkers.
NOTE Confidence: 0.6553215
00:24:14.080 --> 00:24:17.900 So essentially we’re trying to use mouse
NOTE Confidence: 0.6553215
00:24:17.900 --> 00:24:21.400 models, human cells and organization,
NOTE Confidence: 0.6553215
also zebra fish to dissect the molecular mechanisms of causing cancer. That’s what the Project one does.

The project Two, as I told you, there is no epidemiological study on, you know, on 1,4 dioxin. And this was the major obstacle that I had to go through for the resubmission because everybody, when I was putting the stuff about carcinogenist, they said, well, we don’t have epidemiological status. Well, somebody has to do it anyway. To make a Long story short, the budget of this project, it’s not huge. So we did not have money to do
the epidemiological studies.

However, the NIHS said we do want you to do something about it. So what we decided was exposure assessment. So in other words epidemiological studies in much less number of samples. So the Project 3 is something that we're trying to detect the 1.4 dioxin and Co contaminants in areas that they're there. My whole idea in here is can we develop a system that it can be online that you can monitor the area, or the EPA can you know get the information.
It's a difficult task.

Many eliminated Jordan patio that when I talked to them about they said I cannot be done. Anyway, to make a Long story short, I'll show you what we're doing and we're trying to develop that, but the idea of having those sensors is really hot right now in all the aspects that you can do. Finally, the project for as I told you, and this is another very important project, is how we can degrade. So you're well watered, most likely might have 1.4 dioxide. I'm not saying it does,
but if it does, how you can purify it? Well, you can purify it with reverse osmosis, but do you have $15,000 to? So it’s just for reduce versus Moses on your water. And some people may afford it, but how about the people that they cannot? We’re talking about environmental justice as well. So there’s a lot of issues that need to be discussing there. So that’s Project 4. And the Project 4, essentially what it tries to do is trying to use what we
call advanced oxidation,
which is essentially oxidative stress.
And I have more slides to show you,
so you try to utilize hydrogen peroxide,
you break the hydrogen peroxide,
you create reactive oxygen species
and then the reactive oxygen species
that can degrade your chemical.
And this is also we're trying to do
something similar with PFS as well.
But anyway, this is of the record.
Let's go for
project One.
This is the theme that we have.
Essentially Yin Chen leads that I'm
00:27:19.678 --> 00:27:23.084 a Co leader, but I'm following her.

00:27:23.084 --> 00:27:24.797 That's her project.

00:27:24.800 --> 00:27:29.560 And we have of course Georgia from

00:27:29.560 --> 00:27:31.480 from and other people in the lab.

00:27:31.480 --> 00:27:33.016 And this is in collaboration

00:27:33.016 --> 00:27:34.759 Program with Stephen Ferguson,

00:27:34.760 --> 00:27:37.940 who is doing the human

00:27:37.940 --> 00:27:41.120 Hepatocytes and also the human,

00:27:41.120 --> 00:27:43.350 the 3D structures of the of

00:27:43.350 --> 00:27:45.207 the of the human cells that we

00:27:45.207 --> 00:27:47.207 can do the organoids and we

00:27:47.207 --> 00:27:49.235 can test 1.4 dioxin in there.

