BEFORE THE NATIONAL GREEN TRIBUNAL

SOUTHERN ZONE, CHENNAI

(Under Sections 14, 15 r/w Section 18(1) of the National Green Tribunal Act, 2010)

OA No. 86 of 2024

Jakkamsetti Babu Rao son of Anjaneyulu resident of 20-84, Pitanivari Street, Mogulthur, West Godavari, Andhra Pradesh-534281

……Petitioner

Versus

The Andhra Pradesh Pollution Control Board, D.No.22 B-3-2, Kanukolanu Vari Street, Near Power Pet Railway Station, Eluru, Andhra Pradesh 534002. Ph : 0881224966 , Gmail : roelr-ee1@appcb.gov.in & 18 Others.

……Respondents

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It is certified that all the documents contained in the above annexure are true copies.

BEFORE THE NATIONAL GREEN TRIBUNAL

SOUTHERN ZONE, CHENNAI

(Under Sections 14, 15 r/w Section 18(1) of the National Green Tribunal Act, 2010)

OA No. 86 of 2024

Between:-

Jakkamsetti Baburao (aged about 57 years) son of Anjaneyulu, resident of 20-84, Pitanivari Street, Mogulthur, West Godavari, Andhra Pradesh – 534281

Ph : 9298803876 , Gmail : bharathmanoj123@gmail.com

..... Petitioner

Versus

The Andhra Pradesh Pollution Control Board, D.No.22 B-3-2, Kanukolanu Vari Street, Near Power Pet Railway Station, Eluru, Andhra Pradesh 534002. Ph : 0881224966 , Gmail : roelr-ee1@appcb.gov.in & 18 Others.

..... Respondents

REJOINDER FILED BY THE APPLICANT TO THE AFFIDAVIT DATED 30.08.2024 FILED BY THE 3rd RESPONDENT

MOST RESPECTFULLY SUBMITTED:

I, Jakkamsetti Baburao, aged 57 years, son of Anjaneyulu, and a resident of 20-84, Pitanivari Street, Mogalthur, West Godavari, Andhra Pradesh – 534281, do hereby solemnly affirm and sincerely state as follows:

1. It is respectfully submitted that I have reviewed the Affidavit filed by 3rd respondent. It is clearly mentioned in the page number 25 that the Illegal brick kilns illegally operating without permissions and they are causing damage to the environment by violating environmental protection Act 1986 , Air prevention of control Act 1981 and G.O.Ms No.80 Dated: 22.04.2010. And it is clearly mentioned that the Mandal Revenue Inspector, Mogalthur Mandal is directed to evict the 19 Illegal brick kilns in mogalthur U/s.133 of the CRPC 1973 and as per G.O.Ms No.80 Dated: 22.04.2010 and also implement the orders of W.P.No:25459/2007 and W.P.No:12138/2008 issued by the Hon'ble High Court of A.P. It is evident that till the date no

orders are implemented by the government officers and no government officer educated them from the past 50 years that these illegal brick kilns pollute the environment and cause serious health issues such as kidney problems, lung issues, skin cancers, and more.

2. It is respectfully submitted that:

Excerpt from Hon'ble NGT Court Order on 03-07-2024 by Hon'ble Smt. Justice Pushpa Sathyanarayana:

In this regard, we direct the District Collector – West Godavari District, who is the 3rd Respondent, to implement the guidelines with respect to Respondents No.5 to 19 herein. In the event the District Collector finds that there is no proper approval or NOC obtained by these brick kiln owners or operating the same illegally, the District Collector is directed to stop the operations forthwith and file a detailed report before the next date of hearing.

Post the matter on 08.08.2024.

It is nowhere mentioned that an explanation for not stopping illegal activities is needed. Since there are no licenses or permissions, these illegal activities should be stopped immediately. However, in the report filed by R3 the District Collector, only excuses and causes for not closing the illegal brick kilns were mentioned, without any actual closures being carried out. Copy attached as Annexure A1.

3. It is submitted that the respondents i.e. Illegal brick kiln owners have filed a separate case in the Hon'ble High Court against the Revenue Department to evade the closure of their illegal brick kilns. as mentioned in the report by the District Collector. As per High Court Orders in WP 14868/2023, the notice issued by the Gram Panchayat Secretary should be considered as a Show-Cause Notice, and strict action should be taken against illegal brick kilns.

Excerpt from Hon'ble High Court Order in WP 14868/2023:

Be that as it may, as the notice dated 15.03.2023 is in the form of an order containing directions and is not preceded by any Show-

Cause Notice, it is liable to be set aside. This Court deems it appropriate to dispose of the Writ Petition with the following directions:

a) The notice dated 15.03.2023 issued by the 1st respondent shall be treated as a Show-Cause Notice.

b) The petitioners shall file their objections/explanation to the said notice within two weeks.

c) The 1st respondent, on receipt of the objections/explanation, shall pass appropriate orders strictly in accordance with the law, after giving due opportunity of hearing to the petitioners, within a period of four weeks from the date of receipt of the objections/explanation.

d) Until appropriate orders are passed, the Gram Panchayat shall not interfere with the activities of the petitioners.

Copy attached as Annexure A2.

4. It is submitted that the illegal brick kiln owners cleverly filed another case in the Hon'ble High Court against the Tahsildar, alleging that the Tahsildar is trying to stop illegal brick kilns before the Gram Panchayat Secretary takes action as per High Court Orders in WP 14868/2023. This is the reason behind the case being pending in the High Court, as mentioned in the High Court Order WP 17382/2023.

Excerpt from Hon'ble High Court Order in WP 17382/2023:

Let appropriate instructions be obtained with regard to the competency of the Tahsildar in issuing the notices and initiating proceedings in the matter when an order has already been passed in WP 14868/2023, which required the Gram Panchayat to take action. Pending further consideration, no coercive action pursuant to the impugned proceedings shall be resorted to for eight weeks.

Copy attached as Annexure A3.

5. It is submitted that the Hon'ble Andhra Pradesh High Court did not mention granting any stay, and the Gram Panchayat Secretary was asked

to take action. In WP 14868/2023, dated 21/06/2023, the Hon'ble Andhra Pradesh High Court ordered the Gram Panchayat Secretary to take action within four weeks from 23-06-2023. The illegal brick kiln owners filed a case three weeks later, and meanwhile, the Tahsildar sent a notice to stop illegal brick kilns. In WP 17382/2023, dated 14/07/2023, the Hon'ble Andhra Pradesh High Court ordered the Tahsildar to wait for two weeks for the Gram Panchayat Secretary to take action and submit an action-taken report. The Tahsildar requested three more weeks to file a counter, which is still pending in the High Court.

6. It is submitted that government officials and the illegal brick kiln owners have deliberately delayed the process. The Hon'ble NGT Court will consider all these factors and take strict action as per THE ENVIRONMENT (PROTECTION) ACT, 1986.

7. It is submitted that for illegal brick kiln owners:

- As per CHAPTER III Rule Number 15, penalty and imprisonment should be imposed on the illegal brick kiln owners. This issue has been under consideration for the past 3 years. My first complaint against illegal brick kiln owners was made in September 2021, making this a three-year-old issue. Each Illegal brick kiln owner should be found guilty and fined more than three lakhs with imprisonment for a term that may extend to five years.

Exact Rule from ENVIRONMENT (PROTECTION) ACT, 1986 CHAPTER III :

15. PENALTY FOR CONTRAVENTION OF THE PROVISIONS OF THE ACT AND THE RULES, ORDERS AND DIRECTIONS.-

(1) Whoever fails to comply with or contravenes any of the provisions of this Act, or the rules made or orders or directions issued thereunder, shall, in respect of each such failure or contravention, be punishable with imprisonment for a term which may extend to five years with fine which may extend to one lakh rupees, or with both, and in case the failure or contravention continues, with additional fine which may extend to five thousand

rupees for every day during which such failure or contravention continues after the conviction for the first such failure or contravention.

(2) If the failure or contravention referred to in sub-section (1) continues beyond a period of one year after the date of conviction, the offender shall be punishable with imprisonment for a term which may extend to seven years.

8. It is submitted that for government officials who did not take any action on my complaints:

- As per CHAPTER III Rule Number 17, government officials should also be found guilty and punished for arbitrary actions.

Exact Rule from ENVIRONMENT (PROTECTION) ACT, 1986 CHAPTER III

17. OFFENCES BY GOVERNMENT DEPARTMENTS.-

(1) Where an offence under this Act has been committed by any Department of Government, the Head of the Department shall be deemed to be guilty of the offence and shall be liable to be proceeded against and punished accordingly.

Provided that nothing contained in this section shall render such Head of the Department liable to any punishment if he proves that the offence was committed without his knowledge or that he exercise all due diligence to prevent the commission of such offence.

(2) Notwithstanding anything contained in sub-section (1), where an offence under this Act has been committed by a Department of Government and it is proved that the offence has been committed with the consent or connivance of, or is attributable to any neglect on the part of, any officer, other than the Head of the Department, such officer shall also be deemed to be guilty of that offence and shall be liable to be proceeded against and punished accordingly.

Copy attached as Annexure A4.

9. It is submitted that we can clearly understand from the reports filed by R3, the District Collector, that the illegal brick kiln owners sought one year's permission to carry out illegal activities. However, even after one year, they did not close their operations. Many notices were issued by government officers to shut them down, leading the illegal brick kiln owners to temporarily close their operations and sell their existing stock. After that, they resumed their illegal activities, and this cycle has been ongoing for the past two years. No permanent closure of brick kilns has occurred to date. I educated some of the brick kiln owners, and they stopped operations until 3/12/2024 but have since resumed their illegal activities due to a lack of proper action taken against them. Copy attached as Annexure A5.

10. It is submitted that, as per many government studies and research papers all over the world, illegal brick kilns cause lung problems, cancer, and pollution affecting air, soil, and water, leading to kidney problems and serious health issues. If these studies are true, I am entitled to compensation, which should be granted to me. "**Justice delayed is justice denied.**" I am suffering from serious health issues, and this compensation should be useful for my medical treatment, not for funeral procedures. Copy attached as Annexure A6.

Therefore, in the circumstances and for the reasons stated above, it is prayed that this Hon'ble Court may be pleased to pass such other order or orders as this Hon'ble Court may deems fit and proper in the interest of Justice.

Jakkamsetti Babu Rao

Applicant In-person

VERIFICATION

I, Jakkamsetti Baburao, aged 57 years, son of Anjaneyulu, and a resident of 20-84, Pitanivari Street, Mogalthur, West Godavari, Andhra Pradesh – 534281, the Petitioner, do hereby verify and state that the contents of the above paragraphs of the affidavit are true to my personal know1edge and belief. This affidavit is filed on solemn affirmation and oath.

Place: Mogalthur

Date: 31.12.2024

Jakkamsetti Babu Rao

Applicant In-person

ATTESTED

A.G.V.K. SURYA RAO
NOTARY
Appointed by Govt. of A.P
AKANAVARITHOTA
NARSAPUR - MOGALTUR
W G Dt A P INDIA

31-12-2024

Certificate of Practice
Renewed up to 17-12-2027
By G.O. Ms. No: 04
Dated : 08-01-2024

NOTARY A.G.V.K. SURYA RAO Govt. of A.P. INDIA NOTARIAL

Date 31-12-2024
Sl No. 4923 Page No. 1642

Annexure A1

Item No.11:

BEFORE THE NATIONAL GREEN TRIBUNAL
SOUTHERN ZONE, CHENNAI

(Through Video Conference)

Original Application No.86 of 2024(SZ)

IN THE MATTER OF:

Jakkamsetti Baburao,
Andhra Pradesh.

...Applicant(s)

Versus

Andhra Pradesh Pollution Control Board,
Andhra Pradesh and Ors.

...Respondent(s)

Date of hearing: 03.07.2024.

CORAM:

HON'BLE Smt. JUSTICE PUSHPA SATHYANARAYANA, JUDICIAL MEMBER

HON'BLE Dr. SATYAGOPAL KORLAPATI, EXPERT MEMBER

For Applicant(s): Mr. Jakkamsetti Baburao *(Party in Person)*

For Respondent(s): Mr. Laksh Singhvi represented
Mrs. Madhuri Donti Reddy for R1 to R4.
Mr. N. Shanmugam represented
Mr. V. Ramana Reddy for R5 to R19.

ORDER

1. Today, the learned counsel Mr. N. Shanmugam representing Mr. V. Ramana Reddy undertakes to file vakalat on behalf of Respondents No.5 to 19 who are the brick kiln operators.

2. Heard the applicant (party-in-person) as well as the learned counsel appearing for the respondents.

3. The Original Application is questioning the illegal operations of brick kilns in Mogalthur Village, West Godavari District which are causing pollution and adversely affecting the health of the nearby residents. The applicant has enlisted Respondents No.5 to 19 who are the brick kiln operators and alleged about their illegal operations.

4. The applicant has also produced the G.O. Ms. No.80 dated 22.04.2010 of the Environment, Forests, Science and Technology Department, issuing guidelines for the establishment of brick clamps in the State of Andhra Pradesh, as per which, the application for the establishment of brick clamp made to Industries Department shall be accompanied by a no objection/license from the local body (Gram Panchayat, Zilla Parishad, Municipality or Municipal Corporation). It is open to the local body to consider the objections (if any) to make such an application before granting a No Objection Certificate to the applicant.

5. The guideline also further prescribes the distance criteria, siting criteria, mitigating the measures to control pollution, etc. As per the above-referred G.O., the District Collector of the concerned district shall monitor the implementation of the guidelines.

6. Now the allegation of the applicant is that he had obtained information that these brick kilns are operating without any of these approvals or licenses. To support his case, he has produced the letter from the Gram Panchayat Secretary, Mogalthur Village dated 21.04.2023 obtained under the RTI Act. As per the information furnished, these brick kilns have been operating in Mogalthur Village for several decades without any approval. The Tahsildar - Mogalthur Village was requested to take action against the owners of brick kilns that are operating without proper permissions.

7. Above all, the Gram Panchayat which should have given all the approvals, as per the above referred G.O., has not granted any permission to any of the brick kilns operating in Mogalthur Village.

8. As per the RTI information obtained by the applicant, none of these brick kilns seem to have obtained any approval, as the information is obtained from the Gram Panchayat who should have issued the NOC/licenses.

9. The District Collector is the authority to monitor and implement the guidelines stipulated in G.O. Ms. No.80 dated 22.04.2010.

10. In this regard, we direct the District Collector – West Godavari District, who is the 3rd Respondent, to implement the guidelines with respect to Respondents No.5 to 19 herein. **In the event the District Collector finds that there is no proper approval or NOC obtained by these brick kiln owners or operating the same illegally, the District Collector is directed to stop the operations forthwith and file a detailed report before the next date of hearing.**

11. Post the matter on **08.08.2024.**

Sd/-
Smt. Justice Pushpa Sathyanarayana, JM

Sd/-
Dr. Satyagopal Korlapati, EM

O.A. No.86/2024(SZ)
03rd July, 2024. AD.

Annexure A2

IN THE HIGH COURT OF ANDHRA PRADESH :: AMARAVATI

THE HON'BLE SRI JUSTICE NINALA JAYASURYA

WRIT PETITION No.14868 of 2023

Between:

Ponnapalli Krishna & 11 others .... Petitioners

And

The Mogalthur Gram Panchayath,
Rep. by its Panchayath Secretary,
West Godavari District.,
& 4 others .... Respondents

Counsel for the Petitioners	:	M/s. S.R. Sanku & Mr. S.D Ramachandra Rao
Counsel for the R-1	:	Mr. N. Srihari, S.C for Gram Panchayat
Counsel for the R-2 & R-5	:	G.P for Panchayat Raj
Counsel for the R-3 & R-4	:	G.P for Revenue

ORDER:

Heard learned counsel for the petitioners. Also heard learned Standing Counsel for the 1st respondent. With the consent of both sides, the Writ Petition is being disposed of at the stage of admission.

2. The Writ Petition is filed seeking to declare the action of the respondent No.1 in issuing impugned Notice dated 15.03.2023 calling upon the petitioners to stop the Brick Kiln activities, which are

being conducted in their respective premises, as illegal, unjust, arbitrary, etc., to set aside the same and for consequential orders.

3. The learned counsel for the petitioners with reference to the averments made in the Writ Petition advanced arguments. He submits that the petitioners are permanent residents of Mogalthur Village of the West Godavari District. He submits that petitioners belong to Kummari caste (potters), who make earthen vessels, water pots, etc., since the time of their forefathers they have been eking out their livelihood manufacturing bricks and the petitioners inherited the same from their forefathers and it has been their integral part of their daily life since then. He submits that the petitioners are paying Professional Tax and availing electricity supply. He submits that to the petitioners' utter surprise, the impugned notice was issued by the 1st respondent calling upon them to stop the brick kiln activities alleging that their establishments are causing pollution around the area. He submits that the 1st respondent did not conduct any field survey with regard to the cause of pollution in that area. He submits that no opportunity was given to the petitioners, much less, a show-cause notice inviting them to submit their objections. He submits that the procedure adopted by

the 1st respondent is illegal, arbitrary and violative of principles of natural justice. Making the said submissions, the learned counsel seeks appropriate directions.

4. The Learned Standing Counsel for the 1st respondent-Gram Panchayat on the other hand, made submissions in support of the issuance of impugned notice. However, as seen from the said notice, it would appear that the 1st respondent had straight away called upon the petitioner to stop manufacturing of bricks and prior to that no notice, much less, show cause-notice was issued to enable the petitioners to submit their explanation/objections. The action of the 1st respondent is therefore, not sustainable in Law.

5. Be that as it may. As the notice dated 15.03.2023 is in the form of an order containing directions and is not preceded by any Show-Cause Notice and liable to be set-aside, this Court deems it appropriate to dispose of the Writ Petition with the following directions:-

a) The notice dated 15.03.2023 issued by the 1st respondent shall be treated as Show-Cause Notice.

b) The petitioners shall file their objections/explanation to the said notice, within two weeks.

c) The 1st respondent on receipt of the objections/explanation shall pass appropriate orders strictly in accordance with law, after giving due opportunity of hearing to the petitioners, within a period of four weeks from the date of receipt of the objections/explanation.

d) Till passing of appropriate orders as indicated above, the Gram Panchayat shall not interfere with the activities of the petitioners.