00:27:49.240 --> 00:27:51.004 So what we do here at the

00:27:51.004 --> 00:27:52.599 Yale and I'll show you is,
00:27:52.600 --> 00:27:54.556 is we’re doing the mouse work.
NOTE Confidence: 0.5781793
00:27:54.560 --> 00:27:55.640 So NTP,
NOTE Confidence: 0.5781793
00:27:55.640 --> 00:27:58.340 National Toxicology Program is helping
NOTE Confidence: 0.5781793
00:27:58.340 --> 00:28:01.758 us with determining the effects on cells.
NOTE Confidence: 0.5781793
00:28:01.760 --> 00:28:04.917 And Robin Tanway from Ohio State University,
NOTE Confidence: 0.5781793
00:28:04.920 --> 00:28:07.440 which I was there 10 days ago,
NOTE Confidence: 0.5781793
00:28:07.440 --> 00:28:10.734 they’re evaluating our 1.4 dioxin but
NOTE Confidence: 0.5781793
00:28:10.734 --> 00:28:14.003 most importantly the mixtures with the
NOTE Confidence: 0.5781793
00:28:14.003 --> 00:28:16.214 other Co contaminants on zebrafish.
NOTE Confidence: 0.5781793
00:28:16.214 --> 00:28:19.150 Why we do that because to do that
NOTE Confidence: 0.5781793
00:28:19.230 --> 00:28:22.784 in mice you need you know about
NOTE Confidence: 0.5781793
00:28:22.784 --> 00:28:26.672 20 fold budget and much more
NOTE Confidence: 0.5781793
00:28:26.672 --> 00:28:30.200 time to evaluate that in mice.
NOTE Confidence: 0.5781793
00:28:30.200 --> 00:28:33.259 So zebrafish in an is an amazing
NOTE Confidence: 0.5781793
00:28:33.259 --> 00:28:37.053 tool and actually his here facility
NOTE Confidence: 0.5781793
00:28:37.053 --> 00:28:39.384 up in Oregon State for the zebra
fish screening and especially the exposomic studies is truly amazing. So we take advantage of that and actually we're not restricting the science only to carcinogenicity, but we're also doing a lot of stuff for behavioral stuff and also for that could have an effect on mental issues of this compound. So what we really know again this is I'm going to pass, I have covered that quite a bit. We know that causes cancer. We don't know the mechanism. Dioxin is a carcinogen in mice.
We don’t know what is doing and what is going on. So what we’re doing, we’re not just repeating what it has been done before, but we’re trying to use knockout animal models that will have an effect on this. So we’re using models on oxidative stress and I will give you the examples in here. But essentially the first part is we’re using mice and we do high dose and low dose. For the high dose is to get the effect, low dose is to mimic the human exposures.
we’re doing the RNA transcriptome, the metabolomics and also the phenotyping of this mice and we have quite a bit of data so far. So then we’ll combine this on using deep learning, doing the RNA, the metabolomics and you know the not clinical, the phenotyping things and we’re trying to determine the mode of action, the MOA and also the exposure and toxicity biomarkers which we’re going to feed the project to when they do the exposure analysis.
I told you before that we also using the the HEPA RG cells with NTP and the zebra fish for the AM 3.

Here is a little bit of what we know and what we’re currently know regarding the metabolism of 1,4 dioxane.

One of the thing I want to take your attention to it. It is metabolized by cytochrome P452U1. Why this is important? Because cytochrome P452U1 is the activator of many carcinogens, many what we call precarcinogens to very active intermediates that they can cause cancer that can interact with DNA.
So as you can see on the right hand side you can see also you have the TCE and the PCE which have the solvents which can also be metabolized by cytochrome P452. I want you to keep that in mind because what we have found, it’s something that I think we have explained some of these effects. So we’ve already published quite a few papers. In terms of the mechanism, I wish I had too much time to show you, but one of the major findings that we did and nobody has shown that...
before is we found that 1.4 dioxane induced the cytochrome P452E1. And why this is important? Because if you have a Co exposure of cytochrome P452E1 and trichloroethylene or diethyl nitroamine in your cigarette smoke or in, you know, in the smoke food that you eat, then you have higher chances of metabolizing the procarcinosis to carcinosis and they can cause liver cancer. So in other words, it can act as a promoter by inducing the cytochrome P452E1 in addition to the cytochrome P452E1. And you can see it in your left.
We find that there is increased oxidative stress as indicated with four hydroxynone anal and also with the increase of the quinone oxidiridactase, which is a gene involved in the antioxidant response. So I apologize this happens again. You know the the image becomes a little bit but what the highlights of our research are this and this happens to me. I don’t know why this but I have another one that I can show you. But we have find out so far that there is a direct xenotoxic effect for dioxin that includes oxidative stress.
We already published that in 2022.