6. The Writ Petition is accordingly disposed of. There shall be no order as to costs. As a sequel, all pending applications shall stand closed.

JUSTICE NINALA JAYASURYA

Date: 23.06.2023
Note: Issue C.C in one week
B/O
GVK

16.

5

110

THE HON'BLE SRI JUSTICE NINALA JAYASURYA

WRIT PETITION No.14868 of 2023

Date: 23.06.2023

GVK

Annexure A3

[3209]

IN THE HIGH COURT OF ANDHRA PRADESH AT AMARAVATI
FRIDAY ,THE FOURTEENTH DAY OF JULY
TWO THOUSAND AND TWENTY THREE
:PRESENT:
THE HONOURABLE SRI JUSTICE NINALA JAYASURYA
IA No. 1 OF 2023
IN
WP NO: 17382 OF 2023

Between:

1. Ponnapalli Krishna, S/o P. Apparao, aged about 48 years old, Occ- Brick Kiln Business, R/o D.No.20-68, Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
2. Ponnapalli Siva Shankara Rao, S/o P. Apparao, aged about 64 years old, Occ- Brick Kiln Business, R/o Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
3. Ponnapalli Ram Prasad, S/o P. Bhaskar Rao, aged about 48 years old, Occ- Brick Kiln Business, R/o Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
4. Adhurthi Satyanarayana, S/o Narayana Murthy, aged about 65 years old, Occ- Brick Kiln Business, R/o Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
5. Kapa Satyanarayana Rao, S/o K. Muthyala Rao, aged about 70 years old, Occ- Brick Kiln Business, Rio Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
6. Kapa Srinivasa Rao, S/o K. Rama Rao, aged about 54 years old, Occ- Brick Kiln Business, R/o Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
7. Manepalli Satyanarayana, S/o Sesha Rao, aged about 60 years old, Occ- Brick Kiln Business, R/o Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
8. Sakkinetipalli Veera Bhaskara Rao, S/o Venkata Muthyam, aged about 53 years old. Occ- Brick Kiln Business, R/o Vadayar Street, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
9. Bonam Naga Devi, W/o late Veera Raghavalu, aged about 65 years old, Occ- Brick Kiln Business, R/o Canal Road, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
10. Kattula Somaraju, S/o Venkateswara Rao, aged 48 years old, Occ- Brick Kiln Business, R/o near ZPHS, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
11. Medicherla Kumar Raju, S/o Venkateswara Rao, aged about 43 years old, Occ- Brick Kiln Business, R/o Near ZPHS, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh
12. Veldi Lakshmi Narayana, S/o Pullaiah, aged about 55 years old, Occ- Brick Kiln Business, R/o Near Shivalayam, Mogalthur Village and Mandal, West Godavari District (Present Bhimavaram District), Andhra Pradesh

...Petitioners
(Petitioner in WP 17382 OF 2023
on the file of High Court)

AND

1. The Tahsildar, Mogaithur Mandal, West Godavari District, Andhra Pradesh
2. The District Collector, West Godavari District, Andhra Pradesh
3. The Mogalthur Gram Panchayath, Represented by its Panchayath Secretaty, Mogaithur Mandal, West Godavari District, Andhra Pradesh
4. The State of Andhra Pradesh, Represented by its Principal Secretary, Department of Revenue, A.P. Secretariat, Velagapudi, Amaravati, Andhra Pradesh

...Respondents
(Respondents in-do-)

Counsel for the Petitioners : Sri S R Sanku & Kaviti Murali Krishna
Counsel for the Respondent Nos.1,2 & 4 : Assistant GP for Revenue
Counsel for the Respondent No.3: Sri N Srihari, Standing Counsel

Petition under Section 151 CPC is filed praying that in the circumstances stated in the affidavit filed in support of the petition, the High Court may be pleased to suspend the order vide Roc.No.32/2023/A issued by the Respondent No. 1 dated 12-07-2023, duly directing the Respondents not to prevent the Petitioners from engaging their primary avocation, Pending disposal of WP No. 17382 of 2023, on the file of the High Court.

The court while directing issue of notice to the Respondents herein to show cause as to why this application should not be complied with, made the following order.(The receipt of this order will be deemed to be the receipt of notice in the case). The Court made the following

ORDER

"Heard learned counsel for the petitioners and learned Assistant Government Pleader for Revenue.

Learned counsel for the petitioners has brought to the notice of this Court that prior to issuance of the impugned proceedings, the 3rd respondent-Gram Panchayat issued notice dated 15.03.2023, which contains certain directions and challenging the said notice, a writ petition is filed *vide* W.P.No.14868 of 2023 and the same was disposed of *vide* order dated 23.06.2023, wherein the petitioners were directed to submit their explanation and thereafter, the Gram Panchayat was given liberty to pass appropriate orders, in accordance with Law, after giving due opportunity of hearing to the petitioners.

To the petitioners' utter surprise, thereafter some notices were issued to them by the 1st respondent herein and the petitioners have not submitted any explanation as they are under the impression that the Gram Panchayat would have to initiate action in terms of the orders passed in W.P.No.14868 of 2023.

He submits that even though the Gram Panchayat has not passed any orders on the explanation submitted by the petitioners, the proceedings have been issued by the 1st respondent. He also submits that the 1st respondent herein is a party to the said writ petition and in those circumstances, the proceedings impugned in the present writ petition are not sustainable.

Let appropriate instructions be obtained with regard to the competency of the Tahsildar in issuing the notices and initiating proceedings in the matter, when an order has already been passed in W.P.No.14868 of 2023 as per which the Gram Panchayat was required to take action in the matter.

List this case after two (2) weeks in the 'Motion List'.

Pending further consideration, no *coercive* action pursuant to the impugned proceedings shall be resorted to, for a period of eight (8) weeks."

Sd/- B. CHITTI JOSEPH
ASSISTANT REGISTRAR

//TRUE COPY//

For A SECTION OFFICER

To,

1. The Tahsildar, Mogaithur Mandal, West Godavari District, Andhra Pradesh
2. The District Collector, West Godavari District, Andhra Pradesh
3. The Panchayath Secretaty, Mogalthur Gram Panchayath ,Mogaithur Mandal, West Godavari District, Andhra Pradesh
4. The Principal Secretary, Department of Revenue, State of Andhra Pradesh ,A.P. Secretariat, Velagapùdi, Amaravati, Andhra Pradesh(1 to 4 By RPAD)
5. One CC to Sri S R Sanku & Kaviti Murali Krishna ,Advocate [OPUC]
6. Two CCs to GP for Revenue,High Court Of Andhra Pradesh. [OUT]
7. One CC to Sri N Srihari, Standing Counsel [OPUC]
8. One spare copy

RVK

HIGH COURT

NJSJ

DATED:14/07/2023

LIST THIS CASE AFTER TWO (2) WEEKS IN THE 'MOTION LIST'.

ORDER

IA No. 1 OF 2023
IN
WP NO: 17382 OF 2023

DIRECTION

HIGH COURT OF ANDHRA PRADESH :: AMARAVATI

MAIN CASE: **WRIT PETITION No.17382 of 2023**

PROCEEDING SHEET

Sl. No.	DATE	ORDER	OFFICE NOTE
2.	03.8.2023	**NJS, J** W.P. No.17382 of 2023 Learned Assistant Government Pleader for Revenue seeks time to secure instructions and file counter, within a period of three (3) weeks. List the matter after four (4) weeks. **NJS, J** *vasu*	

Annexure A4

THE ENVIRONMENT (PROTECTION) ACT, 1986

(Act No.29 of 1986)

THE ENVIRONMENT (PROTECTION) ACT, 1986

No. 29 OF 1986

[23rd May, 1986.]

An Act to provide for the protection and improvement of environment and for matters connected there with:

WHEREAS the decisions were taken at the United Nations Conference on the Human Environment held at Stockholm in June, 1972, in which India participated, to take appropriate steps for the protection and improvement of human environment;

AND WHEREAS it is considered necessary further to implement the decisions aforesaid in so far as they relate to the protection and improvement of environment and the prevention of hazards to human beings, other living creatures, plants and property;

BE it enacted by Parliament in the Thirty-seventh Year of the Republic of India as follows:-

CHAPTER I

PRELIMINARY

1. SHORT TITLE, EXTENT AND COMMENCEMENT.-

(1) This Act may be called the Environment (Protection) Act, 1986.

(2) It extends to the whole of India.

(3) It shall come into force on such date as the Central Government may, by notification in the Official Gazette, appoint and different dates may be appointed for different provisions of this Act and for different areas[1].

2.DEFINITIONS.-

In this Act, unless the context otherwise requires,--

(a) "environment" includes water, air and land and the inter- relationship which exists among and between water, air and land, and human beings, other living creatures, plants, micro-organism and property;

---

[1] It came into force in the whole of India on 19th November, 1986 vide Notification No. G.S.R. 1198(E) dated 12-11-86 published in the Gazette of India No. 525 dated 12-11-86.

(b) "environmental pollutant" means any solid, liquid or gaseous substance present in such concentration as may be, or tend to be, injurious to environment;

(c) "environmental pollution" means the presence in the environment of any environmental pollutant;

(d) "handling", in relation to any substance, means the manufacture, processing, treatment, package, storage, transportation, use, collection, destruction, conversion, offering for sale, transfer or the like of such substance;

(e) "hazardous substance" means any substance or preparation which, by reason of its chemical or physico-chemical properties or handling, is liable to cause harm to human beings, other living creatures, plant, micro-organism, property or the environment;

(f) "occupier", in relation to any factory or premises, means a person who has, control over the affairs of the factory or the premises and includes in relation to any substance, the person in possession of the substance;

(g) "prescribed" means prescribed by rules made under this Act.

CHAPTER II

GENERAL POWERS OF THE CENTRAL GOVERNMENT

3. POWER OF CENTRAL GOVERNMENT TO TAKE MEASURES TO PROTECT AND IMPROVE ENVIRONMENT.-

(1) Subject to the provisions of this Act, the Central Government, shall have the power to take all such measures as it deems necessary or expedient for the purpose of protecting and improving the quality of the environment and preventing controlling and abating environmental pollution.

(2) In particular, and without prejudice to the generality of the provisions of sub-section (1), such measures may include measures with respect to all or any of the following matters, namely:--

(i) co-ordination of actions by the State Governments, officers and other authorities--

(a) under this Act, or the rules made thereunder, or

(b) under any other law for the time being in force which is relatable to the objects of this Act;

(ii) planning and execution of a nation-wide programme for the prevention, control and abatement of environmental pollution;

(iii) laying down standards for the quality of environment in its various aspects;

(iv) laying down standards for emission or discharge of environmental pollutants from various sources whatsoever:

Provided that different standards for emission or discharge may be laid down under this clause from different sources having regard to the quality or composition of the emission or discharge of environmental pollutants from such sources;

(v) restriction of areas in which any industries, operations or processes or class of industries, operations or processes shall not be carried out or shall be carried out subject to certain safeguards;

(vi) laying down procedures and safeguards for the prevention of accidents which may cause environmental pollution and remedial measures for such accidents;

(vii) laying down procedures and safeguards for the handling of hazardous substances;

(viii) examination of such manufacturing processes, materials and substances as are likely to cause environmental pollution;

(ix) carrying out and sponsoring investigations and research relating to problems of environmental pollution;

(x) inspection of any premises, plant, equipment, machinery, manufacturing or other processes, materials or substances and giving, by order, of such directions to such authorities, officers or persons as it may consider necessary to take steps for the prevention, control and abatement of environmental pollution;

(xi) establishment or recognition of environmental laboratories and institutes to carry out the functions entrusted to such environmental laboratories and institutes under this Act;

(xii) collection and dissemination of information in respect of matters relating to environmental pollution;

(xiii) preparation of manuals, codes or guides relating to the prevention, control and abatement of environmental pollution;

(xiv) such other matters as the Central Government deems necessary or expedient for the purpose of securing the effective implementation of the provisions of this Act.

(3) The Central Government may, if it considers it necessary or expedient so to do for the purpose of this Act, by order, published in the Official Gazette, constitute an authority or authorities by such name or names as may be specified in the order for the purpose of exercising and performing such of the powers and functions (including the power to issue directions under section 5) of the Central Government under this Act and for taking measures with respect to such of the matters referred to in sub-section (2) as may be mentioned in the order and subject to the supervision and control of the Central Government and the provisions of such order, such authority or authorities may exercise the powers or perform the functions or take the measures so mentioned in the order as if such authority or authorities had been empowered by this Act to exercise those powers or perform those functions or take such measures.

4. APPOINTMENT OF OFFICERS AND THEIR POWERS AND FUNCTIONS.-

(1) Without prejudice to the provisions of sub-section (3) of section 3, the Central Government may appoint officers with such designation as it thinks fit for the purposes of this Act and may entrust to them such of the powers and functions under this Act as it may deem fit.

(2) The officers appointed under sub-section (1) shall be subject to the general control and direction of the Central Government or, if so directed by that Government, also of the authority or authorities, if any, constituted under sub- section (3) of section 3 or of any other authority or officer.

5. POWER TO GIVE DIRECTIONS.-

Notwithstanding anything contained in any other law but subject to the provisions of this Act, the Central Government may[1], in the exercise of its powers and performance of its functions under this Act, issue directions in writing to any person, officer or any authority and such person, officer or authority shall be bound to comply with such directions[2]

Explanation--For the avoidance of doubts, it is hereby declared that the power to issue directions under this section includes the power to direct--

(a) the closure, prohibition or regulation of any industry, operation or process; or

(b) stoppage or regulation of the supply of electricity or water or any other service.

6. RULES TO REGULATE ENVIRONMENTAL POLLUTION.-

(1) The Central Government may, by notification in the Official Gazette, make rules in respect of all or any of the matters referred to in section 3.

(2) In particular, and without prejudice to the generality of the foregoing power, such rules may provide for all or any of the following matters, namely:--

(a) the standards of quality of air, water or soil for various areas and purposes;[3]

(b) the maximum allowable limits of concentration of various environmental pollutants (including noise) for different areas;

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1 The Central Government has delegated the powers vested in it under section 5 of the Act to the State Governments of Andhra Pradesh, Assam, Bihar, Gujarat, Haryana, Himachal Pradesh, Karnataka, Kerala, Madhya Pradesh, Mizoram, Orissa, Rajasthan, Sikkim and Tamil Nadu subject to the condition that the Central Government may revoke such delegation of Powers in respect of all or any one or more of the State Governments or may itself invoke the provisions of section 5 of the Act, if in the opinion of the Central Government such a course of action is necessary in public interest, (Notification No. S.O. 152 (E) dated 10-2-88 published in Gazette No. 54 of the same date). These Powers have been delegated to the following State Governments also on the same terms: Meghalaya, Punjab and Uttar Pradesh vide Notification No. S.O.389 (E) dated 14-4-88 published in the Gazette No. 205 dated 14-4-88; Maharashtra vide Notification No. S.O. 488(E) dated 17-5-88 published in the Gazette No. 255 dated 17-5-88; Goa and Jammu & Kashmir vide Notification No. S.O. 881 (E) dated 22-9-88; published in the Gazette No. 749 dated 22.9.88 West Bengal Manipur vide Notification N. S.O. 408 (E) dated 6-6-89; published in the Gazette No. 319 dated 6-6-89; Tripura vide Notification No. S.O. 479 (E) dated 25-7-91 published in the Gazette No. 414 dated 25-7-91.

2 For issuing directions see r.4 of Environment (Protection) Rules, 1986.

3 See r. 3 of Environment (Protection) Rules, 1986 and Schedules thereto.

i. Schedule I lists the standards for emission or discharge of environmental pollutants from the industries, processes or operations and their maximum allowable limits of concentration;

ii. Schedule II lists general standards for discharge of effluents and their maximum limits of concentration allowable (Schedule II omitted by G.S.R.801(E), dated 31.12.1993.)

iii. Schedule III lists ambient air quality standards in respect of noise and its maximum allowable limits; and

iv. Schedule IV lists standards for emission of smoke, vapour etc. from motor vehicles and maximum allowable limits of their emission.

v. Schedule V – furnishing of information to authorities and agencies. Schedule II re-numbered as Schedule V vide G.S.R.422(E), dated 19.5.1993.

vi. Schedule VI – inserted vide GSR422(E), dated 19.5.1993 for General Standards for discharge of Environmental Pollutants,

vii. Schedule VII – inserted vide GSR176 (E), dated 2.4.1996.for National Ambient Air Quality Standards,

(c) the procedures and safeguards for the handling of hazardous substances;[1]

(d) the prohibition and restrictions on the handling of hazardous substances in different areas;[2]

(e) the prohibition and restriction on the location of industries and the carrying on process and operations in different areas;[3]

(f) the procedures and safeguards for the prevention of accidents which may cause environmental pollution and for providing for remedial measures for such accidents.[4]

CHAPTER III

PREVENTION, CONTROL, AND ABATEMENT OF ENVIRONMENTAL POLLUTION

7. PERSONS CARRYING ON INDUSTRY OPERATION, ETC., NOT TO ALLOW EMISSION OR DISCHARGE OF ENVIRONMENTAL POLLUTANTS IN EXCESS OF THE STANDARDS.-

No person carrying on any industry, operation or process shall discharge or emit or permit to be discharged or emitted any environmental pollutants in excess of such standards as may be prescribed[5].

8. PERSONS HANDLING HAZARDOUS SUBSTANCES TO COMPLY WITH PROCEDURAL SAFEGUARDS.-

No person shall handle or cause to be handled any hazardous substance except in accordance with such procedure and after complying with such safeguards as may be prescribed[1].

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1 See r. 13 of Environment (Protection) Rules, 1986, and
i. Hazardous Wastes (Management, Handling and Transboundary Movement) Rules, 2008;
ii. Manufacture, Storage and Import of Hazardous Chemicals Rules, 1989; and
iii. Manufacture, Use, Import, Export and Storage of Hazardous Micro organisms, Genetically/Engineered Organisms or Cells Rules, 1989

2 Rule 13 SUPRA

3 See r. 5 of Environment (Protection) Rules, 1986.

4 See r. 12 of Environment (Protection) Rules and Schedule V (Schedule II renumbered as Schedule V), and relevant provisions of Hazardous Wastes (Management, Handling and Transboundary Movement) Rules, 2008, Manufacture, Storage and Import of Hazardous Chemicals Rules and Manufacture, Use, Import Export and Storage of hazardous Micro-organisms, Genetically Engineered Organisms or Cells Rules, 1989.