There is a dominant role of two one in the metabolism as we have found by metabolomics and also for the liver toxicity.

But also we have not only the induction of 2 E one, we have found the 2nd mechanism which is completely independent of Cytochrome B452E1.

How do we do that?

We’re using knockouts that they have not Cytochrome B450 and we determined that.

So this is what we’re doing.

Specific aim one and specific aim 2

is we’re using knockout mice and again remember we have the metabolism here.

As you can see Cytochrome B450 is
00:33:50.049 --> 00:33:52.679 metabolized the first two animal models, the GCLM knockout is a model of mice that has low glutathione levels so that animal model, it has low antioxidant capacity.

00:34:01.640 --> 00:34:04.480 Nerf 2 knockout model is the Nerf two transcription factor involved in all the genes involving done oxidant response. So if the nerve 2 gets activated, your cell becomes really active.

00:34:07.088 --> 00:34:10.080 Against the insults and we try we’re currently using that, we’re doing the experiments and to do that.

00:34:11.930 --> 00:34:13.040 We’re also using the cytochrome P4
As I said we completed those studies actually and we're using the NQ one and also the aldehydehydrogenase 2. As you can see the Ald H2 could be involved in the last steps. And you know the Ald H2 is a gene that has it's highly polymorphic in a lot of individuals especially those in from the from Asian population quite a bit. So Project 2 is the exposure assessment team led by Co led by Nicole Diesel and Brian Litter. And we have also most of our people from our department in exposures Crystal, Pollet, Zhai and Lu.
And also we have collaborators in North Carolina State, Joe Hoppin and death of Nappy. This as I told you is going to be an exposure model, exposure assessment model here in Long Island and we have already going through that. So the aims again is you go you collect the water you collect the blood from these people and then you're trying to also make much the medical records and you're trying to do the exposure assessment and we're trying to interact all this this.
00:35:51.828 --> 00:35:54.285 project as I told you as we’re using
NOTE Confidence: 0.862863683666667
00:35:54.285 --> 00:35:56.471 metabolomics in this in this project
NOTE Confidence: 0.862863683666667
00:35:56.471 --> 00:35:59.093 and the metabolomics here will be
NOTE Confidence: 0.862863683666667
00:35:59.093 --> 00:36:01.121 coordinated with a metabolomics for
NOTE Confidence: 0.862863683666667
00:36:01.121 --> 00:36:03.816 the first program which is on the
NOTE Confidence: 0.862863683666667
00:36:03.816 --> 00:36:06.196 1st specific aim which is in mice.
NOTE Confidence: 0.862863683666667
00:36:06.200 --> 00:36:10.565 The third project is led by many
NOTE Confidence: 0.862863683666667
00:36:10.565 --> 00:36:14.700 Elimelech from the school of the the
NOTE Confidence: 0.862863683666667
00:36:14.700 --> 00:36:16.700 Department of Chemical Environmental
NOTE Confidence: 0.862863683666667
00:36:16.700 --> 00:36:20.003 Engineering and also you know is Jordan
NOTE Confidence: 0.862863683666667
00:36:20.003 --> 00:36:22.558 Petia and true Gender are from this,
NOTE Confidence: 0.862863683666667
00:36:22.560 --> 00:36:23.706 from this group.
NOTE Confidence: 0.862863683666667
00:36:23.706 --> 00:36:25.616 And again what we’re they’re
NOTE Confidence: 0.862863683666667
00:36:25.616 --> 00:36:28.365 trying to do is they’re trying to
NOTE Confidence: 0.862863683666667
00:36:28.365 --> 00:36:30.275 develop this kind of molecules,
NOTE Confidence: 0.862863683666667
00:36:30.280 --> 00:36:33.472 the eptomers or all this idea that it
can bind to that and then it can be detected and then they can transmit that. It’s stuff we’re not going to accomplish in the first five years, but at least we can develop the sensors to develop and then we can try to find out how we can develop the network. 4th project, and I apologize, I’m trying to give to finish so we can have some time for discussion. 4th project is by Jai Hong Kim and John Faulkner. And as I told you this is relating to develop small devices that
you can use in your house to get rid of 1.4 dioxide and they’re using the advanced oxidation. It will take me about a lecture to explain you that but essentially I think I told you the principle is hydrogen peroxide generate hydroxy radical and this hydroxy radical will hit that. They are using actually two kind approaches in there and I think I have they they are developing some nice things and I’m going to tell you that we have made. We successfully synthesized the catalyst,
the boron doped carbon catalyst shown here and fabricated hydrogen peroxide synthesis cell. We quickly discover that maintaining the performance in the real water metrics would be the key for success of this research to provide a system that can perform for a long period for a household application. We therefore developed a framework on how to optimize post electrolysis to enhance catalytic tolerance against impurities present in water and in to improve overall lifetime of the cell. We discovered that optimized pulsing
sequence enabled improved long term hydrogen peroxide performance to nearly 300 hours and 35 times better than conventional electrolysis even in the presence of most detrimental impurities such as nickel and zinc. These findings make this cell closer to real world implementation for prolonged hydrogen peroxide synthesis and subsequent one for dioxane destruction. Let me share some recent progress. This is the second we have made we successfully synthesized the. I'm sorry it was I thought it was as an. This is the second method destroy one for dioxane in specific
We explore the use of engineered gas phase nano bubbles. We perform extensive characterization of nano bubbles in solution with a focus on hydro thoradical generation and by performing a number of different characterization using degradation of hydro thoradical specific target compounds, electron paramagnetic resonance spectroscopy and a fluorescence based indicator. Through this phase of research we concluded that nano bubble induced or hydro thoradical generation is minimal if not all. But we will continue to study if there is an alternative way to enhance the
So I alternative technology