5 See r. 3 of Environment (Protection) Rules, 1986 and Schedule I.

9. FURNISHING OF INFORMATION TO AUTHORITIES AND AGENCIES IN CERTAIN CASES.-

(1) Where the discharge of any environmental pollutant in excess of the prescribed standards occurs or is apprehended to occur due to any accident or other unforeseen act or event, the person responsible for such discharge and the person in charge of the place at which such discharge occurs or is apprehended to occur shall be bound to prevent or mitigate the environmental pollution caused as a result of such discharge and shall also forthwith--

(a) intimate the fact of such occurrence or apprehension of such occurrence; and

(b) be bound, if called upon, to render all assistance, to such authorities or agencies as may be prescribed[1]

(2) On receipt of information with respect to the fact or apprehension of any occurrence of the nature referred to in sub-section (1), whether through intimation under that sub-section or otherwise, the authorities or agencies referred to in sub-section (1) shall, as early as practicable, cause such remedial measures to be taken as are necessary to prevent or mitigate the environmental pollution.

(3) The expenses, if any, incurred by any authority or agency with respect to the remedial measures referred to in sub-section (2), together with interest (at such reasonable rate as the Government may, by order, fix) from the date when a demand for the expenses is made until it is paid, may be recovered by such authority or agency from the person concerned as arrears of land revenue or of public demand.

10. POWERS OF ENTRY AND INSPECTION.-

(1) Subject to the provisions of this section, any person empowered by the Central Government in this behalf[2] shall have a right to enter, at all reasonable times with such assistance as he considers necessary, any place—

(a) for the purpose of performing any of the functions of the Central Government entrusted to him;

(b) for the purpose of determining whether and if so in what manner, any such functions are to be performed or whether any provisions of this Act or the rules made thereunder or any notice, order, direction or authorisation served, made, given or granted under this Act is being or has been complied with;

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1 For authorities or agencies see r. 12 of Environment (Protection) Rules, 1986 and Schedule V (Schedule II re-numbered as Schedule V).

2 The Central Govt. has empowered 64 persons listed in the Table of Notification No.S.O. 83 (E) published in the Gazette of India No. 66 dated 16-2-87.

(c) for the purpose of examining and testing any equipment, industrial plant, record, register, document or any other material object or for conducting a search of any building in which he has reason to believe that an offence under this Act or the rules made thereunder has been or is being or is about to be committed and for seizing any such equipment, industrial plant, record, register, document or other material object if he has reason to believe that it may furnish evidence of the commission of an offence punishable under this Act or the rules made thereunder or that such seizure is necessary to prevent or mitigate environmental pollution.

(2) Every person carrying on any industry, operation or process of handling any hazardous substance shall be bound to render all assistance to the person empowered by the Central Government under sub-section (1) for carrying out the functions under that sub-section and if he fails to do so without any reasonable cause or excuse, he shall be guilty of an offence under this Act.

(3) If any person willfully delays or obstructs any persons empowered by the Central Government under sub-section (1) in the performance of his functions, he shall be guilty of an offence under this Act.

(4) The provisions of the Code of Criminal Procedure, 1973, or, in relation to the State of Jammu and Kashmir, or an area in which that Code is not in force, the provisions of any corresponding law in force in that State or area shall, so far as may be, apply to any search or seizures under this section as they apply to any search or seizure made under the authority of a warrant issued under section 94 of the said Code or as the case may be, under the corresponding provision of the said law.

11. POWER TO TAKE SAMPLE AND PROCEDURE TO BE FOLLOWED IN CONNECTION THEREWITH.-

(1) The Central Government or any officer empowered by it in this behalf[1], shall have power to take, for the purpose of analysis, samples of air, water, soil or other substance from any factory, premises or other place in such manner as may be prescribed.[2]

(2) The result of any analysis of a sample taken under sub-section (1) shall not be admissible in evidence in any legal proceeding unless the provisions of sub-sections (3) and (4) are complied with.

(3) Subject to the provisions of sub-section (4), the person taking the sample under sub-section (1) shall--

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1 In exercise of powers conferred under sub-section (i) of section 11 the Central Government has empowered 64 officers listed in the Table vide S.O. 84. (E) published in the Gazette No. 66 dated 16-2-87

2 For procedure for taking samples see r. 6 of Environment (Protection) Rules, 1986, also

(a) serve on the occupier or his agent or person in charge of the place, a notice, then and there, in such form as may be prescribed, of his intention to have it so analysed;

(b) in the presence of the occupier or his agent or person, collect a sample for analysis;

(c) cause the sample to be placed in a container or containers which shall be marked and sealed and shall also be signed both by the person taking the sample and the occupier or his agent or person;

(d) send without delay, the container or the containers to the laboratory established or recognised by the Central Government under section 12.

(4) When a sample is taken for analysis under sub-section (1) and the person taking the sample serves on the occupier or his agent or person, a notice under clause (a) of sub-section (3), then,--

(a) in a case where the occupier, his agent or person wilfully absents himself, the person taking the sample shall collect the sample for analysis to be placed in a container or containers which shall be marked and sealed and shall also be signed by the person taking the sample, and

(b) in a case where the occupier or his agent or person present at the time of taking the sample refuses to sign the marked and sealed container or containers of the sample as required under clause (c) of sub-section (3), the marked and sealed container or containers shall be signed by the person taking the samples, and the container or containers shall be sent without delay by the person taking the sample for analysis to the laboratory established or recognised under section 12 and such person shall inform the Government Analyst appointed or recognised under section 13 in writing, about the wilfull absence of the occupier or his agent or person, or, as the case may be, his refusal to sign the container or containers.

12. ENVIRONMENTAL LABORATORIES.-

(1) The Central Government[1] may, by notification in the Official Gazette,--

(a) establish one or more environmental laboratories;

(b) recognise one or more laboratories or institutes as environmental laboratories to carry out the functions entrusted to an environmental laboratory under this Act[2].

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1 The Central Government has delegated its powers under clause (b) of sub-section (i) of section 12 and section 13 of the Act to the Central Pollution Control Board vide Notification No. S.O. 145 (E) dated 21-2-91 published in the Gazette No. 128 dated 27-2-91

2 The list of laboratories/institutes recognised as environmental laboratories: and the persons recognised as Govt. Analysts.

(2) The Central Government may, by notification in the Official Gazette, make rules specifying--

(a) the functions of the environmental laboratory;[1]

(b) the procedure for the submission to the said laboratory of samples of air, water, soil or other substance for analysis or tests, the form of the laboratory report thereon and the fees payable for such report;[2]

(c) such other matters as may be necessary or expedient to enable that laboratory to carry out its functions.

13. GOVERNMENT ANALYSTS.-

The Central Government may by notification in the Official Gazette, appoint or recognise such persons as it thinks fit and having the prescribed qualifications[3] to be Government Analysts for the purpose of analysis of samples of air, water, soil or other substance sent for analysis to any environmental laboratory established or recognised under sub-section (1) of section 12.

14. REPORTS OF GOVERNMENT ANALYSTS.-

Any document purporting to be a report signed by a Government analyst may be used as evidence of the facts stated therein in any proceeding under this Act.

15. PENALTY FOR CONTRAVENTION OF THE PROVISIONS OF THE ACT AND THE RULES, ORDERS AND DIRECTIONS.-

(1) Whoever fails to comply with or contravenes any of the provisions of this Act, or the rules made or orders or directions issued thereunder, shall, in respect of each such failure or contravention, be punishable with imprisonment for a term which may extend to five years with fine which may extend to one lakh rupees, or with both, and in case the failure or contravention continues, with additional fine which may extend to five thousand rupees for every day during which such failure or contravention continues after the conviction for the first such failure or contravention.

(2) If the failure or contravention referred to in sub-section (1) continues beyond a period of one year after the date of conviction, the offender shall be punishable with imprisonment for a term which may extend to seven years.

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1 See r. 9 of Environment (Protection) Rules, 1986.

2 See r. 8 of Environment (Protection) Rules, 1986.

3 For qualifications of Govt. Analyst see r. 10 of Environment (Protection) Rules, 1986.

16. OFFENCES BY COMPANIES.-

(1) Where any offence under this Act has been committed by a company, every person who, at the time the offence was committed, was directly in charge of, and was responsible to, the company for the conduct of the business of the company, as well as the company, shall be deemed to be guilty of the offence and shall be liable to be proceeded against and punished accordingly:

Provided that nothing contained in this sub-section shall render any such person liable to any punishment provided in this Act, if he proves that the offence was committed without his knowledge or that he exercised all due diligence to prevent the commission of such offence.

(2) Notwithstanding anything contained in sub-section (1), where an offence under this Act has been committed by a company and it is proved that the offence has been committed with the consent or connivance of, or is attributable to any neglect on the part of, any director, manager, secretary or other officer of the company, such director, manager, secretary or other officer shall also deemed to be guilty of that offence and shall be liable to be proceeded against and punished accordingly.

Explanation--For the purposes of this section,--

(a) "company" means any body corporate and includes a firm or other association of individuals;

(b) "director", in relation to a firm, means a partner in the firm.

17. OFFENCES BY GOVERNMENT DEPARTMENTS.-

(1) Where an offence under this Act has been committed by any Department of Government, the Head of the Department shall be deemed to be guilty of the offence and shall be liable to be proceeded against and punished accordingly.

Provided that nothing contained in this section shall render such Head of the Department liable to any punishment if he proves that the offence was committed without his knowledge or that he exercise all due diligence to prevent the commission of such offence.

(2) Notwithstanding anything contained in sub-section (1), where an offence under this Act has been committed by a Department of Government and it is proved that the offence has been committed with the consent or connivance of, or is attributable to any neglect on the part of, any officer, other than the Head of the Department, such officer shall also be deemed to be guilty of that offence and shall be liable to be proceeded against and punished accordingly.

CHAPTER IV

MISCELLANEOUS

18. PROTECTION OF ACTION TAKEN IN GOOD FAITH.-

No suit, prosecution or other legal proceeding shall lie against the Government or any officer or other employee of the Government or any authority constituted under this Act or any member, officer or other employee of such authority in respect of anything which is done or intended to be done in good faith in pursuance of this Act or the rules made or orders or directions issued thereunder.

19. COGNIZANCE OF OFFENCES.-

No court shall take cognizance of any offence under this Act except on a complaint made by--

(a) the Central Government or any authority or officer authorised in this behalf by that Government[1], or

(b) any person who has given notice of not less than sixty days, in the manner prescribed, of the alleged offence and of his intention to make a complaint, to the Central Government or the authority or officer authorised as aforesaid.

20. INFORMATION, REPORTS OR RETURNS.-

The Central Government may, in relation to its function under this Act, from time to time, require any person, officer, State Government or other authority to furnish to it or any prescribed authority or officer any reports, returns, statistics, accounts and other information and such person, officer, State Government or other authority shall be bound to do so.

21. MEMBERS, OFFICERS AND EMPLOYEES OF THE AUTHORITY CONSTITUTED UNDER SECTION 3 TO BE PUBLIC SERVANTS.-

All the members of the authority, constituted, if any, under section 3 and all officers and other employees of such authority when acting or purporting to act in pursuance of any provisions of this Act or the rules made or orders or directions issued thereunder shall be deemed to be public servants within the meaning of section 21 of the Indian Penal Code (45 of 1860).

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[1] In exercise of powers conferred under clause (a) of section 19, the Central Government has authorised the officers and authorities listed in the Table of Notification No.S.O. 394 (E) published in the Gazette No. 185 dated 16-4-87, S.O. 237(E) published in the Gazette No. 171 dated 29-3-89 and S.O. 656(E) dated 21-8-89 published in the Gazette No. 519 dated 21-8-89, S.O.624(E), dated 3.9.1996 and G.S.R.587(E), dated 1.9.2006.

22. BAR OF JURISDICTION.-

No civil court shall have jurisdiction to entertain any suit or proceeding in respect of anything done, action taken or order or direction issued by the Central Government or any other authority or officer in pursuance of any power conferred by or in relation to its or his functions under this Act.

23. POWERS TO DELEGATE.-

Without prejudice to the provisions of sub-section (3) of section 3, the Central Government may, by notification in the Official Gazette, delegate, subject to such conditions and limitations as may be specified in the notifications, such of its powers and functions under this Act [except the powers to constitute an authority under sub-section (3) of section 3 and to make rules under section 25] as it may deem necessary or expedient, to any officer, State Government or other authority.

24. EFFECT OF OTHER LAWS.-

(1) Subject to the provisions of sub-section (2), the provisions of this Act and the rules or orders made therein shall have effect notwithstanding anything inconsistent therewith contained in any enactment other than this Act.

(2) Where any act or omission constitutes an offence punishable under this Act and also under any other Act then the offender found guilty of such offence shall be liable to be punished under the other Act and not under this Act.

25. POWER TO MAKE RULES.-

(1) The Central Government may, by notification in the Official Gazette, make rules for carrying out the purposes of this Act.

(2) In particular, and without prejudice to the generality of the foregoing power, such rules may provide for all or any of the following matters, namely--

(a) the standards in excess of which environmental pollutants shall not be discharged or emitted under section 7[1];

(b) the procedure in accordance with and the safeguards in compliance with which hazardous substances shall be handled or caused to be handled under section 8;[2]

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1 See Rule 3 of Environment (Protection) Rules, 1986 and Schedule-I.

2 See r. 13 of Environment (Protection) Rules, 1986, and

i. Hazardous Wastes (Management, Handling and Transboundary Movement) Rules, 2008

ii. Manufacture, Storage and Import of Hazardous Chemicals Rules, 1989; and

iii. Manufacture, Use, Import, Export and Storage of Hazardous Micro organisms, Genetically- engineered organisms or Cells Rules, 1989.

(c) the authorities or agencies to which intimation of the fact of occurrence or apprehension of occurrence of the discharge of any environmental pollutant in excess of the prescribed standards shall be given and to whom all assistance shall be bound to be rendered under sub-section (1) of section 9;[1]

(d) the manner in which samples of air, water, soil or other substance for the purpose of analysis shall be taken under sub-section (1) of section 11;[2]

(e) the form in which notice of intention to have a sample analysed shall be served under clause (a) of sub section (3) of section 11;[3]

(f) the functions of the environmental laboratories,[4] the procedure for the submission to such laboratories of samples of air, water, soil and other substances for analysis or test;[5] the form of laboratory report; the fees payable for such report and other matters to enable such laboratories to carry out their functions under sub-section (2) of section 12;

(g) the qualifications of Government Analyst appointed or recognised for the purpose of analysis of samples of air, water, soil or other substances under section 13;[6]

(h) the manner in which notice of the offence and of the intention to make a complaint to the Central Government shall be given under clause (b) of section 19;[7]

(i) the authority of officer to whom any reports, returns, statistics, accounts and other information shall be furnished under section 20;

(j) any other matter which is required to be, or may be, prescribed.

26. RULES MADE UNDER THIS ACT TO BE LAID BEFORE PARLIAMENT.-

Every rule made under this Act shall be laid, as soon as may be after it is made, before each House of Parliament, while it is in session, for a total period of thirty days which may be comprised in one session or in two or more successive sessions, and if, before the expiry of the session immediately following the session or the successive sessions aforesaid, both Houses agree in making any modification in the rule or both Houses agree that the rule should not be made, the rule shall thereafter have effect only in such modified form or be of no effect, as the case may be; so, however, that any such modification or annulment shall be without prejudice to the validity of anything previously done under that rule.

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1 For authorities or agencies see r. 12 of Environment (Protection) Rules, 1986 and Schedule II.

2 See r.6 of Environment (Protection) Rules, 1986.

3 See r. 7 of Environment (Protection) Rules, 1986.

4 See r. 9 of Environment (Protection) Rules, 1986.

5 For the procedure for submission of samples to laboratories and the form of laboratory report see r. 8 of Environment (Protection) Rules, 1986.

6 See r. 10 of Environment (Protection) Rules, 1986.

7 See r. 11 of Environment (protection) Rules, 1986.

Annexure A5


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Annexure A6

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Environmental risk factors for liver cancer and nonalcoholic fatty liver disease

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Abstract

Purpose of review:

The objective of this review was to summarize recent epidemiologic research examining the associations between environmental exposures and liver cancer and nonalcoholic fatty liver disease (NAFLD).

Recent findings:

There were 28 liver cancer studies showing positive associations for exposures to aflatoxin, air pollution, polycyclic aromatic hydrocarbons, asbestos, chimney sweeping occupation, and paints; an inverse association for ultraviolet radiation; and null/inconsistent results for organic

solvents, pesticides, perfluorooctanoic acid, nuclear radiation, iron foundry occupation, and brick kiln pollution. There were n=5 NAFLD studies showing positive associations for heavy metals, methyl tertiary-butyl ether, and selenium; and no association with trihalomethanes.

Summary:

Evidence suggests that particular environmental exposures may be associated with liver cancer and NAFLD. Future liver cancer studies should examine specific histological subtypes and assess historical environmental exposures. Future NAFLD research should examine incident, biopsy-confirmed cases and the potential role of obesity and/or diabetes in studies of environmental factors and NAFLD.

Keywords: liver cancer, nonalcoholic fatty liver disease, environmental exposures, epidemiology, risk factors

Introduction

Liver cancer incidence and mortality has increased in many regions around the world [1–4]. Liver cancer was the seventh leading cause of cancer and the third leading cause of cancer-related death in 2018 [5]. Liver cancer incidence in 2018 was 13.9 per 100,000 among males and 4.9 per 100,000 among females [5]. Rising incidence is accompanied by low five-year relative survival rates (ranging from 5–30% from 2000–2014) as many cases are diagnosed at a late stage [6]. The most commonly occurring histological subtype of primary liver cancer is hepatocellular carcinoma (HCC), accounting for over 85% of cases [7]. Risk factors vary by geography and include chronic hepatitis B virus (HBV) infection and aflatoxin in parts of Asia, sub-Saharan Africa, and Guatemala; chronic HCV, heavy alcohol consumption, obesity, diabetes, and smoking are risk factors in parts of North America and Europe [8–10]. In the US, upwards of 40.5% of HCC cases are unexplained by known risk factors including chronic HBV, chronic HCV, alcohol consumption, obesity, and diabetes [11].

In addition to the rise in liver cancer incidence is the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) among adults, adolescents, and children [12–14]. NAFLD, a risk factor for HCC [15], is the most common cause of chronic liver disease in the world affecting approximately 24% of the global population [16]. NAFLD is defined as the presence of ≥5% of hepatic steatosis without competing liver disease etiologies (e.g., HCV), use of medications that induce steatosis (e.g., tamoxifen), other chronic liver diseases (e.g., hemochromatosis), and heavy alcohol consumption [17]. NAFLD is projected to be the next global epidemic as the leading cause of liver-related morbidity and mortality in 20 years [18]. NAFLD can progress to nonalcoholic steatohepatitis (NASH), cirrhosis, and HCC. The major risk factors for NAFLD

include obesity, type II diabetes, and dyslipidemia [16]. However, upwards of 30% of NAFLD cases occur among the non-obese (i.e., lean NAFLD; who may have altered metabolic profiles that can lead to diabetes [19]), and up to 52% of cases occur among non-diabetics [20–22].

The liver is susceptible to xenobiotic-induced injury due to its central role in xenobiotic metabolism and its portal location within circulation [23, 24]. Toxic metabolites generated during metabolism are the predominant cause of liver damage, potentially leading to chronic intrahepatic exposures to chemicals that may affect gene expression related to their metabolism [24, 25]. Previous studies have demonstrated that particular environmental exposures, including aflatoxin, vinyl chloride, arsenic, and polycyclic aromatic hydrocarbons (PAHs), are hepatocarcinogenic in humans and animals [24]. Most cases of HCC develop within a background of oxidative stress and inflammation [26, 27]; many of these environmental factors (e.g., PAHs, asbestos) are hypothesized to contribute to liver cancer development through these mechanisms. However, as epidemiologic studies for several of these exposures (apart from aflatoxin) have largely been occupational, the results have been difficult to interpret due to issues such as small sample sizes [24].

To date, research into environmental risk factors for NAFLD has largely been conducted in animal compared to epidemiologic studies [28–30]. As the liver is the central organ controlling lipid homeostasis, exposures to endocrine-disrupting compounds (particularly during early life), such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polychlorinated biphenyls (PCBs), benzo[*a*]pyrene, bisphenol A (BPA), and phthalates, have been implicated in the development of fatty liver disease through mechanisms including binding to nuclear hormone receptors and epigenetic alterations [28–30]. Many of these compounds, including BPA and phthalates, have also been shown to promote obesity, which is a risk factor for NAFLD [30]. Further, toxicant-associated fatty liver disease (TAFLD) is a recognized liver pathology attributed to industrial chemical exposures such as pesticides, PCBs, and dioxin-like compounds (e.g., TCDD) [31, 32]. In addition, individuals with TAFLD may have a low body mass index (BMI) and no insulin resistance, suggesting a pathway unrelated to obesity and diabetes underlying fatty liver disease development in some cases [33].

The environmental epidemiology of liver cancer and NAFLD remain important research areas given existing geographic variation in liver cancer incidence [5, 24] and NAFLD prevalence [34–36], increasing incidence/prevalence [2, 13], HCC and NAFLD cases occurring among individuals without major risk factors [11, 20–22], and demonstrated biological plausibility in the hepatotoxic effects of particular environmental exposures [24, 28–32]. The objective of this narrative review was to summarize recent epidemiologic research examining the associations between environmental exposures and liver cancer and NAFLD.

42.

Methods

Two separate searches of the MEDLINE database (accessed via PubMed) for liver cancer and NAFLD were performed for studies from January 2013 to April 2018. Limits for humans, English language, and original research were applied to the searches. The following terms were searched as exploded MeSH terms and in all fields (e.g., title and abstract): 'environmental exposures AND liver neoplasms' and 'environmental exposures AND non-alcoholic fatty liver disease'. A total of n=359 liver cancer studies and n=31 NAFLD studies were screened by title and abstract for relevance, resulting in n=35 liver cancer studies and n=6 NAFLD studies reviewed for inclusion criteria. Full-text papers were evaluated according to the following *a priori*-determined eligibility criteria for inclusion into the review: an outcome of interest was primary liver cancer or NAFLD (excluding mortality studies due to potential lack of histological confirmation and study results addressing prognosis, e.g., differential survival influenced by socioeconomic factors, rather than cancer development); an exposure of interest was environmental (defined as physical, chemical, biological, social, or economic factors excluding dietary assessments [37]); and appropriate methodological design (.e., studies were excluded if they lacked methodological details to determine the study design, exposure assessment, or statistical analysis) and sufficient reporting of results (i.e., studies were excluded if there were no reported effect estimates). All cited references in each evaluated paper were also examined for inclusion into the review. There were n=28 (n=3 from citation chaining) liver cancer studies and n=5 (n=1 from citation chaining) NAFLD studies included in the review.

Results

Environmental exposures and liver cancer

Summary

There were n=28 liver cancer studies examining the following environmental exposures in Table 1: aflatoxin (4 studies), air pollution (3), polycyclic aromatic hydrocarbons (3), asbestos (3), organic solvents (3), pesticides (6), perfluorooctanoic acid (2), iron foundry occupation (1), radiation (2), brick kiln pollution (1), and parental occupational exposures to chemicals (1) (one study examined multiple exposures) [38–65]. Most studies were conducted in China and Taiwan (n=10) and the US (n=7). There were n=13 epidemiologic studies conducted among occupationally exposed individuals [38, 40, 42, 43, 45, 46, 53, 57, 60–62, 64, 65]. Environmental exposure assessments included biomonitoring, occupational titles, job-exposure matrices (JEMs), self-report, and geospatial-based methods linking residential locations with exposure models using geographic information systems (GIS). Most studies examined liver cancer combining multiple histologies (e.g., HCC and intrahepatic bile duct cancer).

43.

Table 1.

Epidemiologic studies examining environmental risk factors for liver cancer (2013–2018)

Study	Location	Study design	Time period	Study population	Exposure
Aflatoxin					
Long et al. (2013) [47]	China	Retrospective case-control, GxE	2004–2010	Hospital-based; n=2,045 healthy controls matched on age, sex, ethnicity, HBV, HCV	Aflatoxin

44.

Study	Location	Study design	Time period	Study population	Exposure
Yao et al. (2014) [63]	China	Retrospective case-control, GxE	2004–2012	Hospital-based; n=1,996 healthy controls matched on age, sex, ethnicity, HBV, HCV	Aflatoxin
Chu et al. (2017) [41]	Taiwan	Prospective nested casecontrol	1991–2004	Chronic HBV carriers; n=577 controls matched on age, sex, residence, date of blood collection	Aflatoxin

45.

Study	Location	Study design	Time period	Study population	Exposure
Lai et al. (2014) [46]	China	Retrospective case-control	1994–2013	Sugar and papermaking factory workers; n=150 healthy controls who worked for same company	Aflatoxin
Air pollution					
Pan et al. (2016) [49]	Taiwan	Prospective cohort	1991–2009	Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study (n=22,062)	$PM_{2.5}$

46.

Study	Location	Study design	Time period	Study population	Exposure
Pedersen et al. (2017) [51]	Austria, Denmark, Italy	Prospective cohort	1985–2012	Four cohorts in European Study of Cohorts for Air Pollution Effects (ESCAPE) study (n=174,770)	Available for all cohorts: NO_2 and NO_x; available for Denmark and Austria only: $PM_{1(}$ PM2.5, PM2.5–10, PM absorbance (soot), traffic density

47.

Study	Location	Study design	Time period	Study population	Exposure
Niu et al. (2016) [48]	China	Retrospective case-control	2011–2014	Residents of Xiamen; n=346 healthy controls frequency-matched on age, sex	Indoor air pollution, pesticides, environmental tobacco smoke (ETS)
Polycyclic aromatic hydrocarbons					

48.

Study	Location	Study design	Time period	Study population	Exposure
Su et al. (2014) [54]	China	Retrospective case-control	2007–2009	Hospital-based; n=961 healthy controls matched on age, sex, ethnicity	B[*a*]P

49.

Study	Location	Study design	Time period	Study population	Exposure
Tian et al. (2016) [55]	China	Retrospective case-control	Not reported	Hospital-based; n=99 healthy volunteers	B[*a*]P
Hogstedt et al. (2013) [43]	Sweden	Retrospective cohort	1958–2006	Male chimney sweep trade union members (n=6,320)	Chimney sweepin occupation
Asbestos					
Boulanger et al. (2015) [38]	France	Retrospective cohort	1978–2009	Asbestos-exposed workers (n=2,024)	Asbestos

50.

Study	Location	Study design	Time period	Study population	Exposure
Wu et al. (2015) [61]	Taiwan	Retrospective cohort	1985–2008	Shipbreaking Workers Union; n=4,427 shipbreaking workers and population-based cohort (n=22,135) matched on age, sex, place of residence	Asbestos
Wu et al. (2014) [62]	Taiwan	Retrospective cohort	1985–2008	Shipbreaking Workers Union (n= 4,155 males)	Asbestos
Organic solvents					

51.

Study	Location	Study design	Time period	Study population	Exposure
Hansen et al. (2013) [42]	Denmark, Finland, Sweden	Prospective cohort	1958–2008	Workers exposed to TCE (n=5,553)	TCE

52.

Study	Location	Study design	Time period	Study population	Exposure
Vlaanderen et al. (2013) [57]	Denmark, Finland, Iceland, Norway, Sweden	Prospective nested casecontrol	1960–2005	Nordic Occupational Cancer Cohort (n>45 million); n=119,480 controls matched on age, sex, country	TCE and PER
Press et al. (2016) [52]	US	Cancer cluster	1988–2011	Greater Bay Area Cancer Registry catchment area in California	TCE
Pesticides					

53.

Study	Location	Study design	Time period	Study population	Exposure
Yi et al. (2014) [64]	Korea	Prospective cohort	1992–2003	Korean Veterans Health Study (n=180,251 males)	Agent Orange
Yi et al. (2013) [65]	Korea	Cross-sectional	2004	Korean Veterans Health Study (n=114,562)	Agent Orange

54.

Study	Location	Study design	Time period	Study population	Exposure
Silver et al. (2015) [53]	US	Prospective cohort	1993–2011	Agricultural Health Study (n=49,616)	Metolachlor
VoPham et al. (2015) [59]	US	Retrospective case-control	2000–2009	SEER-Medicare; n=14,991 controls frequency-matched on age, sex, race, duration of California residence, year	Pesticides (organochlorines, organophosphate: carbamates)

55.

Study	Location	Study design	Time period	Study population	Exposure
Kachuri et al. (2017) [40]	Canada	Retrospective cohort	1991–2010	Canadian Census Health and Environment Cohort (CanCHEC) (n=2,051,315)	Agricultural occupation
Perfluorooctanoic acid					

56.

Study	Location	Study design	Time period	Study population	Exposure
Vieira et al. (2013) [56]	US	Retrospective case-control	1996–2005	C8 Health Project (n=25,107 cancer cases) residents living near DuPont Teflonmanufacturing plant; other-cancer controls excluding kidney, pancreatic, testicular, and liver	PFOA
Barry et al. (2013) [39]	US	Retrospective cohort	1952–2011	Residents of MidOhio Valley as part of C8 Health Project and DuPont Worker Cohort (n=32,254)	PFOA
Iron foundry occupation					
Westberg et al.	Sweden	Prospective cohort	1958–2004	Iron foundry workers (n=3,045	Iron foundry occupation

Study	Location	Study design	Time period	Study population	Exposure
(2013) [60]				males)	
Radiation					
Labutina et al. (2013) [45]	Russia	Prospective cohort	1948–2004	Mayak nuclear workers (n=22,373)	Radiation: nuclear
VoPham et al. (2017)	US	Ecological	2000–2014	SEER	Radiation: ultraviolet (UV)

58.

Study	Location	Study design	Time period	Study population	Exposure
[58]					
Brick kiln pollution					
Pasetto et al. (2013) [50]	Italy	Retrospective cohort	1994–2007	Residents in East quadrant, Ferrara, Italy (n=2,578)	Brick kiln pollutio (e.g., vinyl chloride, chlorinated ethenes, ethanes)
Parental occupational exposures to chemicals					
Janitz et al. (2017)	US	Retrospective case-control	2000–2008	HOPE study; n=387 birth certificate	Parental occupational

59.

Study	Location	Study design	Time period	Study population	Exposure
[44]				controls frequency-matched on sex, region of birth, birth weight	exposures (e.g., plastics, paints, diesel)

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Abbreviations: AFB1, aflatoxin B1; AFP, alpha-febottomrotein; ALT, alanine aminotransferase; B[*a*]P, benzo[*a*]pyrene; BMI, body mass index; BPDE, benzo[*a*]pyrene diolepoxide; CI, confidence interval; GIS, geographic information system; GxE, gene-environment interaction; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; int, interaction; IRR, incidence rate ratio; JEM, job-exposure matrix; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; OR, odds ratio; PER, perchloroethylene; PFOA, perfluorooctanoic acid; PM_{10}, particulate matter <10 microns; $PM_{2.5}$, particulate matter <2.5 microns; $PM_{2.5-10}$, particulate matter 2.5–10 microns; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results; SES, socioeconomic status; SIR, standardized incidence ratio; TCE, trichloroethylene; U-TCA, urinary trichloroacetate.

Aflatoxin

Aflatoxin, produced by fungi forming on food such as corn and rice in moist conditions, is a hepatocarcinogen acting through DNA damage mechanisms [7]. Although aflatoxin is an established risk factor for HCC [66], several studies in China and Taiwan conducted novel investigations into potential gene-environment interactions (GxE) [47, 63], the role of aflatoxin

in the etiology of cirrhotic vs. non-cirrhotic HCC [41], and airborne aflatoxin exposure (compared to dietary exposure) [46]. Two retrospective case-control studies showed evidence of GxE interactions between AFB1-albumin and DNA adducts and variants for DNA repair genes (*XRCC1*, *XRCC3*, *XRCC7*, *XRCC4*, *XPC*, *XPD*) on HCC risk [47, 63]. A prospective nested case-control study among chronic HBV carriers showed that higher AFB1-albumin adducts were associated with an increased risk for cirrhotic HCC (adjusted OR 5.47, 95% CI 2.20–13.63) and non-cirrhotic HCC (adjusted OR 5.39, 95% CI 1.11–26.18) [41]. Aflatoxin was also associated with an increased risk for cirrhosis (adjusted OR 2.45, 95% CI 1.51–3.98) and cirrhotic HCC compared to cirrhotic controls (adjusted OR 3.04, 95% CI 1.11–8.30) [41]. Most HCC cases occur among cirrhotics [67]. These results demonstrate that aflatoxin may contribute to the development of cirrhosis, progression of cirrhosis to liver cancer, and the development of liver cancer without inducing cirrhosis. In a retrospective case-control study of sugar and papermaking factory workers, self-reported occupational exposure to airborne aflatoxin was associated with increased HCC risk (adjusted OR 5.24, 95% CI 2.77–9.88) [46].

Air pollution

Air pollution includes a mixture of substances (e.g., PAHs, particulate matter [PM]) from natural and anthropogenic sources and is classified as an International Agency for Research on Cancer (IARC) Group 1 human carcinogen (mainly based on lung cancer evidence) [68]. In particular, PM <2.5 microns in diameter ($PM_{2.5}$) has been shown to induce oxidative damage, inflammation, and genotoxicity in the liver [69]. Two prospective cohort studies in Taiwan and Europe showed generally positive associations between geospatial-based residential PM and nitrogen oxides (NO_x) exposures and liver cancer risk [49, 51]. $PM_{2.5}$ exposure was associated with increased HCC risk on the Taiwan Penghu Islands (adjusted HR 1.22, 95% CI 1.02–1.47 per IQR 0.73 μg/m^3 increase), although no association was observed on the Main Island [49]. In the European Study of Cohorts for Air Pollution Effects (ESCAPE) study, there were positive but non-statistically significant associations between exposures (such as to NO_x and $PM_{2.5}$) and liver cancer risk (adjusted HRs ranging from 1.04–1.44) [51]. In a retrospective case-control study in China, self-reported indoor air pollution (adjusted OR 2.46, 95% CI 1.47–4.14), environmental tobacco smoke (ETS) at home (adjusted OR 2.16, 95% CI 1.25–3.72), and ETS at work (adjusted OR 1.90, 95% CI 1.08–3.35) were associated with increased HCC risk [48].

Polycyclic aromatic hydrocarbons (PAHs)

PAHs are chemicals forming from incomplete combustion of materials such as coal, gasoline, tobacco, and grilled meats [70]. Benzo[*a*]pyrene (B[*a*]P) and occupational exposure of chimney sweepers (such as to soot, which contains toxic agents including PAHs) are IARC Group 1 human carcinogens [71, 72]. A retrospective case-control study in China showed higher levels

of B[*a*]P in blood was associated with increased HCC risk (adjusted OR 7.44, 95% CI 5.29–10.45) [54]. Another retrospective study in China demonstrated higher levels of serum BPDE-albumin adducts and *GSTP* (detoxification gene) hypermethylation among HCC cases compared to controls and evidence of their interaction on HCC risk [55]. However, as blood was measured at enrollment, it is unclear if these epigenetic alterations are a driver or result of hepatocarcinogenesis [73, 74]. In a retrospective cohort study in Sweden, chimney sweeping occupation was associated with increased liver cancer risk (SIR 2.48, 95% CI 1.47–3.91) compared to the general Swedish male population [43].

Asbestos

Asbestos, an IARC Group 1 human carcinogen acting through mechanisms inducing genotoxicity, inflammation, and oxidative stress, includes naturally occurring mineral silicate fibers that were widely used in industrial and commercial applications including roofing and insulation [75]. Although asbestos has been banned in many countries, occupational exposure may still occur such as through shipbreaking [61]. Three retrospective studies examined occupational asbestos exposure in France and Taiwan [38, 61, 62]. Compared to the general population in France, there was an increased risk for liver cancer among asbestos-exposed workers for males (SIR 1.85, 95% CI 1.09–2.92), but not for females among whom there was n=1 case [38]. Liver cancer incidence was higher among shipbreaking workers in Taiwan compared to a population-based cohort matched on age, sex, and place of residence (adjusted HR 1.50, 95% CI 1.16–1.94) [61]. Similar positive associations were observed among highly exposed flame cutters and among those with high Total Exposure Potential scores [61]. In a study restricted to a smaller study population of male shipbreaking workers in Taiwan [62], liver cancer incidence was not elevated among shipbreaking workers, although this analysis had fewer cases compared to the more recent study [61] and the comparison group was the general population in Taiwan [62].