I wouldn’t be able to tell you that. So

that’s why I sent my daughter my

daughter’s first year in governmental

engineering in Boulder, Co.

So the next is our the next is

our community engagement core,

which will have Iris,

Kaminski and Andrea and Esposito.

Call it Derry Woods,

executive director of the Citizens

Campaign of the Environment.

And we, you know, she’s very big,

big in terms of community

engagement and we’re doing quite
a bit in community engagement. We're ready and we utilize community engagement actually to recruit people for the project too. This has been fascinating so far, but we're not staying only in Log Island or even Vermont. We're expanding in other areas too. So the other areas that I'm working right now and I will tell you is the New Hampshire in North Carolina, Michigan, and recently I have been engaged by Florida. Believe it or not, there is an area over there,
Lake Mary, 
that has even 30,000 times higher levels of 1.4 dioxin in their surface water.
Anyway, this is some of the stuff that we’ve already done and the publicity that the centre is getting and I have more and more, but I’m just leaving you that we’re using that as a tool and we communicate, you know, people calling me in the office, they said we want to register for this study and you, they need more information. And this has not been studying only in Long Island.
And you know, newspapers have taken the centre because of the importance, as I told you, of 1.4 dioxin discovered in many states. So we’re getting a lot training component. I think I was smart on that. I took our Jordan, Chris Judy is our esteemed director of a graduate program at way SPH. And this too made a dream team and you know it had actually the
best one of the best scores on the components they had almost 1012 on their application and Yin Chen is also part Co investigator on that. So the way building up training education capacity going from even under graduates with an R-25 that they have on training undergraduate students to MPH students and also PhD students and post doctoral. This is classic regular the schedule we’re doing for the training of our PhD. Last but not least and I kept the picture in here of Peter Petuzzi, although he retired and he just stepped down right now,
but I love Peter and that was another another dream team here of Hong Yu Zhao and Peter Petuzzi that they do the data management and analysis core team which essentially bring all the projects together.