Organic solvents

Trichloroethylene (TCE), a volatile organic compound primarily used for cleaning and degreasing metal parts, is an IARC Group 1 human carcinogen primarily based on evidence for kidney cancer, with some positive associations observed for liver cancer [76]. Two prospective studies in Europe examined occupational exposure to TCE and/or perchloroethylene (PER) [42, 57]. There was higher incidence of liver cancer among workers exposed to TCE compared to the general population in Denmark, Finland, and Sweden (SIR 1.93, 95% CI 1.19–2.95) (similar results were observed among males but not females), although urinary trichloroacetic acid (TCE metabolite), measured in a subset of participants, were not associated with liver cancer risk [42]. Occupational TCE was not associated with liver cancer risk in the Nordic

Occupational Cancer Cohort, although there was a suggestive positive association between occupational PER exposure and liver cancer risk (HR 1.13, 95% CI 0.92–1.38) [57]. A cancer cluster investigation in the US showed that residence near a US Environmental Protection Agency Superfund study area with suspected TCE contamination was not associated with increased liver cancer incidence, although there was a limited number of cases and exposure was based on residential addresses at diagnosis [52].

Pesticides

Pesticides are chemicals used to treat pests such as insects, hypothesized to impact hepatocarcinogenesis through mechanisms of oxidative stress, genotoxicity, and immunotoxicity [77]. Dichlorodiphenyltrichloroethane (DDT), an organochlorine insecticide, has been associated with increased HCC risk in several studies (IARC Group 2A) [77, 78]. In a prospective analysis of the Korean Veterans Health Study, occupational Agent Orange exposure (an herbicide contaminated with TCDD used for military tactical use during the Vietnam War) was associated with increased liver cancer risk (adjusted HR 1.16, 95% CI 1.01–1.34) [64]. Associations were stronger when examining those who served in the Vietnam War for >6 months and among those who served in a military unit with a defined tactical area of responsibility [64]. Similar results were observed in a cross-sectional study in the same study population, although liver cancer was based on self-report [65]. In the US-based Agricultural Health Study prospective cohort, higher intensity-weighted lifetime days of occupational metolachlor exposure (an herbicide) was associated with increased liver cancer risk (adjusted RR 3.18, 95% CI 1.10–9.22) [53]. In a retrospective case-control study in the US, geospatial-based residential exposure to pesticides (from organochlorines, organophosphates, and carbamates) was not associated with HCC risk [59], although a suggestive positive association was observed for organochlorine pesticides in analyses limited to study participants residing in agriculturally intensive areas. In a retrospective case-control study in China, self-reported pesticide exposure (adjusted OR 1.99, 95% CI 1.10–3.60) was associated with increased HCC risk [48]. In a retrospective analysis of the Canadian Census Health and Environment Cohort, there was an inverse association with liver cancer risk among male agricultural workers (adjusted HR 0.51, 95% CI 0.38–0.68) and no association among female agricultural workers compared to all other employed individuals; results may have been influenced by the healthy worker effect and/or residual confounding from smoking and alcohol consumption [40].

Perfluorooctanoic acid (PFOA)

PFOA is produced from industrial and consumer products such as Teflon [79]. Animal studies have shown that the liver is an established target for PFOA-induced toxicity; potential mechanisms for carcinogenesis include peroxisome proliferator-activated receptor-α activation

and cytotoxicity [80]. In a retrospective study as part of the US-based C8 Health Project, residence in a water district contaminated by a DuPont Teflon-manufacturing plant and predicted serum PFOA levels were not associated with liver cancer risk [56]. In another retrospective study as part of the C8 Health Project and DuPont Worker Cohort, predicted serum PFOA levels were not associated with liver cancer risk [39]. Null associations may be due to low exposure prevalence, a small number of cases, inclusion of HCC and other histologies, usage of other cancer controls, and/or residual confounding [39, 56].

Iron foundry occupation

Although occupational exposures in iron foundries, including from quartz, PAHs, benzene, and asbestos, are considered carcinogenic to humans (IARC Group 1) [72], a prospective cohort study in Sweden based on a small number of cases showed no association with liver cancer risk compared to the general population [60].

Radiation

An excess in liver cancer incidence has been observed in atomic bomb survivors [81]. In a prospective analysis of nuclear workers in Russia, external gamma (ionizing) radiation measured using individual film badges was not associated with liver cancer risk, although there was a positive association between internal plutonium dose and liver cancer risk based on a small sample size [45]. In contrast, an ecological study in the US showed that ultraviolet (UV) radiation (UV-B wavelengths are involved in cutaneous vitamin D production) was associated with decreased HCC risk (adjusted IRR 0.83, 95% CI 0.77–0.90 per IQR 32.4 mW/m^2 increase) [58].

Brick kiln pollution

Industrial waste from brick kiln-related activities led to groundwater contamination from compounds such as vinyl chloride (established risk factor for liver angiosarcoma and HCC [72]), chlorinated ethenes, and ethanes [50]. In a retrospective cohort study in Italy, there was no observed excess in liver cancer incidence associated with residence in the contaminated East quadrant, a crude proxy for exposure, compared to the general population [50].

Parental occupational exposures to chemicals

A retrospective case-control study of children <15 years old in the US examined self-reported and JEM-based parental occupational exposures from chemicals, such as plastics and paints, in

relation to risk for hepatoblastoma, a rare pediatric liver tumor [44]. Likely paternal exposure to paints was associated with increased risk for hepatoblastoma (adjusted OR 1.71, 95% CI 1.04–2.81), although no association was observed for maternal exposures [44].

Environmental exposures and NAFLD

There were n=5 NAFLD studies examining the following environmental exposures in Table 2: heavy metals (2 studies), trihalomethanes (1), methyl tert-butyl ether (1), and selenium (1) [33, 82–85]. All studies were cross-sectional and conducted in China, Taiwan, and the US. One study was conducted among occupationally exposed individuals [84]. Environmental exposure assessments included biomonitoring, personal sampling, and a residential location-based measure. NAFLD was defined using biochemical measures (e.g., alanine aminotransferase or ALT) and/or imaging.

65.

Table 2.

Epidemiologic studies examining environmental risk factors for NAFLD (2013–2018)

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment
Heavy metals						
Lin et al. (2017) [33]	Taiwan	Crosssectional	2014	Hospital-based; n=1,137 individuals receiving transabdominal sonography	Heavy metals: arsenic, cadmium, chromium, copper, lead, mercury, nickel, zinc	Residential township linked with survey of soil heavy metal concentrations
Hyder et al. (2013) [83]	US	Crosssectional	1988–1994	National Health and Nutrition Examination Survey (NHANES)	Heavy metals: cadmium	Creatinine-corrected urinary cadmium

66.

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment
Trihalomethanes						
Burch et al. (2015) [82]	US	Crosssectional	1999–2006	NHANES	THM	Blood THM

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment
Methyl tert-butyl ether						
Yang et al. (2016) [84]	China	Crosssectional	2014	Petrol station attendants (n=71)	MTBE	Personal exposure monitoring using charcoal-based organic vapor monitor
Selenium						

68.

Study	Location	Study design	Time period	Study population	Exposure	Exposure assessment
Yang et al. (2016) [85]	China	Crosssectional	2011–2012	Shanghai subsample of Risk Evaluation of Cancers in Chinese Diabetic Individuals: a Longitudinal study (REACTION) (n=8,550)	Selenium	Plasma selenium

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; MTBE, methyl tert-butyl ether; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; SBP, systolic blood pressure; SES, socioeconomic status; TC, total cholesterol; TG, triglyceride; THM, trihalomethane; WBC, white blood cell.

Heavy metals

Environmental contamination from heavy metals is primarily sourced from industrial and agricultural activities, potentially promoting NAFLD development through mechanisms related to inflammation and insulin resistance [33, 83, 86]. In Taiwan, residential township-based heavy metals exposure (from arsenic, cadmium, chromium, copper, lead, mercury, nickel, and zinc – several of which are IARC Group 1 human carcinogens [75]) was associated with NAFLD among males (adjusted OR 1.83, 95% CI 1.16–2.90) but not females [33]. Although those with heavy alcohol consumption were not excluded, the authors noted that subjects with a history of alcohol consumption were light drinkers [33]. Statistically significant positive associations were observed for copper, chromium, nickel, and zinc (adjusted ORs ranging from 1.01–1.06), and for heavy metals (combined) among lean individuals with BMI <24 kg/m^2 [33]. Sex-based differences were also observed in the US-based National Health and Nutrition Examination Survey (NHANES), where urinary cadmium levels were associated with NAFLD among males (adjusted OR 1.30, 95% CI 1.01–1.68) but not females [83]. Positive associations were also observed for hepatic necroinflammation (elevated liver enzymes) and NASH (progressive form of NAFLD), providing potential evidence for metals-induced hepatotoxicity being associated with a spectrum of liver disease outcome measures [83].

Trihalomethanes (THMs)

THMs are by-products formed from chlorination of drinking water, likely contributing to hepatotoxicity through oxidative stress [82]. Using NHANES, total THM levels in blood were not associated with NAFLD, although a positive association was observed for dibromochloromethane (adjusted OR 1.35, 95% CI 1.02–1.79) [82].

Methyl tertiary-butyl ether (MTBE)

MTBE is a component of gasoline that induces oxidative stress in animal studies [84]. Among petrol station attendants in China, there was a suggestive positive association between

occupational MTBE exposure from personal monitoring and NAFLD (adjusted OR 1.52, 95% CI 0.93–1.61) [84].

Selenium

Selenium, a naturally occurring trace element that is also formed from industrial activities in electronics and glass, has been associated with increased insulin resistance and triglycerides in animal studies [85]. Plasma selenium levels were associated with NAFLD in China (adjusted OR 1.54, 95% CI 1.13–2.18) [85].

Discussion

In this narrative review of recent epidemiologic literature on environmental risk factors for liver cancer and NAFLD, there were n=28 liver cancer studies examining the effects of aflatoxin, air pollution, PAHs, asbestos, organic solvents, pesticides, PFOA, iron foundry occupation, radiation, brick kiln pollution, and parental occupational exposures to chemicals [38–65] and n=5 NAFLD studies examining the effects of heavy metals, THMs, MTBE, and selenium [33, 82–85].

Studies on the environmental epidemiology of liver cancer in recent years have expanded to provide new perspectives on established risk factors (i.e., aflatoxin) through conducting GxE research. Several studies demonstrated evidence of GxE interactions between serum aflatoxin and genetic polymorphisms in DNA repair genes (e.g., *XRCC4*) [47, 63], highlighting potential biological mechanisms through which aflatoxin may impact the development of HCC and identifying individuals who may be more susceptible to aflatoxin-induced liver cancer. Future GxE research should consistently conduct and report formal tests for interaction [87]. In addition, one prospective study investigated the impact of aflatoxin on cirrhosis and cirrhotic and non-cirrhotic HCC, which would be informative to explore in a study population that is not entirely comprised of chronic HBV carriers [41].

Environmental-focused liver cancer studies have also expanded to investigate factors classified as IARC Group 1 human carcinogens that have been less extensively studied in liver cancer (e.g., air pollution). For example, several prospective epidemiologic studies suggested a positive association between residential air pollution, particularly $PM_{2.5}$, and liver cancer risk [49, 51]. Geospatial-based methods in linking geocoded residential addresses to exposure models using GIS have enabled the objective estimation of ambient environmental exposures within these large population-based studies [49, 51]. Positive associations in the ESCAPE study were not statistically significant [51]; inconsistent findings may be associated with examining HCC and other histologies [51] and temporal mismatches where exposures were estimated after liver

cancer cases were diagnosed [49, 51]. Nonetheless, these air pollution findings are bolstered by how smoking is a risk factor for liver cancer [88] and several constituents in air pollution (e.g., PAHs, heavy metals such as cadmium) are also present in tobacco smoke [89]. Another study showed positive associations between self-reported indoor air pollution and ETS and HCC risk [48]. Further, B[*a*]P (a PAH) and occupational exposure among chimney sweepers to soot (which contains compounds such as PAHs and asbestos) were associated with increased liver cancer risk [43, 54, 55], with one study revealing evidence of an interaction between serum B[*a*]P and epigenetic alterations in *GSTP* hypermethylation [55]. Future research should examine historical exposures relevant to hepatocarcinogenesis to address a potential latency period (e.g., up to 20 years before diagnosis) and consider potential confounding by factors such as diabetes (associated with both $PM_{2.5}$ and HCC [90, 91]). HBV and HCV may not be strong confounders in study populations with low prevalence of these infections and as they may not be related to the fine-scale spatial distribution of air pollution (although they may be associated with general urban-rural patterns) [51].

Several retrospective studies demonstrated positive associations between occupational asbestos exposure and liver cancer risk, although they did not adjust for liver cancer risk factors and/or were limited in sample size [38, 61]. An ecological study showed an inverse association between UV radiation and HCC risk, which is consistent with previous epidemiologic research showing that serum vitamin D is associated with decreased HCC risk [92]. Additional research is needed using higher resolution exposure measures and accounting for individual-level HCC risk factors [58]. Although several recent studies examining pesticides were mixed [40, 48, 59], three studies (two were prospective) showed geospatial-based occupational Agent Orange exposure [64, 65] and occupational metolachlor exposure [53] increased liver cancer risk. This is consistent with evidence implicating organochlorine compounds with the development of HCC [77]; the insecticide DDT and TCDD, as a contaminant in Agent Orange, are organochlorines. Self-reported paternal occupational exposure to paints was associated with increased risk for hepatoblastoma, although results may be impacted by recall bias [44]. These findings should be further investigated.

Several studies showed null or inconsistent associations with organic solvents (TCE and PER) [42, 52, 57], pesticides [40, 48, 59], PFOA [39, 56], radiation [45], iron foundry occupation [60], and brick kiln pollution [50]. Several of these studies were occupational, characterized by a small number of cases, inconsistent case definitions, potential residual confounding from known liver cancer risk factors such as alcohol consumption and smoking, crude exposure assessments, and/or the healthy worker effect [40, 42, 45, 57, 60]. Non-occupational studies were also limited by sample size [39, 50, 52]. Differences in case confirmation as well as examination of different histological subtypes of liver cancer (including HCC and intrahepatic bile duct cancer) may have contributed to null/inconsistent results, as risk factor associations have varied by histology [93]. Limitations in exposure assessment may have also influenced

results, such as using coarse-scale geographic variables within which exposures may vary, residential location at diagnosis, and self-report [48, 50, 52, 56, 59].

Compared to the literature on liver cancer, the environmental epidemiology of NAFLD is a nascent field, reflected in the relatively modest number of studies included in this review. Several studies showed positive associations between exposures to selenium [85], heavy metals such as cadmium, copper, chromium, nickel, and zinc [33, 83] measured in urine or based on residential location and NAFLD. Sex-based differences in heavy metals adversely affecting males but not females may be due to the anti-inflammatory properties of estrogen [33]. Interestingly, heavy metals exposure was positively associated with NAFLD among individuals with BMI <24 kg/m^2, suggesting that adipose tissue may sequester toxins [33, 94]. In addition, there was a suggestive positive association for occupational exposure to MTBE and NAFLD [84] and no association with THMs [82].

However, the NAFLD studies included in this review were cross-sectional examining NAFLD prevalence, precluding the determination of a temporal relationship between exposure and outcome and making it difficult to interpret the findings. In addition, NAFLD was determined based on biochemical tests and/or imaging subject to outcome misclassification compared to the gold standard of liver biopsy. Prospective studies ascertaining biopsy-confirmed NAFLD with long-term follow-up to evaluate incidence are needed. In addition, as these environmental exposures are suspected to affect NAFLD development through mechanisms related to increased triglycerides, insulin resistance, oxidative stress, and/or inflammation, future research should explore if obesity and/or diabetes may mediate these potential associations, as well as identify risk factors among the non-obese to investigate the etiology of lean NAFLD.

Conclusions

Recent epidemiologic studies demonstrated that particular environmental factors may be associated with liver cancer risk, including air pollution; PAHs such as B[*a*]P; asbestos; chimney sweeping occupation; ultraviolet radiation; and paternal occupational exposure to paints. There was evidence of GxE interactions between aflatoxin, an established liver cancer risk factor, and genetic polymorphisms in DNA repair genes. Exposures to organic solvents such as TCE; pesticides; PFOA; nuclear ionizing radiation; iron foundry occupation; and brick kiln pollution showed null or inconsistent associations with liver cancer. Several studies showed generally positive associations between heavy metals (e.g., cadmium), selenium, MTBE, and NAFLD; no association was observed for THMs. Additional studies are needed to confirm these findings. Future liver cancer research should examine specific histological subtypes (e.g., HCC) and examine historical environmental exposures to address a potential latency period. Future

NAFLD research should examine biopsy-confirmed, incident NAFLD cases, mediation by major NAFLD risk factors such as obesity and diabetes, and associations among lean NAFLD cases.

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Footnotes

Compliance with Ethical Standards

Conflict of Interest

Trang VoPham declares no potential conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Air pollution and kidney disease: review of current evidence

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Abstract

Along with amazing technological advances, the industrial revolution of the mid-19th century introduced new sources of pollution. By the mid-20th century, the effects of these changes were beginning to be felt around the world. Among these changes, health problems due to environmental air pollution are increasingly recognized. At the beginning, respiratory and cardiovascular diseases were emphasized. However, accumulated data indicate that every organ system in the body may be involved, and the kidney is no exception. Although research on air pollution and kidney damage is recent, there is now scientific evidence that air pollution harms the kidney. In this holistic review, we have summarized the epidemiology, disease states and mechanisms of air pollution and kidney damage.

Keywords: acute kidney injury, air pollution, chronic kidney disease, heavy metals, particulate matter

INTRODUCTION

The adverse health effects of ambient (outdoor) air pollution have been recognized since increased mortality due to smog was reported in London in 1952 [1, 2]. Since then, ambient air

pollution is recognized as one of the leading causes of global disease burden [3, 4]. Air pollution is a complex mixture of gaseous components and solid and liquid particles suspended in the air and can vary substantially in chemical composition between different cities. There are various sources of these pollutants (Table 1).

87.

Table 1.