And I’m not going to go to all specific aims, but essentially it’s coordination between projects and cores, fostering, data sharing and interoperability. So we’re trying to develop all this cloud systems and finally and most importantly is data quality assurance, quality control and data integration. So this is huge and we get really good.
So I am almost at my 45 minute mark and essentially what I would like to say, the establishment of our Yale Superfan Centre marks a significant milestone of our departmental commitment to addressing emerging contaminants linked to cancer. Our strategic plan includes the development of peripheral research projects for exposure assessment and we get the budget cut of almost 50% of our initial budget, not only us, everybody did because they withdrew some money from that project to support the climate change in a number of institutes. So what we’re trying to do is we’re trying to develop peripheral research projects for exposure assessment and
various locations across United States, fostering international collaboration and broadening the impact of our work. We aim to strengthen the partnerships of course with Cancer Center, with the liver center, with diabetes Center, leveraging their expertise and resources for more comprehensive approach to our research in vendors. And as we advance, our focus will extend beyond the scope of the 1,4 dioxin and the volatile compounds. And we try, I'm going to try to get more emerging contaminant with particular emphasis to PFAS.
And actually PFAS is, you know, because of their ability to be endocrine disruptors, they have been linked now to obesity and diabetes. And as I told you before, we find something similar and there are a lot of interaction. Another thing about PFAS induces kidney cancer, OK, it’s the major cancer that induces is kidney cancer. So what is the, you know, the interaction of this between them?

This is something that we need to explore.
So this expansion will involve in depth exploration between links and the PFAS especially as I told you kidney cancer and obesity bringing virus insight to the scientific community.

I’m going to stop with that and I’m going to take questions and we’re happy to discuss anything you wish.

Yes, great. Thank you.

The whole project began with the involvement of the community alerting you to 1 dioxide. So at the Cancer Center, liver cancer is a priority. Cancer that is in the strategic
plan given its increased rates in Connecticut as well as nationally. So I’d love to think about collaborations to how we can do more on the epidemiologic or clinical aspect and link it, you know with patients coming in newly diagnosed with liver cancer. Could there be a case control study where water is collected from their home blood questionnaires and then have a controlled sample. So there’s so much opportunity. I think here that’s what David said. That’s why he invited me to give the talk here.
We need to get this, Melinda, this is a very good point. If we can get more and actually, you know, we can explore the possibilities and if we have more blood samples of that, we can do much better, much, much more. And that's a very good point. Yes. Going to Long Island for Thanksgiving, get your water with you. Is there a safe like what do you recommend? What is there a brand of like bottled water that doesn't that's guaranteed to not be contaminated? Depends. Now listen, I mean there are areas in Long Island,
there is this interactive map that you can find which areas they have high levels.

But to be on the safe side, you know, I was going to say use public water, but this public water over there comes from well water.

I don’t know how the late status is, but it might not be a bad idea to use some bottled water.

First of all, I want to echo on you and Melinda set because there are tremendous opportunities here that are aligned in many ways with the forthcoming Cancer Center strategic plan.