Major sources of common air and other environmental pollutants

Pollutant	Source	References
PM	Mostly traffic-related air pollution (mainly local emission)	[5, 6]
	Other (domestic heating, industries, etc.)	
NO_X	Mainly derived from road traffic and the industrial burning of fuels	[7, 8]
	Strongly related to diesel motor vehicles	
SO_X	Industrial production of sulphur-based products	[9]
O_3	Industrial combustion and processes	[10]
CO	Road traffic and industrial fuel burning	[7]
Cadmium	Diet in non-smokers	[11]
	Tobacco in smokers	
Lead	Gasoline, batteries, pipes and ammunition	[11]
	In the past, paints and ceramic glazes	
	Occupational exposure to the inorganic form of Pb (Pb^{2+}): welding manufacture of Pb-containing batteries, Pb melting and refining, and production of pottery	
	Children ingesting Pb^{2+} contaminated soil	
Mercury	Occupational, environmental and dietary sources	[11]
	Mainly through ingestion of food contaminated with CH_3Hg^+	
Arsenic	Primary route of human exposure is ingestion of contaminated drinking water	[11]
	Methylated forms of As (MAs and DMAs) from pesticides used in cotton crops	
Uranium	Mining and milling	[11]

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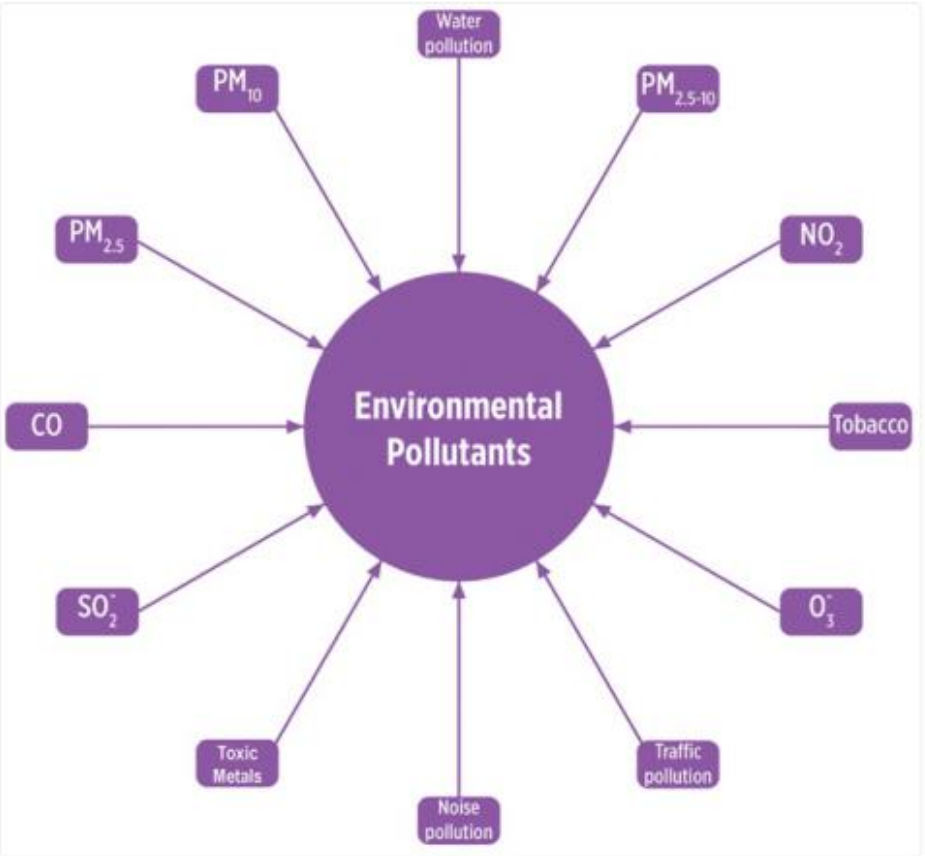
Particulate matter (PM), which primarily comprises solid particles derived from the combustion of coal, gasoline and diesel fuels, is the major element of air pollution that causes the most adverse health effects [12, 13]. Environmental air pollution may be composed of additional components (Figure 1), such as different sized PM (e.g. PM_{10} having an aerodynamic diameter ≤10 μm; $PM_{2.5}$ which are ≤2.5 μm and $PM_{2.5–10}$), gaseous pollutants [e.g. nitrogen dioxide (NO_2), carbon monoxide (CO), sulphur dioxide (SO_2) and ozone (O_3)] and heavy metals [e.g. cadmium (Cd), lead (Pb) and mercury (Hg)] [14–16]. Over the past decade, a growing body of research has suggested a causal relationship between ambient air pollution exposure and adverse cardiovascular health [17].

89.

FIGURE 1.



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Components of environmental pollution.

Chronic kidney disease (CKD) is another worldwide public health problem with a variety of adverse outcomes, including premature death, and it is regarded as a cardiovascular disease (CVD) risk equivalent [18]. Apart from traditional risk factors, such as hypertension and diabetes, an increasing body of evidence demonstrates that air pollution may be a novel environmental risk factor for CKD [5, 19, 20]. In the present review, we systemically summarized the current data regarding air pollution and kidney disease.

METHODS

A literature search was performed using electronic databases MEDLINE, Ovid/MEDLINE (1988–2018), PubMed/MEDLINE, EMBASE and ISI Web/Web of Science for published studies from January 1988 to March 2018. We searched for relevant studies using the keywords 'air pollution and chronic kidney disease', 'air pollution and end-stage renal disease', 'air pollution and proteinuria', 'environmental pollution and chronic kidney disease', 'air pollution and diabetes', 'air pollution and hypertension', 'toxic metals and chronic kidney disease' and 'heavy metals and chronic kidney disease', limiting the search to research articles involving humans and published in English. Neither unpublished data nor abstracts were included.

NEPHROTOXIC METALS AND RENAL DISEASE

Heavy metals are among the best-known environmental pollutants causing kidney disease. It is less well known that they are also air pollutants, particularly Cd, Pb and Hg, but also arsenic (As) and uranium (http://www.euro.who.int/__data/assets/pdf_file/0007/78649/E91044.pdf).

Arsenic and CKD

Environmental, occupational and dietary exposure to As appear to contribute to the incidence of renal injury and the development of renal disease [11]. Contamination of drinking water with As has been linked to the development of hypertension and renal injury [21, 22]. Findings from a cross-sectional study of patients in Taiwan showed a positive correlation between urinary As and the incidence of CKD. It was concluded that high levels of urinary As may increase the risk of developing CKD by 4-fold [23]. Acute As-induced renal intoxication may lead to tubulointerstitial nephritis and acute tubular necrosis manifested by hypercalciuria, albuminuria, nephrocalcinosis and necrosis of the renal papillae [24, 25].

Cadmium and CKD

Cd is a prevalent nephrotoxic environmental pollutant. In non-smokers, diet is the primary source for Cd exposure. However, in smokers, the major source of exposure is related to tobacco products that contain high concentration of Cd. As paediatric age increases, Cd exposure is also increased [26]. Environmental tobacco smoke exposure was the most important determinant of Cd status in school-aged children. Moreover, serum Cd levels were higher in active smoker teenagers than in non-smokers. Interestingly, higher serum Cd concentration was associated with higher alpha-1-microglobulinuria in adolescents, suggesting subclinical renal toxicity after

several years of cumulative exposure [27]. Cd is also present in air and drinking water, although the concentration of Cd in air is relatively low, and drinking water is normally not a major source of exposure for the general population. However, Cd contamination of drinking water and vegetables has been observed in some cities and regions [26]. Exposure to Cd is often assessed by measuring the concentration of Cd in urine and/or blood. In fact, urinary Cd excretion is considered as one of the most reliable indicators of renal and body burden of Cd [11].

Cd is directly nephrotoxic and can induce renal tubular damage (polyuria, generalized tubular dysfunction, i.e. Fanconi syndrome) and progressive loss of glomerular filtration rate (GFR) [28–30]. Long-term Cd exposure is thought to accelerate the CKD-related decline in GFR [31–33]. Cross-sectional studies have shown that Cd exposure is a risk factor for the development of CKD [34, 35]. Epidemiological studies have demonstrated a positive correlation between CKD and the renal accumulation of Cd in individuals exposed chronically to this metal [36, 37]. The most frequent long-term consequence of Cd exposure is proteinuria, and it may precede a slowly progressive and irreversible renal tubular dysfunction [38]. Proteinuria has been ascribed to the loss of megalin and cubilin, which mediate endocytosis of filtered proteins along the proximal tubule [39–41]. The incidence of kidney stones also increases in individuals exposed chronically to or to larger Cd dose, possibly due to the increased concentration of calcium in tubular fluid and urine [11]. Last but not least, Cd exposure has been associated with the severity of diabetes [42] and hypertension [43], which themselves are risk factors for CKD.

Lead and CKD

Together with bone, kidney is a primary site of Pb accumulation as Pb is excreted by kidneys [44]. The major kidney cellular effect of exposure to Pb is the induction of mitochondrial oxidative stress [45] and inflammation [11]. This results in lipid oxidation and DNA fragmentation [46]. Low-level Pb exposure early in life causes glomerular hypertrophy, which may disrupt glomerular development [11]. Acute Pb intoxication causes proximal tubular dysfunction (Fanconi syndrome) [47], and chronic intoxication leads to progressive tubulointerstitial nephritis [48]. There is convincing preclinical and clinical evidence supporting a direct relationship between Pb exposure and development of kidney disease [49, 50]. Additionally, cross-sectional general population studies in Mexico and Korea found a correlation between serum creatinine and blood Pb levels [51, 52].

Mercury and CKD

All forms of Hg are nephrotoxic through various mechanisms. Hg is well absorbed following inhalation, and air levels correlate with exposure estimated by urinary Hg excretion. Hg has

been associated with CKD progression [11, 53]. The pars recta of the proximal tubule appears to be most sensitive to the Hg toxicity [54, 55]. Acute exposure causes altered mitochondrial structure, endoplasmic reticulum dilation and nuclear pyknosis [56]. After 12 h, microvilli are lost and cell death is associated with plasma membrane rupture and cell detachment from the basement membrane [57].

Chronic exposure to mercuric compounds can lead to glomerular injury [11]. In rats, chronic exposure to methyl Hg caused glomerulosclerosis and glomerular immunoglobulin deposition. In North West England, ambient background Hg concentration (3 ng/m^3) is higher than the average background level in the UK (1.78 ng/m^3). There were significant exposure–response relations between modelled estimates of Hg exposure (low: >3 to <4; medium: 4 to 10; high: >10; or very high exposure: >20 ng/m^3) and risk of kidney disease mortality in both men and women after adjustment for age and socio-economic deprivation (test for trend: P = 0.02 for men and P = 0.03 for women) [58]. In another case–control study, occupational exposure in 272 men and women with CKD was compared with 272 controls matched for age, sex and region of residence. Hg exposure was independently associated with an increased risk of CKD [odds ratio (OR) = 5.13, 95% confidence interval (CI) 1.02–25.7] [59].

Uranium and CKD

Uranium toxicity, although relatively rare, may also cause renal damage and indeed, the kidney is the primary target for uranium toxicity following inhalation or ingestion. Approximately 40% of plasma uranium is complexed to transferrin and the remaining 60% is complexed with carbonate or bicarbonate, which are filtered by the glomerulus. In proximal tubules, the complexed uranium dissociates with decreasing pH, releasing the reactive uranyl ion, which can interact with the proximal tubule membrane. The most frequently used guideline for uranium kidney burdens is the International Commission on Radiological Protection value of 3 µg/g, a value that is based largely upon chronic animal studies [60]. A risk model equation to assess potential outcomes of acute uranium exposure was derived from 27 previously published case studies of acute exposure to soluble uranium compounds in workplace accidents. Kidney burdens of uranium for these individuals were determined from urine uranium, and correlated with health effects observed over a period of up to 38 years. Based upon the severity of health effects, each individual was assigned a score (– to 3+) and then placed into a Renal Effects Group (REG). A discriminate analysis was used to build a model equation to predict the REG based on the amount of kidney uranium [60] (Table 2).

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Table 2.

Acute renal effects and predicted outcomes of kidney uranium accumulation

REG	Kidney uranium concentration (μg/g)	Acute renal effect	Predicted outcome
0	≤2.2	None	No clinically detectable effects
1	>2.2 to ≤6.4	Possible transient indicators of renal dysfunction	Not likely to become ill
2	>6.4 to ≤18	Possible protracted indicators of renal dysfunction	May become ill
3	>18	Possible severe clinical symptoms of renal dysfunction	Likely to become ill

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TOBACCO AND CKD

Smoking is also an air pollutant detrimental for kidney health [61]. A recent meta-analysis investigated the relationship between cigarette smoking and CKD in the general population. Summary relative risks (SRRs) and 95% CIs were calculated using a random effects model. A total of 15 prospective cohort studies, including 65 064 incident CKD cases, were included. Compared with never-smokers, the SRRs of incident CKD were 1.34 (95% CI 1.23–1.47) for current smokers and 1.15 (95% CI 1.08–1.23) for former smokers. The SRRs for end-stage renal disease (ESRD) development were 1.91 (95% CI 1.39–2.64) for current smokers and 1.44 (95% CI 1.00–2.09) for former smokers. However, the authors noted that there was considerable heterogeneity among these studies [62]. In African Americans from the Jackson Heart Study, after adjustment for various factors, the incidence of renal function decline was higher in current smokers than in never-smokers (incidence rate ratio 1.83, 95% CI 1.31–2.56). Current smokers of 1–19 and ≥20 cigarettes daily had an increased incidence rate ratio of residual renal function decline: 1.75 (95% CI 1.18–2.59) and 1.97 (95% CI 1.17–3.31), respectively. In addition, there was a significant progressive reduction in estimated GFR (eGFR) from Visits 1 to 3 in current and past smokers compared with never-smokers [63].

Apart from these findings, there is also evidence linking tobacco exposure to proteinuria in those with and without kidney disease [64–67]. In 990 middle-aged men recruited from a chemical plant, proteinuria was found in 4.6% of current smokers and 1.5% of never-smokers [68]. A meta-analysis of the relationship between tobacco smoking on the development of diabetic nephropathy (DN) in type 1 diabetes mellitus (T1DM) and T2DM, identified 19 observational studies (1 case–control, 8 cross-sectional and 10 prospective cohort studies), involving more than 78 000 participants and a total of 17 832 DN cases. The relative risk (RR) (95% CI) of DN was higher in ever-smokers with T1DM (1.31, 1.06–1.62; P = 0.006) or T2DM (1.44, 1.24–1.67; P < 0.001) than in never-smokers. In T1DM ever-smokers, the RR was 1.25 (95% CI 0.86–1.83) for microalbuminuria, 1.27 (95% CI 1.10–1.48) for macroalbuminuria and 1.06 (95% CI 0.97–1.15) for ESRD. In T2DM ever-smokers, the RR was 1.46 (95% CI 0.94–2.26) for microalbuminuria, 1.72 (95% CI 1.04–2.84) for macroalbuminuria and 1.10 (95% CI 0.36–3.33) for ESRD [69]. Thus, it appears that the highest risk associated with smoking is for macroalbuminuria, likely over a basis in incipient DN.

Passive smoking has also been associated with renal damage. Assessment of the nicotine metabolite cotinine in serum and in urine has been used to quantify smoking exposure. In a cohort of 366 children with CKD aged 1–16 years, secondhand smoke exposure obtained via questionnaire and urine cotinine was associated with the prevalence odds of nephrotic range proteinuria (OR = 2.64, 95% CI 1.08–6.42) [70]. In active (n = 24) and passive (n = 20) smokers, serum cotinine levels were higher than in controls (n = 20), as was the urinary albumin–creatinine ratio, whereas serum creatinine was higher in active smokers [71].

This evidence suggests that smoking harms the kidneys, but how? Several mechanisms may be at play. Cigarette smoking has been associated with idiopathic nodular glomerulosclerosis and microalbuminuria or overt proteinuria in healthy individuals, and with more severe proteinuria in individuals with pre-existing renal disease such as DN [72–74]. A correlation between smoking and nephrosclerosis and glomerulonephritis was found in a nationwide population-based case–control study that included Swedish subjects, 926 cases and 998 control [75]. Smoking promoted the progression of hypertensive [67, 76] and diabetic nephropathies [77]. Cigarette smoking has been directly associated with endothelial dysfunction, intimal hyperplasia and wall thickening of myocardial and renal arterioles and arteries.

Tobacco smoke caused mesangial proliferation, glomerulosclerosis and tubulointerstitial fibrosis in experimental studies [72, 78]. Specifically, nicotine activation of nicotine receptors promotes human mesangial cell extracellular matrix production [79]. Acrolein, an aldehyde from tobacco smoke, induces renal cell reactive oxygen species (ROS) production and apoptosis [80, 81]. Smoking also increases Cd levels and this could contribute to CKD progression. Smokers have 4- to 5-fold higher Cd levels in blood and 2- to 3-fold higher kidney Cd than non-smokers [82]. Indeed, NHANES 1999–2006 data for adults without CKD showed that urine Cd

levels were highest for current smokers (3- to 13-fold higher), followed by former smokers (2- to 3-fold) compared with non-smokers. Cigarette smoking greatly increases RR of exceeding renal risk-associated urine Cd levels, particularly in former smokers [28].

Passive smoking has also being associated with renal fibrosis. Glomerulosclerosis comparable to the findings in idiopathic nodular glomerulosclerosis in human beings and upregulation of interstitial fibrosis-related genes has been observed in the absence of proteinuria, suggesting that histological changes precede biochemical changes [26]. Elevated sympathetic activity, blood pressure (BP), GFR and intraglomerular capillary pressure are candidate mechanisms for smoking-induced renal damage [72]. It was also suggested that chronic environmental tobacco smoke exposure induces systemic oxidative stress, which may subsequently trigger production of profibrotic factors [83].

However, there are also contradictory findings. In healthy rats exposed to smoke soon after birth for 4 months, as a model of passive smoking, the mean number of renal vessels, glomerulosclerosis and myointimal hyperplasia did not significantly differ from control rats [84]. However, it is unclear whether the timing was appropriate to observe any effect. No differences were found in the prevalence of glomerulosclerosis between non-smokers (51 patients, 47.7%) and ever-smokers (56 patients, 52.3%) in kidney biopsy. However, the number of glomeruli obtained at biopsy may have been insufficient for assessing glomerulosclerosis [85].

TRAFFIC AND NEARBY INDUSTRIAL POLLUTION AND CKD

Traffic air pollution is another kind of air pollution. Among 8497 Taipei city residents, regression models were used to estimate the participants' 1-year exposures to PM of different sizes and traffic-related exhaust, $PM_{2.5}$ absorbance, NO_2 and nitrogen oxidases (NO_x). Interquartile range (IQR) increments of $PM_{2.5}$ absorbance (0.4×10^{-5}/m) and NO_2 (7.0 mg/m^3) were associated with 1.07 and 0.84% lower eGFR, respectively. Similar associations were also observed for PM_{10} and $PM_{2.5-10}$. Two-pollutant models showed that PM_{10} and $PM_{2.5}$ absorbances were associated with lower eGFR. Authors conclude that 1-year exposures to traffic-related air pollution were associated with lower eGFR, higher CKD prevalence and increased risk of CKD progression among the elderly. Of note, there were no significant findings with regard to proteinuria, but albuminuria was not assessed [5]. Among 1103 consecutive Boston-area patients hospitalized with acute ischaemic stroke between 1999 and 2004, linear regression was used to evaluate the association between eGFR and categories of residential distance to major roadway (0 to ≤50, 50 to ≤100, 100 to ≤200, 200 to ≤400, 400 to ≤1000 and >1000 m) adjusting for age, sex, race, smoking, comorbid conditions, treatment with angiotensin-converting enzyme inhibitor and neighbourhood-level socioeconomic

characteristics. Patients living closer to a major roadway had lower eGFR than patients living farther away (P_{trend} = 0.01). Comparing patients living 50 m versus 1000 m from a major roadway, patients living within 50 m had 3.9 mL/min/1.73 m^2 lower eGFR (95% CI 1.0–6.7; P = 0.007), a difference comparable in magnitude to the reduction in eGFR observed for a 4-year increase in age in population-based studies. The magnitude of this association did not differ significantly across categories of age, sex, race, history of hypertension, diabetes or socioeconomic status. However, as this study involved patients who were hospitalized with acute ischaemic stroke, the generalizability of the results to the general population is questionable. Proteinuria was not studied [86]. Excess kidney disease mortality was found in persons living within 2 km of industrial plants potentially releasing renal toxicants in Runcorn, UK: the standardized mortality ratio in males was 131 (95% CI 90–185) and in females 161 (95% CI 118–214) compared with a reference population living at 2.01–7.5 km [87].

PM AND CKD: EPIDEMIOLOGIC STUDIES

There are many studies showing association with various PM and CKD. A weak acceleration in the progression of albuminuria was observed during chronic exposure to PM_{10} in Multi-Ethnic Study of Atherosclerosis cohort [88]. In China, long-term exposure to $PM_{2.5}$ was associated with an increased risk of membranous nephropathy in a nonlinear pattern in 71 151 native kidney biopsy samples from 938 hospitals in 282 cities. During the study period, $PM_{2.5}$ exposure varied from 6 to 114 μg/m^3 (mean 52.6 μg/m^3) among the 282 cities. Each 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with 14% higher odds of a patient developing membranous nephropathy (OR = 1.14, 95% CI 1.10–1.18) in regions with $PM_{2.5}$ levels >70 μg/m^3, but the effect size in regions with $PM_{2.5}$ <60 μg/m^3 was greatly attenuated [89].

Another longitudinal observational cohort study that enrolled 2 482 487 US veterans demonstrated the association of $PM_{2.5}$ concentrations with higher risk of incident CKD and progression to ESRD [90]. One-year $PM_{2.5}$ exposure was associated with a lower eGFR among older men [91]. Among 21 656 Taiwanese adults, individual exposures to PM_{10}, coarse particles (PM_{coarse}) or $PM_{2.5}$ were related to renal function. An IQR increase in PM_{10} (5.83 μg/m^3) was negatively associated with eGFR by −0.69 (95% CI −0.89 to −0.48) mL/min/1.73 m^2 and positively associated with the prevalence of CKD with adjusted OR = 1.15 (95% CI 1.07–1.23). An IQR increase in PM_{coarse} (6.59 μg/m^3) was significantly associated with lower eGFR by −1.07 (95% CI −1.32 to −0.81) mL/min/1.73 m^2 and with CKD with OR = 1.26 (95% CI 1.15–1.38). In contrast, neither outcome was significantly associated with $PM_{2.5}$. Stratified analyses indicated that associations of CKD with both PM_{10} and PM_{coarse} were limited to participants <65 years of age and were stronger in (for PM_{10}) or limited to (PM_{coarse}) women. Associations also appeared to be stronger in those without hypertension than in those with hypertension, and in normal versus overweight participants [19].

In a recent cohort study, Bowe *et al.* [92] investigated the associations regarding coarse PM, NO_2 and CO with the risk of kidney disease. The authors evaluated the association between PM_{10}, NO_2 and CO concentrations and risk of incident eGFR of <60 mL/min/1.73 m^2, incident CKD, eGFR decline of ≥30% and ESRD. Participants were followed-up over a median of 8.52 years (IQR: 8.05–8.80). This study is one of the biggest, involving 2 010 398 participants. Among those individuals, the median concentration for PM_{10} was 20.45 μg/m^3 (IQR: 14.64–24.81), NO_2 was 14.54 parts per billion (9.69–17.91) and CO was 0.51 parts per million (0.40–0.64). An increased risk of eGFR <60 mL/min/1.73 m^2 was associated with an IQR increase in concentrations of PM_{10} [hazard ratio (HR) = 1.07, 95% CI 1.06–1.08], NO_2 (HR = 1.09, 95% CI 1.08–1.10) and CO (HR = 1.09, 95% CI 1.08–1.10). An increased risk of incident CKD was associated with an IQR increase in concentrations of PM_{10} (HR = 1.07, 95% CI 1.05–1.08), NO_2 (HR = 1.09, 95% CI 1.08–1.11) and CO (HR = 1.10, 95% CI 1.08–1.11). An increased risk of an eGFR decline of ≥30% was associated with an IQR increase in concentrations of PM_{10} (1.08, 95% CI 1.07–1.09), NO_2 (1.12, 95% CI 1.10–1.13) and CO (1.09, 95% CI 1.08–1.10). An increased risk of ESRD was associated with an IQR increase in concentrations of PM_{10} (1.09, 95% CI 1.06–1.12) and NO_2 (1.09, 95% CI 1.06–1.12). This study, which has a high statistical power, showed that higher concentrations of PM_{10}, NO_2 and CO are associated with increased risk of incident CKD, eGFR decline and ESRD [92].

AIR POLLUTION AND BP

Air pollution has been associated with increased cardiovascular morbidity and mortality in numerous epidemiological studies. One of the proposed mechanisms involves increased BP, which is a risk factor for the development of CKD [93]. Large population studies showed that higher PM levels are associated with higher BP levels, even based on one BP measurement [94–99]. Data from the Nurses' Health Study revealed that exposure to PM_{10} was associated with a slight increased risk of incident self-reported hypertension (PM_{10}, HR 1.02, 95% CI 1.00–1.04) [100]. Similar findings were also observed in a Taiwanese study, which found that long-term exposure to $PM_{2.5}$ was associated with increased risk of hypertension [101]. In another study, among 24 845 adults in Northeastern China, long-term exposure to air pollution was associated with increased odds of hypertension and more strongly with prehypertension [102]. Additionally, a recent systematic review and meta-analysis reported a positive association between ambient air pollution and elevated odds of hypertension [95, 103–108].

Apart from these studies, a very recent meta-analysis searched for the global association between ambient air pollution and BP. Seven international and Chinese databases encompassing 0.7 million participants from 16 countries were searched for studies examining the associations of $PM_{2.5}$, $PM_{2.5-10}$ or PM_{10} and gaseous (SO_2, NO_2, NO_x, O_3, CO) air pollutants with hypertension or BP. The overall meta-analysis showed significant associations of long-term exposures to $PM_{2.5}$ with hypertension (OR = 1.05), and of PM_{10}, $PM_{2.5}$ and NO_2 with diastolic

BP (b-values: 0.47–0.86 mmHg). In addition, short-term exposures to four (PM_{10}, $PM_{2.5}$, SO_2, NO_2), two ($PM_{2.5}$ and SO_2) and four air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) were significantly associated with hypertension (ORs = 1.05–1.10), systolic BP (b-values: 0.53–0.75 mmHg) and diastolic BP (b-values: 0.15–0.64 mmHg), respectively. Stratified analyses showed a generally stronger relationship among men, Asians, North Americans and areas with higher air pollutant levels [103]. Additional studies have observed that not only single BP measurements but repeated BP measurements are also related to PM levels [106, 109–111].

An analysis of the association of exposure to PM_{10} (average concentration 23.5 ± 13.6μg/m^3) with ambulatory BP and with sodium excretion in 359 adults disclosed that after controlling for potential confounders, a 10 μg/m^3 increase in PM_{10} levels was positively associated with nighttime systolic BP, nighttime diastolic BP and negatively associated with nocturnal systolic BP dipping and daytime urinary sodium excretion, but not with nighttime sodium excretion. The effect sizes per 10 μg/m^3 of PM_{10} were in the order of 1.0 mmHg for nighttime systolic BP and 0.5 mmHg for nighttime diastolic BP. The associations of short-term increase in PM_{10} with higher nighttime BP and blunted systolic BP dipping were preceded by associations with reduced ability of the kidney to excrete sodium during daytime. The authors suggested that the underlying mechanism linking air pollution to increased cardiovascular risk may include disturbed circadian rhythms of renal sodium handling and BP [112]. Smaller studies (48 healthy vehicular traffic controllers and 10 patients with impaired lung function) did not find any association between air pollution and ambulatory BP [113, 114].

Air pollution has also been associated with BP in children. A study of Chinese children aged 5–17 years found a positive association between short-term (2 years) exposure to ambient air pollution and elevated BP [115]. The interaction between exposure to pet ownership and air pollutants on hypertension was studied in 9354 Chinese children (aged 5–17 years) from 24 elementary and middle schools during 2012–13. Four-year average concentrations of PM_{10}, SO_2, NO_2 and O_3 were collected from 2009 to 2012. Hypertension was defined as average diastolic or systolic BP (three measurements) in the 95th percentile or higher based on height, age and sex. Children not exposed to pets exhibited consistently stronger effects of air pollution than those exposed to pets. The highest ORs per 30.6 mg/m^3 increase in PM_{10} were 1.79 (95% CI 1.29–2.50) in children without current pet exposure compared with 1.24 (95% CI 0.85–1.82) in children with current pet exposure. As for BP, only O_3 had an interaction for all exposure to pet ownership and showed lower BP in children exposed to pets. The increases in mean diastolic BP per 46.3 mg/m^3 increase in O_3 were 0.60 mmHg (95% CI 0.21–0.48) in children without pet exposure *in utero* compared with 0.34 mmHg (95% CI 0.21–0.48) in their counterparts. When stratified by age, pet exposure was more protective among younger children. This suggests that pet ownership reduces susceptibility to the health effects of pollutants [17].

However, there are also conflicting findings. For instance, a meta-analysis that examined the association between long-term exposure to air pollution and arterial BP in the European Study of Cohorts for Air Pollution Effects (n = 164 484) revealed that NO_2 exposure was associated with a weak inverse relationship with systolic BP (0.29; 95% CI −0.70 to 0.12) among individuals not taking BP-lowering medication [116]. There are also some studies that found either no association [113, 117] or a negative association [118] of PM with BP. It should be noted that these negative studies are smaller in number and a large body of evidence still suggests a positive correlation between air pollution and hypertension.

AIR POLLUTION AND DIABETES

Diabetes is an ever-increasing worldwide health problem. Systematic reviews, meta-analyses and epidemiological studies confirm that exposure to air pollution may be associated with the incidence or prevalence of DM [119–124]. Several cohort studies also showed greater T2DM risk with exposure to higher levels of NO [125, 126] and $PM_{2.5}$ [127, 128].

The effect of long-term exposure to ambient PM on the prevalence of T2DM and hypertension was explored in Iranian adults grouped by PM_{10} concentration <100 μg/m^3 (5-year average 83.95 ± 7.81 μg/m^3) or >100 μg/m^3 (5-year average 120.15 ± 6.81 μg/m^3). The prevalence of T2DM (13.8% versus 10.7%, P = 0.01; OR = 1.32, 95% CI 1.03–1.69) and hypertension (15.7 versus 11.9%, P = 0.005; OR = 1.55, 95% CI 1.20–1.99) was higher in the city with higher PM_{10} exposure [129]. The association between long-term exposure to PM, NO_x and O_3 and baseline prevalence and incidence of T2DM was also studied in a large administrative cohort in Rome, Italy. A total of 1 425 580 subjects aged 35+ years in January 2008 were assessed and followed for 6 years. A positive association was found between NO_x exposures and prevalence of diabetes with ORs up to 1.010 (95% CI 1.002–1.017) and 1.015 (95% CI 1.009–1.021) for NO_2 and NO_x, respectively, per 10 μg/m^3 and 20 μg/m^3. They also found some evidence of an association between NO_x and O_3 and incidence of diabetes with HRs of 1.011 (95% CI 1.003–1.019) and 1.015 (95% CI 1.002–1.027) per 20 and 10 μg/m^3 increases, respectively. The association with O_3 with incident diabetes was stronger in women than in men and among those aged <50 years [6]. However, no association was found between PM_{10}, $PM_{2.5}$ or $PM_{2.5–10}$, and diabetes. In the Netherlands, long-term exposure to NO_2 was associated with prevalence of diabetes (OR = 1.07, 95% CI 1.05–1.09 per IQR increases) after adjustment for individual confounders such as body mass index (BMI) and physical activity [130].

In a very large-scale prospective study involving 1 729 108 participants who were followed-up for a median of 8.5 years, the relationship between $PM_{2.5}$ and the risk of incident diabetes was investigated. All models were adjusted for age, race, sex, eGFR, systolic BP, hyperlipidaemia, chronic lung disease, CVD, cancer, BMI, smoking status, use of an angiotensin-converting

enzyme inhibitor or angiotensin receptor blocker and other covariates. In adjusted models, a 10 μg/m^3 increase in $PM_{2.5}$ was associated with increased risk of diabetes (HR = 1.15, 95% CI 1.08–1.22). The authors concluded that there is a significant association between increased $PM_{2.5}$ exposure and the risk of diabetes with variable geographical distribution. More importantly, the risk is significant at concentrations below those recommended by regulatory agencies. This suggests that even a low concentration of air pollution might be unsafe, and adverse effects of air pollution become obvious at relatively low concentrations below those currently considered as safe by regulatory agencies [131]. In 429 overweight and obese African American and Latino Los Angeles children, both NO_2 and $PM_{2.5}$ were associated with higher fasting glycaemia and insulin, lower insulin sensitivity and higher insulin secretion. Specifically, each SD increase in NO_2 and $PM_{2.5}$ exposure was associated with 22.8% ($P < 0.001$) and 24.7% ($P < 0.001$) higher fasting insulin, respectively. At the same time, each SD increase in NO_2 and $PM_{2.5}$ exposure was associated with a 1.6% ($P < 0.001$) and 1.6% ($P < 0.001$) higher fasting glucose, respectively. HOMA-IR was 25.1% ($P < 0.001$) and 26.9% ($P < 0.001$) higher and insulin sensitivity 8.5% ($P = 0.03$) and 11.2% ($P = 0.003$) lower for each SD increase in NO_2 and $PM_{2.5}$ exposure. Regarding adiposity estimates, only elevated annual exposure to $PM_{2.5}$ was associated with a higher BMI z-score ($\beta = 0.05$; $P = 0.04$). Each SD increase in non-freeway NO_x exposure was related to a 12.1% higher fasting insulin ($P < 0.001$), 0.7% higher fasting glucose ($P = 0.047$), 12.9% higher HOMA-IR ($P < 0.001$) and 6.9% lower insulin sensitivity ($P = 0.02$) [132]. In a large American cohort (Cancer Prevention Study-II participants), a strong effect of ozone on diabetes-related mortality was found (HR = 1.16, 95% CI 1.07–1.26 per fixed increment of 10 parts per billion, equal to 20 μg/m^3 O_3) [133]. Rats exposed to realistic concentrations of ozone (0.8 parts per million = 1.69 μg/m^3) developed insulin resistance induced by c-Jun N-terminal kinase activation that disrupted insulin signalling in skeletal muscles, suggesting a cause-and-effect relationship between ozone and insulin resistance [134]. The association of long-term residential exposure to $PM_{2.5}$ with the prevalence and incidence of T2DM was studied in 61 447 elderly Hong Kong residents enrolled in 1998–2001, following participants without DM at baseline to 31 December 2010 to ascertain the first hospital admissions for T2DM. Over a mean follow-up of 9.8 years, 806 incident cases of T2DM occurred. After adjusting for potential confounders, the OR for every IQR (3.2 μg/m^3) increase of $PM_{2.5}$ concentration was 1.06 (95% CI 1.01–1.11) for prevalent DM, while the corresponding HR was 1.15 (95% CI 1.05–1.25) for incident T2DM [135]. These findings were in accordance with prior finding regarding $PM_{2.5}$ and DM [136, 137] and with prospective cohort studies that examined the effect of long-term $PM_{2.5}$ exposure on T2DM incidence [125, 127, 128].

Although all these findings suggest a strong relationship between air pollution and DM, some conflicting findings exist. Exposure to SO_2 and PM_{10} was significantly related to the prevalence of T2DM in women, but not in men, suggesting gender differences [122]. Other prospective cohort studies also low in numbers failed to observe statistically significant associations between long-term $PM_{2.5}$ exposure and incident DM [126, 138]. In the Framingham Offspring

cohort, participants living 64 m (25th percentile) from a major roadway had 0.28% (95% CI 0.05–0.51%) higher fasting plasma glucose than participants living 413 m (75th percentile) away, and the association appeared to be driven by participants who lived within 50 m from a major roadway. Higher exposures to 3- to 7-day moving averages of black carbon and NO_x were associated with higher plasma glucose, whereas the associations for ozone were negative, but there was no association with insulin resistance as evaluated by the HOMA-index [139].