I’d like to add to that education because you have cancer education programs running
that are cancer connected education programs running that are complementary to our other training programs.
The question for you though is you began with a challenge from the state of Connecticut, but I noticed all the collaborations are out of state. Can you tell us more about how this work might impact our state and our catchment community? It’s the same thing. There are certain areas that they have 1.4 dioxane in the state of Connecticut. However, the state of Connecticut has...
taken very good care of the public water
and their public water is pretty safe.
You are as long as you are in public water,
they're taking good care how it's
going to have a major impact.
It's going to have a major impact on liver cancer.
But you know the problem,
it might not be completely here,
but it has several aspects of you know,
getting engaged with
agencies, the state agencies addressing that.
And as Melita said, there is an increased rate of liver cancer,
which brings the other point
you were talking about.
I also have AT32 program with the livers with psychiatry essentially. But it’s my point of view is my other lab that I have is alcohol and cancer and I actually organized the International Conference on Alcohol and Cancer. So this is another area that I think the increased levels of alcohol consumption is a very good contributor and that along with obesity. So if you add another factor which is 1.4 dioxin even if it’s in low levels for example in the state of Connecticut, what we saw in here there is an increase of the Cytochrome P CNY452.00.
So if you get that in combination with smoking nitroazamines or other exposures you can increase the rate of cancer in the area. Yes, well that’s a good point. Listen, we have done a lot of risk evaluation risk for water sources in on wells water. I wouldn’t say that 1.4 dioxin is a major concern because we know what the were the areas of 1.4 dioxin. My concern would have been more on the PFAS. So my recommendation is test your well water for PFAS, that’s the only suggestion. I don’t think in Connecticut we
have that major issue of 1.4 dioxin.

Well, if you test, that’s a very good point. If you test it, if you test your well and it’s positive for 1.4 dioxin, you don’t have to wait for Jihong Kim to develop these devices. What you do is you use plastic water, I mean plastic water from, bottles. Of course you can have some things from there, but it’s at least safer. If you find that there is P fast, the P fast, you can filter them with charcoal and stuff like that. So there are devices that
00:51:30.490 --> 00:51:31.960 they’re relatively cheap.
NOTE Confidence: 0.29898286

00:51:31.960 --> 00:51:34.100 But one of the things that I want to tell
NOTE Confidence: 0.29898286

00:51:34.152 --> 00:51:36.238 you is the importance of drinking water.
NOTE Confidence: 0.29898286

00:51:36.240 --> 00:51:37.680 Because you’re going to drink,
NOTE Confidence: 0.29898286

00:51:37.680 --> 00:51:39.520 you may avoid drinking alcohol,
NOTE Confidence: 0.29898286

00:51:39.520 --> 00:51:42.640 you may avoid smoking cigarettes,
NOTE Confidence: 0.29898286

00:51:42.640 --> 00:51:43.879 but you’re going to drink your water.
NOTE Confidence: 0.29898286

00:51:43.880 --> 00:51:44.280 Yes,
NOTE Confidence: 0.45110154

00:51:47.520 --> 00:51:48.320 you’re safe,
NOTE Confidence: 0.45110154

00:51:51.080 --> 00:51:51.880 you’re safe,
NOTE Confidence: 0.45110154

00:51:55.080 --> 00:51:56.280 You cover both of them.
NOTE Confidence: 0.7347072

00:51:58.920 --> 00:52:00.770 Well, the other thing is
NOTE Confidence: 0.7347072

00:52:00.770 --> 00:52:03.040 you know in terms of the,
NOTE Confidence: 0.7347072

00:52:03.040 --> 00:52:05.536 the Cancer Center is the liver
NOTE Confidence: 0.7347072

00:52:05.536 --> 00:52:08.666 center and also there is a high
NOTE Confidence: 0.7347072

00:52:08.666 --> 00:52:10.976 incidence of alcohol induced liver
cancers and not only the liver cancer but also colorectal cancers. And the incidence of colorectal cancers are really high as well throughout not only the nation internationally and especially the early onsets. Usually the stages are, you start from steatosis, you go to fibrosis, you go to cirrhosis and then some cases you know you go to a patel cellular carcinoma.
It is possible that you can go without cirrhosis. Yes, I mean in animal models they go without any signs of cirrhosis at all. But one of the problems, well, talking about the animals and humans and stuff like that, you know that alcohol, it is well known that causes liver cirrhosis, right? If you try to do the same thing in mice, there is no way you can do it. But you can take a mouse and you can put carbon to trichlorate for 3-4 weeks, you’ll get cirrhosis 100%.
So that’s the challenges that you have between animal models and human thing and that’s what we’re trying to do the organoids as a complementary to the mouse studies. All right. Thank you very much.