Generally, in short-term exposure studies, exposure to air pollution was associated with higher levels of glucose, insulin or HOMA-IR [140, 141], whereas in longer term exposure, most of the positive associations were found with glucose but not with insulin or HOMA-IR [142, 143].

MESOAMERICAN NEPHROPATHY

MesoAmerican nephropathy (MeN) is another recently recognized endemic form of CKD. MeN can be considered as an environmental disease since it mostly affects people working in agricultural areas and with a tendency to be found in specific geographical locations, such as Nicaragua and El Salvador and other Central American countries. Additionally, global warming is thought to contribute to the increased incidence of MeN. Patients with MeN present with elevated creatinine levels, no hypertension and urine albumin levels are normal or of non-nephrotic range. The cause and pathogenesis of MeN are still not fully known; however, the repeated dehydration hypothesis is thought to play a role in the development of kidney disease. In this scenario, occupational heat exposure with repeated episodes of volume and salt depletion occurs during the disease process. Potential mechanisms include the development of hyperosmolarity with the activation of the aldose reductase–fructokinase pathway in the proximal tubule leading to local injury and inflammation, and the possibility that renal injury may be the consequence of repeated uricosuria and urate crystal formation as a consequence of both increased generation and urinary concentration, similar to a chronic tumour lysis syndrome. The epidemic is postulated to be increasing due to the effects of global warming. The renal morphology shows glomerulosclerosis of varying degrees, glomerular hypertrophy and signs of chronic glomerular ischaemia, together with mild to moderate chronic tubulointerstitial damage [131, 144, 145]. As MeN is considered as an environmental disease due to global warming, interventional studies to reduce heat stress may be of great importance. Indeed, a recent Phase 1 study showed that after an intervention with sugarcane workers, self-reported water consumption increased 25% and symptoms associated with heat stress and dehydration decreased [146]. It is now evident that new health problems with environmental and climate changes such as MeN will be of more interest in the near future, and preventive measures will be of the utmost importance for the prevention of a MeN epidemic.

BALKAN ENDEMIC NEPHROPATHY AND CHINESE HERB NEPHROPATHY

Balkan endemic nephropathy (BEN) is a kind of endemic nephropathy associated with upper urethelial cancer with specific geographical distribution along tributaries of the Danube River in Bosnia–Herzegovina, Croatia, Macedonia, Serbia, Bulgaria and Romania. Several hypotheses on the cause of BEN have been suggested such as mycotoxins, heavy metals, viruses and trace element insufficiencies. However, recent evidence suggests that chronic dietary exposure to aristolochic acid (AA)—a principal component of *Aristolochia clematitis*—which grows as a weed in the wheat fields of the endemic regions—is the cause of BEN [147].

BEN is described as a familial clustering and a slowly progressive kidney disease. The clinical signs and symptoms of BEN are non-specific and often remain latent for years and even decades. After an initial asymptomatic stage, patients suffer from weakness and lassitude, mild lumbar pain and pallor of the skin. At a later stage, anaemia is associated with a significant loss of renal function. Proteinuria of tubular type and specifically, β_2-microglobulinuria is observed. Histologically, BEN is characterized by tubular atrophy with extensive hypocellular fibrosis decreasing from the outer to the inner cortex of the kidney [148, 149]. Nowadays, BEN is considered as an environmental disease since environmental exposure to AA by BEN patients has been confirmed [150, 151]. Other evidence of BEN being an environmental disease comes from the fact that in the last few decades, exposure to AA has decreased due to the significant improvement in farming and milling practices, disabling and preventing the contamination of flour [152].

Chinese herb nephropathy (CHN) is another nephropathy that is also related to AA. This nephropathy appeared to be the dramatic consequence of a substitution of *Stephania tetrandra* by *Aristolochia fangchi*, which is rich in AA, because both herbs share the same common name and one can be used instead of the other in traditional Chinese medicine irrespective of their botanical classification. The true incidence of aristolochic acid nephropathy (AAN) is largely unknown and probably underestimated, as numerous ingredients known or suspected to contain AA are used in traditional medicine in China, Japan and India. CHN is characterized by a rapidly progressive interstitial nephritis, leading to ESRD and urothelial malignancy [153]. In most of the cases, urinary sediment was unremarkable, and dipstick analysis for albuminuria was negative. Macroscopically, the kidneys were shrunk, asymmetric in about half of the cases with irregular outlines in one-third [154].

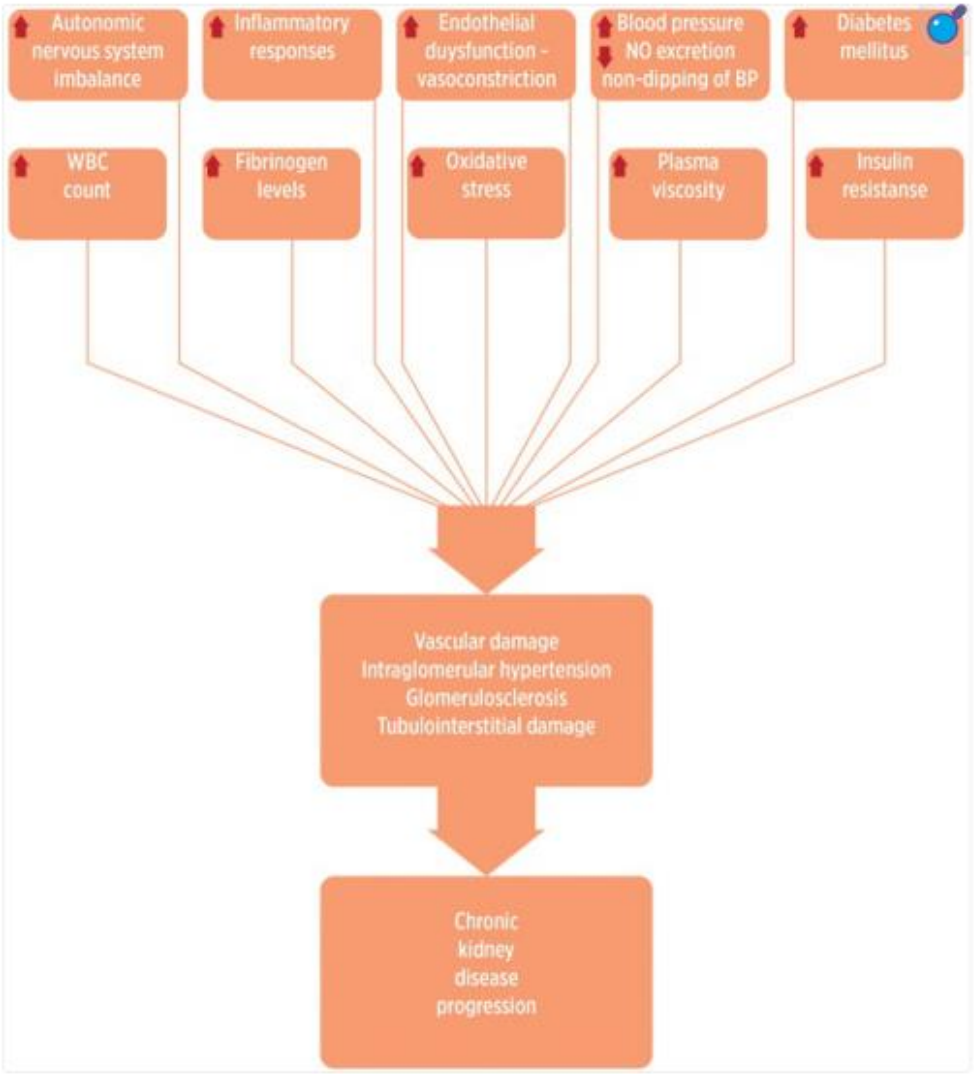
Microscopically, an extensive interstitial fibrosis with atrophy and loss of proximal tubules was the predominant lesion, which was mainly located in the superficial cortex and progressed towards the deep cortex. The glomeruli were relatively spared, although, in the later stage of the disease, they displayed a mild collapse of the capillaries and a wrinkling of the basement membrane [155]. Some suggest that BEN and CHN can be considered as two faces of Janus; however, recent evidence suggests that except in specific cases of acute tubular necrosis, no similarity could be found in the tubulointerstitial compartment with histological lesions

observed in BEN and CHN [153]. However, as discussed above, both BEN and CHN can be considered as specific forms of nephropathy with specific geographical distribution.

PATHOGENESIS

Several mechanisms have been proposed to link exposure to air pollution with BP and kidney damage (Figure 2). Inhaled PM can trigger acute autonomic nervous system imbalance and systemic proinflammatory responses and can activate vascular endothelial dysfunction and arterial vasoconstriction [156, 157]. Impaired sodium excretion associated with PM [112] may also increase BP since an impaired capacity to excrete sodium during daytime would lead to a non-dipping pattern [158]. Long-term exposure to traffic pollution leads to vascular endothelial injury, systemic inflammation, atherosclerosis and microvascular changes [13, 159]. Evidence from Apo-E knockout mice and hyperlipidaemic rabbits indicates that long-term exposure to urban air pollution causes increased atherosclerosis with inflammatory characteristics [160, 161]. Moreover, in community-dwelling adults, traffic-related pollution is positively associated with carotid intima–media thickness [162, 163]. Mice chronically and continuously exposed to ambient levels of air pollution for 4 months developed significant more thickening (decreased lumen/wall ratios) in pulmonary and coronary arteries than mice exposed to filtered air in which PM_{10} and NO_2 were reduced by 50 and 75%, respectively. However, no evidence of influence of air pollution was detected in intra parenchymal renal arteries, which are well-known targets of systemic hypertension. One possibility is that pulmonary and cardiac effects were promoted by highly reactive substances present in the air, which may not reach sufficiently high levels in the renal circulation [164]. A recent experimental study reported that 16 weeks of exposure to concentrated ambient PM (average 13.3 $\mu g/m^3$) versus filtered air was positively associated with glomerulosclerosis in rat T1DM [165]. Air pollution has been associated with objective markers of cardiovascular risk, such as circulating white cell counts, plasma fibrinogen levels and decreased heart rate variability [166, 167]. PM has been reported to be associated with increased plasma viscosity [168], changes in blood characteristics [169] and indicators of abnormal autonomic function of the heart, including increased heart rate, decreased heart rate variability and increased cardiac arrhythmias [170].

FIGURE 2.



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Pathogenic mechanisms of environmental pollutants leading to kidney damage. WBC, white blood cell.

Smoking is an independent risk factor for CKD and might result in intraglomerular hypertension, vascular damage or glomerulosclerosis via multiple complex interactions of non-haemodynamic (angiotensin II, transforming growth factor-β1, endothelin-1) and haemodynamic factors [171], and occupational exposures to Cd and Pb may affect the magnitude of kidney damage conferred by smoking [172].

An interaction with obesity has also been described. Concentrated PM and ozone exposures induced inflammation and oxidative stress in peri-renal adipose tissue in rats [173]. Ambient fine PM matter may exaggerate adipose inflammation, induce insulin resistance and oxidative stress, mitochondrial functions and gene expression in adipose tissue [174–176]. Furthermore, diabetes and obesity may enhance the associations between $PM_{2.5}$ and biomarkers of systemic inflammation [177], which in turn would lead to diminished insulin action [178]. Air pollution may also be associated with dysregulated release of peptides or proteins (adipokines) secreted by adipose tissue that regulates carbohydrate metabolism [174, 175, 179]. Mice exposed to $PM_{2.5}$ developed a non-alcoholic steatohepatitis-like phenotype of impaired hepatic glycogen storage, glucose intolerance and insulin resistance. Moreover, exposure to $PM_{2.5}$ activated inflammatory response pathways mediated through cJun N-terminal kinase, nuclear factor kappa B and toll-like receptor 4, and suppressed the insulin receptor substrate 1-mediated signalling [180].

RESEARCH NEEDS

The detrimental effects of air pollution on the kidney have just begun to be acknowledged. Various pollutants (toxic metals, PM, cigarette smoke and gases) may harm the kidney. However, it is not exactly known which pollutant by itself specifically causes damage or what type of damage.

Despite all accumulating data regarding pollution and its adverse health effects, there are still gaps that have to be recognized. This issue is very important since pollution is a global health threat that was responsible for an estimated 9 million premature deaths as well as for 268 million disability-adjusted life-years in 2015, which means great economic losses. The majority —71%—of the deaths attributed to pollution are caused by non-communicable diseases. To end neglect of pollution and advance prevention of pollution-related disease, commissions have been formed such as the Lancet Commission on Pollution and Health. The Commission identified substantial gaps in knowledge about pollution and noted that these gaps result in underestimation of pollution's contribution to the global burden of disease. To close these gaps and guide prevention, the Commission made research recommendations and proposed creation of a Global Observatory on Pollution and Health. It is of no doubt that successful pollution research needs transdisciplinary collaborations among exposure science, epidemiology, data

science, engineering, health policy and economics. Studies must be stimulated regarding the burden of disease due to pollution in cities and countries that include options for pollution control and disease prevention, source apportionment studies that analyse the amounts of pollution, country-level analyses of the burden of disease and loss of human capital attributable to various pollutants and all pollution in specific countries. These studies are essential for identifying the pollution sources with the most significant effects on human health and for prioritizing interventions [181].

Besides these issues, specific mechanisms of kidney injury are not known. PM is a complex mixture of chemical compounds, the behaviour of which strongly depends on the atmospheric conditions. Furthermore, it is not clear regarding the mechanisms that lead to development of CKD. For example, $PM_{2.5}$ is associated both with DM and hypertension. However, it is not clear how much of the association of $PM_{2.5}$ to CKD development is attributed to DM and hypertension separately. These issues are important to plan preferential preventive measures according to dominant-associated mechanisms. Last but not the least, more needs to be known about the causal relationship between exposure to levels of environmental pollution and ultimately cause-specific mortality. Further studies are needed to explore which compound(s) within PM might be responsible for the observed associations and what manoeuvres may prevent or treat these adverse effects.

Prospective studies should explore whether improving air pollution, setting preventive measures for clean air and using green energy have beneficial effects on hard endpoints, such as reduction in the incidence of diabetes, hypertension and CKD. Additionally, more longitudinal studies in different parts of the world with different pollution levels are needed to directly compare the effects of air pollution on human health. Recent initiatives to restrict the use of diesel fuels for urban transportation in Europe offer the opportunity to design and fund such studies.

CONCLUSION

The classic view that air pollution is a risk factor for upper and lower respiratory airways is now challenged by evidence that air pollution may also impact other organs such as heart, vessels and kidneys. The inflammatory mediators induced by PM and other pollutants in the lungs could spill over into the circulation, resulting in systemic inflammation, oxidative stress and damage to distant organs including kidneys [13]. However, there is also evidence of direct harm to the kidneys. The pathogenesis is still not fully understood. Studies are needed to characterize which type of air pollutant is primarily responsible for specific disease processes. It is necessary to raise awareness and recruit into action policy-makers, industry representatives establishing air quality standards, emissions controls and promoting the use of

greener energy. More detailed longitudinal studies and also experimental designs are needed to demonstrate cause-and-effect relationships between specific air pollutants and kidney damage as well as the impact of manoeuvres that decrease air pollution.

CONFLICT OF INTEREST STATEMENT

None declared.

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Brick kiln pollution and its impact on health: A systematic review and meta-analysis

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Abstract

Brick kiln emissions adversely affect air pollution and the health of workers and individuals living near the kilns; however, evidence of their impacts remains limited. We conducted a systematic review of brick kiln pollution (emissions, source contributions and personal exposures) and its effects on health. We extracted articles from electronic databases and through manual citation searching. We estimated pooled, sample-size-weighted means and standard deviations for personal exposures by job type; computed mean emission factors and pollutant concentrations by brick kiln design; and meta-analyzed differences in means or proportions for health outcomes between brick kiln workers and controls or for participants living near or far away from kilns. We identified 104 studies; 74 were conducted in South Asia. The most evaluated pollutants were particulate matter (PM; n = 48), sulfur dioxide (SO_2; n = 24) and carbon monoxide (CO; n = 22), and the most evaluated health outcomes were respiratory health (n = 34) and musculoskeletal disorders (n = 9). PM and CO emissions were higher among traditional than improved brick kilns. Mean respirable silica exposures were only measured in 4 (4%) studies and were as high as 620 μg/m^3, exceeding the NIOSH recommended exposure limit by a factor of over 12. Brick kiln workers had consistently worse lung function, more respiratory symptoms, more musculoskeletal complaints, and more inflammation when compared to unexposed participants across studies; however, most studies had a small sample size and did not fully describe methods used for sampling or data collection. On average, brick kiln workers had worse health outcomes when compared to unexposed controls but study quality supporting the evidence was low. Few studies reported silica concentrations or personal exposures, but the few that did suggest that exposures are high. Further research is needed to better understand the relationship between brick kiln pollution and health among workers, and to evaluate exposure mitigation strategies.

Keywords: Ambient air pollution; Brick kiln emissions; Health; Occupational exposures; Silica.

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Short-term Exposure to Air Pollution and Attributable Risk of Kidney Diseases: A Nationwide Time-series Study

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Abstract

Background: Several studies have shown that long-term exposure to air pollution is associated with reduced kidney function. However, less is known about effects of short-term exposure to air pollution on kidney disease aggravation and resultant emergency room (ER) burden. This study aimed to estimate excess ER visits attributable to short-term air pollution and to provide evidence relevant to air pollution standards to protect kidney patients.

Methods: We conducted time-series analysis using National Health Insurance data covering all persons in South Korea (2003-2013). We collected daily data for air pollutants (particulate matter ≤10 μm [PM10], ozone [O3], carbon monoxide [CO], and sulfur dioxide [SO2]) and ER visits for total kidney and urinary system disease, acute kidney injury (AKI), and chronic kidney disease (CKD). We performed a two-stage time-series analysis to estimate excess ER visits attributable to air pollution by first calculating estimates for each of 16 regions, and then generating an overall estimate.

Results: For all kidney and urinary disease (902,043 cases), excess ER visits attributable to air pollution existed for all pollutants studied. For AKI (76,330 cases), we estimated the highest impact on excess ER visits from O3, while for CKD (210,929 cases), the impacts of CO and SO2 were the highest. The associations between air pollution and kidney ER visits existed for days with air pollution concentrations below current World Health Organization guidelines.

Conclusion: This study provides quantitative estimates of ER burdens attributable to air pollution. Results are consistent with the hypothesis that stricter air quality standards benefit kidney patients.

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